

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

**APPLICATION NUMBER: 20-154/S-028
20-155/S-020
20-156/S-021**

**CLINICAL PHARMACOLOGY/
BIOPHARMACEUTICS REVIEW**

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 20,154; S-028
[20,155]
[20,156]

Submission Date: July 1, 1998

Drug Product: Didanosine Chewable/Dispersible Tablets (NDA 20,154)
[Didanosine Buffered Powder for Oral Solution (NDA 20,155)]
[Didanosine Pediatric Powder for Oral Solution (NDA 20,156)]

Trade Name: VIDEX®

Sponsor: Bristol-Myers Squibb
Wallingford, CT

Type of Submission: Labeling Supplement

OCPB Reviewer: Philip M. Colangelo, Pharm.D., Ph.D.
OCPB Log-In Date: July 8, 1998

I. BACKGROUND

This submission is a labeling supplement to NDA 20,154 (S-028), Didanosine Chewable/Dispersible (buffered) Tablets, with cross-reference made to NDA 20,155, Didanosine Buffered Powder for Oral Solution and NDA 20,156, Didanosine Pediatric Powder for Oral Solution. The primary goal of the submission was to provide additional clinical information/data on the use of didanosine (ddl) in combination with other anti-retroviral drug regimens for the treatment of HIV infected patients in order to support the proposed revisions for the relevant sections of the label. This information also included data and other supportive evidence with respect to pharmacokinetic (PK) drug interactions when ddl was given in combination with other anti-retroviral drugs.

The revisions as proposed by the sponsor to the VIDEX® label in annotated (i.e., side-by-side) format are provided as **Appendix 1 (included with this review)**.

II. SUMMARY of CLINICAL PHARMACOLOGY INFORMATION

As indicated above, information was provided to support label revisions regarding pharmacokinetic interactions between ddl (a nucleoside HIV reverse transcriptase inhibitor) and the following other anti-retroviral drugs: indinavir (HIV protease inhibitor), nelfinavir (HIV protease inhibitor), delavirdine (non-nucleoside HIV reverse transcriptase inhibitor), nevirapine (non-nucleoside HIV reverse transcriptase inhibitor), and zalcitabine (HIV reverse transcriptase inhibitor). A major issue associated with the potential for ddl to produce an alteration in the pharmacokinetics of these drugs when co-administered is that ddl is apparently degraded rapidly under acidic conditions, and thus, requires co-administration with antacids to protect it against acid-induced hydrolysis in the stomach. Because of this, VIDEX® chewable/dispersible tablets and powder for oral solution are formulated to contain buffering agents (i.e., calcium carbonate and magnesium hydroxide in the tablets; citrate-phosphate buffer in the powder). The ability of these buffering ingredients to potentially alter the local pH of the stomach and/or other portions of the gastrointestinal tract may consequently alter the absorption and systemic availability of the other co-administered drugs.

The sponsor conducted two separate clinical studies to evaluate the interactions of ddl with indinavir and with nelfinavir and provided the associated study reports and PK data for review.

For the interactions of ddl with delavirdine, nevirapine, and ritonavir, the sponsor provided literature articles and/or the approved labeling for the respective co-administered agents to support the labeling revisions proposed for VIDEX®.

A brief summary of this information immediately follows, with more detailed reviews provided in Appendix 2 (available on request).

1. Protocol AI454-137: Single Dose Pharmacokinetic Interaction Study of Didanosine and Indinavir Sulfate in Healthy Subjects Following Oral Administration

The potential for pharmacokinetic interaction between ddl and indinavir was assessed in 16 healthy male and female subjects following single therapeutic doses of 200 mg ddl (2 x 100 mg VIDEX® chewable/dispersible tablets) and 800 mg indinavir (2 x 400 mg CRIXIVAN® capsules). Four treatments were administered in crossover fashion and all under fasting conditions: ddl alone; indinavir alone; ddl + indinavir simultaneously; indinavir then ddl 1 hr later.

Minor reductions were observed in the systemic availability of ddl when simultaneously administered with indinavir or when ddl was given 1 hr after indinavir (i.e., reductions in C_{max} and AUC ≤ 17%). These decreases in systemic availability of ddl were statistically and/or presumably deemed to be clinically non-significant. Substantial reductions were observed in the systemic availability of indinavir when simultaneously administered with ddl (i.e., reductions in C_{max} and AUC ~80%), which were highly statistically significant and deemed to be clinically significant. Minor reductions in indinavir C_{max} and AUC were observed when ddl was given 1 hr after indinavir (i.e., reductions ≤ 11%).

