CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-183

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-183
Submission Dates: 01/17/2000, 07/14/2000, 10/27/2000
Product: VIDEX® EC (didanosine)
Formulation: Enteric Coated Capsules
Strengths: 125/200/250/400 mg ddI/capsule
Applicant: Bristol-Myers Squibb Company

Reviewer: Robert O. Kumi, Ph.D.

I. EXECUTIVE SUMMARY

Didanosine is a nucleoside reverse transcriptase inhibitor that is indicated for the treatment of HIV in combination with other antiretroviral agents. Didanosine is given as buffered formulations in twice daily (BID) or once daily (QD) regimens. The buffer protects didanosine from degradation in the stomach. A new didanosine enteric-coated (EC) formulation, VIDEX EC, was developed for use in the QD regimen. Unlike the currently available didanosine powder and tablet formulations, the EC capsule formulation does not have buffers. Therefore, VIDEX EC is expected to eliminate undesirable drug-drug interactions that occur due to the presence of the buffer, and may improve tolerability.

The EC formulation is not bioequivalent to the currently marketed tablet formulation; therefore, bioequivalence can not be used as a basis of approval of VIDEX EC. Also, exposure-response information is not available for didanosine. Thus, clinical trials were conducted in support of the VIDEX EC application. Doses used in the trials were 400 mg and 250 mg didanosine QD for patients $\geq$ 60 kg and < 60 kg, respectively. Clinical efficacy of didanosine following QD administration with either VIDEX EC or VIDEX tablets was comparable after 24 weeks of treatment. However, a concern exists with didanosine administered in a QD regimen, because the efficacy of QD didanosine in a combination regimen was inferior to a comparator regimen following 48 weeks of treatment, even though efficacy was comparable in both regimens after 24 weeks of treatment. These findings suggested that administration of didanosine once daily may not provide sufficient additive activity in the combination regimen to result in a high rate of durable antiviral response.

Due to the concerns with efficacy of the QD regimen, the didanosine label reinforces twice-daily administration as the recommended dosing frequency for didanosine, but the once-daily dosing option was retained for patients whose management may require QD management. The clinical division intends to approve VIDEX EC for treatment of HIV-1 infection in adults whose management requires once-daily administration.

II. QUESTIONS/ISSUES

1. Can the new enteric-coated didanosine formulation (VIDEX EC) be used in place of the marketed didanosine tablet in once daily didanosine containing regimens?

2. Are there any significant advantages presented by VIDEX EC that are absent with VIDEX tablets?

III. BACKGROUND

Didanosine (ddI) is a nucleoside reverse transcriptase inhibitor that is used for the treatment of HIV in combination with other antiretroviral agents. The approved dosage regimens of ddI are 200 mg BID and 400 mg QD, using ddI buffered formulations (VIDEX tablets). The use of ddI in a QD regimen was approved recently based on similar efficacy of a combination regimen including QD VIDEX tablets to a comparator combination regimen following 24 weeks of treatment. QD ddI regimens are considered a second line treatment option, because of observed inferiority of the QD regimen to the comparator treatment regimen following 48 weeks of treatment. Historical data indicate the efficacy of combination regimens including ddI BID was similar to comparator regimens following 48 weeks of treatment. The differences in efficacy between ddI dosed QD and ddI dosed BID, may be due to the short plasma half-life (2 hr) of ddI. When administered QD, there may be a significant portion of the day with very little ddI present in plasma. The applicant postulates that ddI QD should be effective because the active triphosphate form of ddI has a long intracellular half-life.

The enteric-coated ddI formulation (VIDEX EC) was developed for use in the QD regimen. VIDEX EC does not contain a buffer; therefore, pharmacokinetic drug-drug interactions between ddI and coadministered drugs due to the presence of buffers are eliminated. The clinical efficacy studies that were conducted by the applicant to support approval of VIDEX EC are:

• Study AI454-152 (n= 510)	**400 mg ddI QD** (Videx EC) + d4T (Zerit) + NFV (Viracept)	vs.	ZDV+3TC (Combivir) + NFV (Viracept)
• Study AI454-158 (n= 138)	**400 mg ddI QD** (Videx EC) + d4T (Zerit) + NFV (Viracept)	vs.	**400 mg ddI QD** (Videx tablet) + d4T (Zerit) + NFV (Viracept)
• Study AI454-148* (n= 756)	**400 mg ddI QD** (Videx tablet) + d4T (Zerit) + NFV (Viracept)	vs.	ZDV + 3TC + NFV (Viracept)

* AI454-148 was conducted for approval of QD dosing with VIDEX tablets, not VIDEX EC
Abbreviations used for study drugs are, ddI- didanosine , d4T- stavudine, 3TC- lamivudine , ZDV- zidovudine, and NLF- nelfinavir mesylate.

Bioequivalence, drug interaction, food effect, and dissolution studies were conducted with the EC formulation and were reviewed. The application includes articles from the literature, supporting studies, and analyses that demonstrate relationships between pharmacokinetics (PK) and pharmacodynamics of NRTIs. These data will not be reviewed or addressed in detail in this review, because they have been previously reviewed by OCPB.

Approval Requirements for VIDEX EC: FDA and BMS Discussions

Prior to submission of this NDA, the applicant and Agency had numerous discussions and meetings regarding the requirements for developing and registering VIDEX EC. Two of these discussions played a significant role in the application process, therefore the proceedings of these two meetings are summarized in some detail in a later section (See Highlights from FDA-BMS Discussions, Page 12) . The most significant meetings between the FDA and BMS were held in December 1998 and in September 1999. The conclusion reached was that a clinical efficacy trial with the VIDEX EC formulation would be required to establish efficacy of the EC formulation. This demonstration of efficacy was required because the new ddI EC formulation was not bioequivalent to VIDEX tablet and exposure-response relationships for ddI are not established.

The mean AUCs for the two formulations were equivalent, but the mean C_{max} for VIDEX EC was 40 % less than the mean C_{max} for VIDEX tablets. The applicant claimed that the lack of BE between the two formulations, due to rate of absorption, would not necessarily limit the efficacy of VIDEX EC. The applicant's reason for this claim is based on the following