Overall, the results suggested that ddl should not be co-administered with indinavir, but rather, if ddl and indinavir are to be used as combination therapy in HIV infected patients, dosing should be separated by at least 1 hour. There appeared to be no significant safety issues associated with the co-administration of ddl and indinavir. **The sponsor recommended that indinavir be given 1 hour prior to dosing with ddl. The approved labeling for indinavir sulfate capsules (CRIXIVAN®; PDR 1998, p 1625-1628, issued March 1997) is also consistent with this recommendation. The CRIXIVAN® label states that if indinavir and ddl are given concomitantly, they should be administered at least 1 hour apart on an empty stomach.**

The reviewer agrees with the sponsor's study results and conclusions.

2. Protocol AI455-054: A Pilot Study of Safety and Antiviral Activity of the Combination of Stavudine (d4T), Nelfinavir (AG1343), and Didanosine (ddl) in HIV-Infected Patients

A sub-study to Protocol AI455-054 was conducted to evaluate the effects of oral administration of ddl 200 mg (2 x 100 mg VIDEX® chewable/dispersible tablets) on the systemic availability of oral nelfinavir 750 mg (3 x 250 mg VIRACEPT® tablets) in 10 HIV infected male patients who were treatment naïve. On the first day of the PK study, the 10 patients received a single oral 750 mg dose of nelfinavir with a light meal, as recommended in the approved labeling. On the following day, patients received a single 200 mg dose of ddl buffered tablets on an empty stomach (as per the approved labeling), followed at 1 hr later by a single 750 mg dose of nelfinavir with the light meal.

When nelfinavir was given with a light meal (as recommended in the approved labeling) at 1 hr after the administration of ddl, there was no substantial effect of ddl on the C_{max} (~8% increase), AUC (~15% increase), or T_{max} of nelfinavir. These results suggested that nelfinavir can be administered 1 hour after administration of ddl. **The sponsor recommended that nelfinavir be administered 1 hour after the administration of ddl during combination therapy with these two drugs. The approved labeling for nelfinavir mesylate tablets and oral powder**

(VIRACEPT®; PDR 1998, p 476-480, label issued July, 1997) is also consistent with this recommendation. The VIRACEPT® label recommends that ddl be administered on an empty stomach, and therefore, nelfinavir should be given with a light meal at 1 hour after or more than 2 hours before ddl.

The reviewer agrees with the sponsor's study results and conclusions.

3. Didanosine Interaction With Delavirdine

Evidence to support the proposed wording in the revised ddl labeling for this interaction was provided via inclusion of the approved package insert for Delavirdine Mesylate Tablets (RESCRIPTOR®; Pharmacia-Upjohn Full Prescribing Information, label revised August 1997) and an article from the scientific literature (Morse GD, Fischl MA, et.al. Single Dose Pharmacokinetics of Delavirdine Mesylate and Didanosine in Patients with HIV Infection. *Antimicrobial Agents and Chemotherapy*, 1997; 41(1): 169-174).

The approved delavirdine labeling indicates that in 9 HIV-1 infected patients, simultaneous administration of ddl (125 mg bid as buffered powder or 200 mg bid as buffered tablets) with delavirdine (400 mg tablets tid) for 2 weeks (i.e., at steady-state) resulted in a decrease in AUC of both ddl and delavirdine of ~20% as compared to when the two drugs were given at least 1 hour apart. **Thus, the approved delavirdine label recommends that administration of ddl and delavirdine should be separated by at least 1 hour.**

The literature paper was a single dose, crossover study of ddl (200 mg buffered tablets) and delavirdine (400 mg) in 12 HIV-1 infected patients. Similar results were obtained with this study as that in the steady-state study cited above from the approved delavirdine label. However, the magnitude of the reductions in delavirdine C_{max} and AUC were greater when co-administered with ddl after single doses of each drug. The mean C_{max} and AUC of delavirdine were decreased ~50% and ~40%, respectively, when co-administered with ddl. The mean C_{max} and AUC of ddl were also reduced ~30% and ~20%, respectively, when co-administered with delavirdine. These reductions in delavirdine and ddl systemic availability were found to be statistically significant (i.e., p values ≤ 0.05). The mean T_{max} of either drug was not significantly effected with concurrent administration. When given 1 hour apart, the mean C_{max}, AUC, and T_{max} estimates of ddl and delavirdine were not significantly altered. These results suggested that ddl and delavirdine should be administered at least 1 hour apart to avoid a significant reduction in the systemic availability of both drugs. **The sponsor's recommendation was that delavirdine be administered 1 hour prior to ddl.**

The reviewer agrees with the sponsor's use of the results provided through the approved delavirdine labeling and the literature to support the ddl label recommendation that delavirdine be administered at least 1 hour prior to dosing with ddl.

4. Didanosine Interaction With Nevirapine

Evidence to support the proposed wording in the revised ddl labeling for this interaction was provided via inclusion of the approved package insert for Nevirapine Tablets (VIRAMUNE®; Boehringer Ingelheim Pharmaceuticals Full Prescribing Information, 1996). The nevirapine label cites two studies that demonstrated the lack of a pharmacokinetic interaction with ddl. In one study, the steady-state exposure (i.e., AUC₉) to nevirapine in 6 HIV infected patients was not significantly altered by co-administration of ddl buffered tablets. In the second study, which was a crossover study in 18 HIV-1 infected patients, nevirapine (400 mg/day) had no significant effect on the steady-state pharmacokinetics of ddl (200-300 mg/day). **The approved labeling for**

nevirapine indicates that nevirapine may be administered with or without food, antacids, and ddl, and that no dosage adjustments are required when nevirapine is taken in combination with ddl.

The reviewer agrees with the sponsor's use of the results available through the approved nevirapine labeling to support the ddl label indicating that multiple dose studies have shown no significant pharmacokinetic interaction between ddl and nevirapine.

5. Didanosine Interaction With Ritonavir

Evidence to support the proposed wording in the revised ddl labeling for this interaction was through inspection of the approved package insert for Ritonavir Capsules and Oral Solution (NORVIR®; PDR 1998, p 459-464; label revised March 1997). In addition, in the current submission for the revised ddl label the sponsor provided an abstract from the literature, the results of which apparently were the same as those cited in the approved ritonavir label (Cato A, Qian J, Carothers L, et.al. Evaluation of the Pharmacokinetic Interaction Between Ritonavir and Didanosine. 97th Annual Meeting of the Society for Clinical Pharmacology & Therapeutics, Walt Disney World, FL, 1996; Abstract PI-59). The study was a multiple dose, crossover trial of ritonavir (600 mg q12hr) and ddl (200 mg q12hr), given separately and concurrently to 12 HIV-positive male subjects for 4 days. The results showed no significant effect of ddl co-administration on ritonavir Cmax and AUC (i.e., ≤ 6% increases with ddl). However, the mean Cmax and AUC of ddl were reduced by an average (95% CI) of 16% (5, 26%) and 13% (0, 23%), respectively, when co-administered with ritonavir. **The authors of this abstract concluded that although the systemic availability of ddl was reduced by ritonavir, the magnitude of the reduction was most likely to be of minor clinical importance. Thus, a dosage adjustment for either ddl or ritonavir was not warranted when the two drugs are co-administered.**

*The label revision for ddl indicates that a multiple dose study has shown no clinically significant PK interaction between VIDEX® and ritonavir. However, in the approved ritonavir label it is recommended that although ddl may be administered without dosage adjustment to patients taking ritonavir, dosing with the two drugs should be separated by 2.5 hours to avoid formulation incompatibility**. The reviewer*

****In the ritonavir-ddl interaction study submitted with NDA's 20659 and 20680 for NORVIR®, ritonavir was only administered 2.5 hours after ddl in the combination regimen.**

Overall Conclusions:

A substantial reduction in the systemic availability (i.e., Cmax and AUC) of indinavir and delavirdine were observed when concomitantly administered with ddl and was deemed to be clinically significant for both drugs. Since no significant alteration in systemic availability of indinavir and delavirdine occurred when given 1 hour prior to ddl, they should be given as such.

There was no substantial effect of ddl on the systemic availability of nelfinavir when nelfinavir was given with a light meal (as recommended in the approved label) and administered at 1 hour after ddl administration. No evaluation of the simultaneous administration of ddl and nelfinavir was provided.

Co-administration of ritonavir with ddl did not produce clinically significant alterations in the systemic availability of either drug. However, in order to be consistent with the approved ritonavir

labeling, _____

No substantial pharmacokinetic alterations were reported for both nevirapine and ddl when the two drugs are co-administered.

IV. RECOMMENDATION

The labeling supplement under NDA 20,154 (S-028) for didanosine has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and was found to be acceptable. The comments provided below pertain to the proposed labeling and are to be conveyed to the sponsor.

V. COMMENTS TO BE CONVEYED TO THE SPONSOR

1. With regard to the interaction of didanosine and ritonavir, the reviewer agrees with the sponsor's conclusion that co-administration of ritonavir with ddl did not produce clinically significant alterations in the systemic availability of either drug. The revised VIDEX® label also indicates this, and thus, would imply that the two drugs could be given concurrently. However, in the approved ritonavir label (*NORVIR®*, PDR 1998, p 459-464; revised March 1997), it is recommended that although ddl may be administered without dosage adjustment to patients taking ritonavir, dosing with the two drugs should be separated by 2.5 hours to avoid formulation incompatibility. The reviewer _____

An example of such wording, which should be included under **PRECAUTIONS, Drug** _____

ISI

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division

ISI

RD/FT signed by Kellie Reynolds, Pharm.D. (TL) _____

cc:

- Div. File: NDA 20,154, S-028; [NDA 20,155]; [NDA 20,156]
- HFD-590 (R. Fleischer, MO)
- HFD-590 (M. Truffa, PM/CSO)

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- ✓ HFD-880 (Division File)
- ✓ HFD-880 (K. Reynolds; P. Colangelo)
- ✓ CDR (Barbara Murphy)

APPENDIX 1:

**LABELING REVISIONS
PROPOSED BY THE SPONSOR
(June 30, 1998)**

APPENDIX 2:
REVIEWS OF PHARMACOKINETIC DRUG INTERACTION STUDIES
AND
OTHER INFORMATION
WITH DDI

1. Protocol AI454-137: Single Dose Pharmacokinetic Interaction Study of Didanosine and Indinavir Sulfate in Healthy Subjects Following Oral Administration

Objectives:

To assess the pharmacokinetic (PK) interaction between didanosine (ddl) and indinavir and the safety of the two drugs when co-administered following oral doses of 200 mg ddl and 800 mg indinavir to healthy subjects.

Formulations/Treatments:

Didanosine Chewable/Dispersible Tablets (VIDEX®) – 100 mg
Indinavir Sulfate Capsules (CRIXIVAN®) – 400 mg

Subjects:

16 healthy males (N = 13) and females (N = 3); mean age 37 yr. (range 21-49 yr.); mean weight 75.3 kg (range 58.5-89.1 kg)

Study Design and Methods:

Randomized, open label, single dose, 4-way crossover design. All 16 subjects received the following four treatments on separate occasions, separated by a washout period of 7 days:

- Treatment A: ddl 200 mg (2 x 100 mg) alone
- Treatment B: Indinavir 800 mg (2 x 400 mg) alone
- Treatment C: ddl 200 mg + Indinavir 800 mg simultaneously
- Treatment D: Indinavir 800 mg, then ddl 200 mg at 1 hour later

In treatment D, ddl was given at 1 hr after indinavir since the T_{max} of indinavir is ~1 hr. Subjects were administered all treatments under fasted conditions (at least 10 hrs), and continued to fast for 4 hrs postdose. The ddl tablets were administered according to the approved label directions, i.e., chewed thoroughly (either together or in rapid succession) and swallowed with water.

Plasma samples were obtained from 0 (predose) to 9 hrs postdose for determination of ddl and/or indinavir concentrations. Safety during the study was monitored via vital signs, EKG's, and routine laboratory tests.

Analytical Methods:

ddl plasma concentrations were determined by radioimmunoassay (RIA) which was validated over the range from _____ ng/mL (LLOQ = _____).

Both the performance and validation of the RIA were acceptable.

Indinavir plasma concentrations were determined by HPLC-UV which was validated over a linear dynamic range from _____ ng/mL (LLOQ: _____).

Both the performance and validation of the HPLC-UV assay were acceptable.

Data Analysis:

The PK parameters for ddl and indinavir were determined using standard noncompartmental methods. Statistical analyses included ANOVA for crossover design and determination of the 90% confidence intervals (CI) for log-transformed AUC(inf) and C_{max} using the two one-sided test procedure. For T_{max} and T₂, the untransformed data were used in the ANOVA and pairwise comparisons or 90% CI determinations. The reference treatments were ddl given alone (A) and indinavir given alone (B) for the assessment of the interaction when the two drugs are coadministered, i.e., treatments C and D.

For the 90% CI for AUC(inf) and C_{max}, an interval of (0.75, 1.33) was chosen by the sponsor as the criteria for claiming the lack of an interaction. This appeared to be based on the approved labeling for both drugs and the magnitude of change in PK reported with other drug-drug or drug-food interaction studies. That is, an increase in the indinavir AUC of 32% or less when co-

administered with other drugs does not warrant a change in the indinavir dose. For ddl, the label reported a reduction in the AUC and Cmax of ~50% in the presence of food, and consequently recommends that ddl be administered on an empty stomach.

From this information, the (0.75, 1.33) interval is acceptable.

Results:

Didanosine

The mean plasma concentration-time profiles for ddl following treatments **A** (alone), **C** (co-administered with indinavir), and **D** (1 hr after indinavir) are illustrated in Figure 1. These plots indicated only minor changes in mean ddl concentrations for treatments **C** and **D**. The mean PK parameters are summarized in Table 1 and the statistical results are provided in Table 2. In addition to Table 1, the following table below summarizes the variability in Cmax, AUC, and T2 of ddl, with respect to %CV, range, and fold variability in the range for treatments **A**, **C**, and **D**.

VARIABILITY IN SELECTED PK PARAMETERS FOR DIDANOSINE

Treatment	Cmax	AUC(inf)	T2
A (Alone)			
CV	44%	32%	13%
Range	200 – 1764 ng/mL	572 – 2505 ng.hr/mL	1.27 – 2.01 hr
Fold Variability in Range	9-fold	4-fold	1.6-fold
C (with Indinavir)			
CV	35%	22%	11%
Range	406 – 1432 ng/mL	890 – 2238 ng.hr/mL	1.21 – 1.83 hr
Fold Variability in Range	3.5-fold	2.5-fold	1.5-fold
D (1 hr after Indinavir)			
CV	44%	30%	20%
Range	279 – 1636 ng/mL	667 – 2144 ng.hr/mL	0.77 – 1.88 hr
Fold Variability in Range	6-fold	3-fold	2.4-fold

When co-administered with indinavir (i.e., **C** vs. **A**), there was a minor reduction in the geometric mean ddl Cmax and AUC of ~8% and ~6%, respectively (Table 2). The 90% CI and p values (i.e., for the pairwise comparisons) for Cmax and AUC indicated that there was no significant effect of indinavir on the systemic availability of ddl (Table 2). There was also no statistically significant effect of indinavir on Tmax and T2 of ddl.

When given 1 hr after indinavir (i.e., **D** vs. **A**), the geometric mean Cmax and AUC of ddl were reduced ~13% and ~17%, respectively (Table 2). The lower bounds of the 90% CI for both Cmax (i.e., 0.72) and AUC (i.e., 0.73) fell outside of the protocol specified criteria of (0.75, 1.33) to show lack of an interaction (Table 2). The p value for the pairwise comparison of Cmax was non-significant (p = 0.21), but was significant for AUC (p = 0.01). As shown in the table directly above, the range of individual Cmax and AUC values between treatments **D** and **A** overlapped to a great extent. The Tmax of ddl was found to be significantly prolonged (0.75 vs. 0.50 hrs, p = 0.01) and mean T2 of ddl was significantly shorter (1.43 vs. 1.58 hrs, p = 0.02).

Indinavir

The mean plasma concentration-time profiles for indinavir following treatments **B** (alone), **C** (co-administered with ddl), and **D** (1 hr before ddl) are illustrated in Figure 2. These plots indicated only minor changes, if any, in mean indinavir concentrations for treatment **D**, but substantial reductions in mean indinavir concentrations at all timepoints for treatment **C**. The mean indinavir PK parameters are summarized in Table 3 and the statistical results are provided in Table 4. In

addition to Table 3, the following table below summarizes the variability in C_{max}, AUC, and T₂ of indinavir, with respect to %CV, range, and fold variability in the range for treatments B, C, and D.

VARIABILITY IN SELECTED PK PARAMETERS FOR INDINAVIR

Treatment	C _{max}	AUC(inf)	T ₂
B (Alone)			
CV	26%	36%	8%
Range	2146 – 10645 ng/mL	2630–29553 ng.hr/mL	0.96 – 1.28 hr
Fold Variability in Range	5-fold	11-fold	1.3-fold
C (with ddl)			
CV	81%	106%	12%
Range	251 – 5849 ng/mL	708–14152 ng.hr/mL	1.11 – 1.72 hr
Fold Variability in Range	23-fold	20-fold	1.5-fold
D (1 hr before ddl)			
CV	40%	46%	11%
Range	1690 – 13449 ng/mL	2111–31695 ng.hr/mL	0.91 – 1.36 hr
Fold Variability in Range	8-fold	15-fold	1.5-fold

When co-administered with ddl (i.e., C vs. B), there was a substantial reduction in the geometric mean indinavir C_{max} and AUC of ~82% and ~84%, respectively (Table 4). The 90% CI and p values (i.e., for the pairwise comparisons) for C_{max} and AUC indicated that there was a significant effect of ddl on the systemic availability of indinavir (Table 4). As seen from the table directly above, the variability in the C_{max} and AUC estimates for indinavir were demonstrably higher when co-administered with ddl. There was no statistically significant effect of ddl on indinavir T_{max}, but T₂ of indinavir was significantly prolonged from 1.10 to 1.39 hrs (p < 0.001).

When given 1 hr before ddl (i.e., D vs. B), the geometric mean C_{max} and AUC of indinavir were reduced only ~4% and ~11%, respectively (Table 4). However, the lower bounds of the 90% CI for both C_{max} (i.e., 0.70) and AUC (i.e., 0.68) fell outside of the protocol specified criteria of (0.75, 1.33) to show lack of an interaction. The p values for the pairwise comparisons of C_{max} and AUC were non-significant (p = 0.81 and 0.46, respectively). Additionally, the table directly above shows a high degree of overlap in the range of values for C_{max} and AUC between treatments D and B. No statistically significant differences were detected in the T_{max} and T₂ of indinavir when given 1 hr before ddl.

Safety/Adverse Events:

There were no significant safety issues with this study. No subjects withdrew from the study because of adverse events (AE's), and no serious adverse events were reported. There were a total of 27 AE's reported, 8 at pre-study and the remaining 19 during the study. All AE's were characterized as being mild to moderate in severity. It appeared that the simultaneous administration of ddl and indinavir (treatment C) was associated with a higher number of AE's (9), as compared to treatments A (2), B (4), and D (4).

Summary/Conclusions:

The potential for pharmacokinetic interaction between ddl (VIDEX® 100 mg chewable/dispersible tablets) and indinavir (CRIXIVAN® 400 mg capsules) was assessed in healthy subjects following single therapeutic doses of 200 mg ddl and 800 mg indinavir.

When co-administered with indinavir there was a minor reduction observed in the mean ddl C_{max} and AUC estimates of ~8% and ~6%, respectively. The 90% CI and p values (i.e., for the pairwise comparisons) for C_{max} and AUC indicated that there was no significant effect of indinavir on the systemic availability of ddl. **When given 1 hr after indinavir**, the mean C_{max}

and AUC of **ddl** were reduced ~13% and ~17%, respectively. The lower bounds of the 90% CI for both C_{max} (i.e., 0.72) and AUC (i.e., 0.73) fell outside of the protocol specified criteria of (0.75, 1.33) to show lack of an interaction. The p value for the pairwise comparison of C_{max} was non-significant ($p = 0.21$), but was significant for AUC ($p = 0.01$).

*In light of the modest reductions in **ddl** C_{max} (~13%) and AUC (~17%), the relatively high degree of overlap observed in the individual C_{max} and AUC values between treatments **D** and **A**, and the lack of an interaction when **ddl** and indinavir were administered simultaneously, the changes in the systemic availability of **ddl** when given 1 hr after indinavir are most likely to be of little clinical importance.*

When co-administered with **ddl**, there was a substantial reduction in the mean indinavir C_{max} and AUC of ~82% and ~84%, respectively. The 90% CI and p values (i.e., for the pairwise comparisons) for C_{max} and AUC indicated that there was a significant effect of **ddl** on the systemic availability of indinavir. **When given 1 hr before **ddl****, the mean C_{max} and AUC of indinavir were reduced only ~4% and ~11%, respectively. However, the lower bounds of the 90% CI for both C_{max} (i.e., 0.70) and AUC (i.e., 0.68) fell outside of the protocol specified criteria of (0.75, 1.33) to show lack of an interaction. The p values for the pairwise comparisons of C_{max} and AUC were non-significant ($p = 0.81$ and 0.46, respectively).

*Although the 90% CI suggested an interaction for treatment **D** compared to **B**, the magnitude of the reductions in indinavir C_{max} (~4%) and AUC (~11%) were minor. In addition, there was a relatively high degree of overlap in the individual C_{max} and AUC values between treatments **D** and **B**. Thus, the small changes observed in the systemic availability of indinavir when given 1 hr before **ddl** are most likely to be of little clinical importance.*

Overall, the results suggested that **ddl** should not be co-administered with indinavir, but rather, if **ddl** and indinavir are to be used as combination therapy in HIV infected patients, dosing should be separated by at least 1 hour. There appeared to be no significant safety issues associated with the co-administration of **ddl** and indinavir. **The sponsor recommended that indinavir be given 1 hour prior to dosing with **ddl**. The approved labeling for indinavir sulfate capsules (CRIXIVAN®; PDR 1998, p 1625-1628, label issued March 1997) is also consistent with this recommendation, i.e., the CRIXIVAN® label states that if indinavir and **ddl** are given concomitantly, they should be administered at least 1 hour apart on an empty stomach.**

The reviewer agrees with the sponsor's study results and conclusions.

2. Protocol AI455-054: A Pilot Study of Safety and Antiviral Activity of the Combination of Stavudine (d4T), Nelfinavir (AG1343), and Didanosine (ddl) in HIV-Infected Patients

Objective:

A sub-study to Protocol AI455-054 was conducted to evaluate the effects of co-administered didanosine (ddl) buffered tablet formulation on the pharmacokinetics (PK) of oral nelfinavir.

Formulations/Treatments:

Nelfinavir Mesylate Tablets (VIRACEPT®) – 250 mg

Didanosine Chewable/Dispersible Tablets (VIDEX®) – 100 mg

Patients for PK Study:

10 HIV-infected males, mean age 36 yr. (range 29-48 yr.), mean weight 81 kg (range 62-116 kg). None of the patients received any previous treatment with stavudine, ddl, or protease inhibitors.

PK Study Design and Methods:

Non-randomized, open label, single-arm, pilot study designed to evaluate the safety and efficacy of the triple combination of oral stavudine (40 mg bid) + nelfinavir (750 mg tid) + ddl (200 mg bid) for 12 weeks in a total of 20 HIV infected patients who were treatment naïve. Of these 20 patients, the effects of co-administered ddl on the pharmacokinetics of nelfinavir was evaluated in a subset of 10 patients, the demographic characteristics of whom are described above. On day -1 of the PK study, these 10 patients received a single oral 750 mg dose of nelfinavir (3 x 250 mg tablets) with a light meal, as recommended in the approved labeling. The light meal consisted of orange juice (200 mL), 2% milk (150 mL), cereal (50 g), 2 slices of toast with low-fat spread (20 g) and jam (20 g). On day 1 of the PK study, the same 10 patients received a single 200 mg dose of ddl buffered tablets (2 x 100 mg chewable tablets) on an empty stomach (as per the approved labeling), followed at 1 hr later by a single 750 mg dose of nelfinavir with the light meal.

Plasma samples were obtained for determination of nelfinavir concentrations from 0 (predose) to 8 hrs postdose on PK study days -1 and 1. Predose samples were also obtained for nelfinavir C_{min} determinations on days 14 and 28 (i.e., weeks 1 and 2, respectively).

Analytical Methods:

Nelfinavir concentrations in plasma were determined using an HPLC-UV method validated over a linear dynamic range from: _____ (LLOQ _____)

The validation and performance of the assay was found to be acceptable.

Data Analysis:

Nelfinavir PK parameters were determined by standard noncompartmental methods. Statistical analyses were performed using a two-way ANOVA. The 90% confidence intervals (CI) were constructed on the log-transformed C_{max} and AUC(0-8) [also called AUC(tau)] data, i.e., the day 1/day -1 ratios of treatment means. The untransformed T_{max} data were analyzed based on the Wilcoxon signed rank test. Significance was assessed at the _____ level and all treatment comparisons were two-sided.

Results:

The PK parameters for nelfinavir were determined in all 10 patients. The mean nelfinavir plasma concentration-time profiles are illustrated in Figure 1 for day -1 (nelfinavir alone) and day 1 (nelfinavir 1 hr after ddl). This plot suggested that mean concentrations of nelfinavir were similar between treatment days. The individual and mean PK data are summarized in Table 1 and the statistical results are summarized below.

	Geometric Means			Ratio of Means		
	N	Day -1: Nelfinavir Alone	Day 1: ddl + Nelfinavir	2-sided p value	Point Estimate	90% Confidence Interval
Cmax (mcg/mL)	10	2.94	3.17	0.22	1.08	(0.97, 1.20)
AUC(0-8) (mcg.hr/mL)	10	13.72	15.77	0.047	1.15	(1.03, 1.28)
Tmax (hr)	10	4* (3, 5)	5* (3, 5)	0.22	NC**	NC**

*Median values (min, max)

**NC = not calculated

The results showed increases of 8% and 15% in the mean Cmax and AUC(0-8) estimates, respectively, when ddl was given 1 hr before nelfinavir. For Cmax, the increase was not statistically significant. For AUC, the increase was marginally significant (p = 0.047) and the 90% CI barely excluded 1.0 (i.e., 1.03, 1.28). The difference in Tmax was non-significant between day 1 and day -1.

Summary/Conclusions:

The effects of oral administration of ddl 200 mg (as 2 x 100 mg chewable buffered tablets) on the systemic availability of oral nelfinavir 750 mg (3 x 250 mg tablets) was evaluated in 10 HIV infected patients who were treatment naïve.

When nelfinavir was given with a light meal (as recommended in the approved labeling) at 1 hr after the administration of ddl, there was no substantial effect of ddl on the Cmax (8% increase), AUC (15% increase), or Tmax of nelfinavir. These results suggested that nelfinavir can be administered 1 hour after administration of ddl. **The sponsor recommended that nelfinavir be administered 1 hour after the administration of ddl during combination therapy with these two drugs. The approved labeling for nelfinavir mesylate tablets and oral powder (VIRACEPT®; PDR 1998, p 476-480, label issued July, 1997) is also consistent with this recommendation, i.e., the VIRACEPT® label recommends that ddl be administered on an empty stomach, therefore, nelfinavir should be given with food (light meal) at 1 hour after or more than 2 hours before ddl.**

The reviewer agrees with the sponsor's study results and conclusions.

3. Didanosine Interaction With Delavirdine

Evidence to support the proposed wording in the revised ddl labeling for this interaction was provided via inclusion of the approved package insert for Delavirdine Mesylate Tablets (RESCRIPTOR®; *Pharmacia-Upjohn Full Prescribing Information, label revised August, 1997*) and an article from the scientific literature (Morse GD, Fischl MA, et.al. Single Dose Pharmacokinetics of Delavirdine Mesylate and Didanosine in Patients with HIV Infection. *Antimicrobial Agents and Chemotherapy, 1997; 41(1): 169-174*).

The approved delavirdine labeling indicates that in 9 HIV-1 infected patients, simultaneous administration of ddl (125 mg bid as buffered powder or 200 mg bid as buffered tablets) with delavirdine (400 mg tablets tid) for 2 weeks (i.e., at steady-state) resulted in a decrease in AUC of both ddl and delavirdine of ~20% as compared to when the two drugs were given at least 1 hour apart. **Thus, the approved delavirdine label recommends that administration of ddl and delavirdine should be separated by at least 1 hour.**

The literature paper was a single dose, three-way crossover study of ddl (200 mg buffered tablets) and delavirdine (400 mg) in 12 HIV-1 infected patients. The PK of each drug was evaluated when ddl and delavirdine were each given alone (treatments A and B, respectively), concurrently (treatment C), and when ddl was given 1 hour after delavirdine (treatment D). Similar results were obtained with this study as that in the steady-state study cited above from the approved delavirdine label. However, the magnitude of the reductions in delavirdine C_{max} and AUC were greater when co-administered with ddl after single doses of each drug (i.e., C vs. B). The mean C_{max} and AUC of delavirdine were decreased ~50% and ~40%, respectively when co-administered with ddl. Likewise, the mean C_{max} and AUC of ddl were also reduced ~30% and ~20%, respectively, when co-administered with delavirdine (i.e., C vs. A). These reductions in delavirdine and ddl PK parameters were found to be statistically significant (i.e., p values ≤ 0.05). The mean T_{max} of either drug was not significantly effected with concurrent administration. When given 1 hour apart, the mean C_{max}, AUC, and T_{max} estimates of either ddl or delavirdine were not significantly altered. These results suggested that ddl and delavirdine should be administered at least 1 hour apart to avoid a significant reduction in the systemic availability of both drugs. **The sponsor's recommendation was that delavirdine be administered 1 hour prior to ddl.**

The reviewer agrees with the sponsor's use of the results provided through the approved delavirdine labeling and the literature to support the ddl label recommendation that delavirdine be administered at least 1 hour prior to dosing with ddl.

4. Didanosine Interaction With Nevirapine

Evidence to support the proposed wording in the revised ddl labeling for this interaction was provided via inclusion of the approved package insert for Nevirapine Tablets (VIRAMUNE®; *Boehringer Ingelheim Pharmaceuticals Full Prescribing Information, 1996*). The nevirapine label cites two studies that have demonstrated the lack of a pharmacokinetic interaction with ddl. In one study, the steady-state exposure (i.e., AUC₀₋₉) to nevirapine in 6 HIV infected patients was not significantly altered by co-administration of ddl buffered tablets. In the second study, which was a crossover study in 18 HIV-1 infected patients, nevirapine (400 mg/day) had no significant effect on the steady-state pharmacokinetics of ddl (200-300 mg/day). **The approved labeling for nevirapine indicates that nevirapine may be administered with or without food, antacids, and ddl, and that no dosage adjustments are required when nevirapine is taken in combination with ddl.**

The reviewer agrees with the sponsor's use of the results available through the approved nevirapine labeling to support the ddl label indicating that multiple dose

studies have shown no significant pharmacokinetic interaction between ddl and nevirapine.

5. Didanosine Interaction With Ritonavir

Evidence to support the proposed wording in the revised ddl labeling for this interaction was through inspection of the approved package insert for Ritonavir Capsules and Oral Solution (NORVIR®; PDR 1998, p 459-464; label revised March, 1997). In addition, in the current submission for the revised ddl label the sponsor provided an abstract from the literature, the results of which apparently were the same as those cited in the approved ritonavir label (Cato A, Qian J, Carothers L, et.al. Evaluation of the Pharmacokinetic Interaction Between Ritonavir and Didanosine. 97th Annual Meeting of the Society for Clinical Pharmacology & Therapeutics, Walt Disney World, FL, 1996; Abstract PI-59). The study was a multiple dose, crossover trial of ritonavir (600 mg q12hr) and ddl (200 mg q12hr), given separately and concurrently to 12 HIV-positive male subjects for 4 days. The results showed no significant effect of ddl co-administration on ritonavir Cmax and AUC (i.e., ≤ 6% increases with ddl). However, the mean Cmax and AUC of ddl were reduced by an average (95% CI) of 16% (5, 26%) and 13% (0, 23%), respectively, when co-administered with ritonavir. **The authors of this abstract concluded that although the systemic availability of ddl was reduced by ritonavir, the magnitude of the reduction was most likely to be of minor clinical importance. Thus, a dosage adjustment for either ddl or ritonavir was not warranted when the two drugs are co-administered.**

In the approved ritonavir label, under Drug Interactions, it is recommended that although ddl may be administered without dosage adjustment to patients taking ritonavir, dosing with the two drugs should be separated by 2.5 hours to avoid formulation incompatibility**. The reviewer

*****In the ritonavir-ddl interaction study submitted with NDA's 20659 and 20680 for NORVIR®, ritonavir was only administered 2.5 hours after ddl in the combination regimen.***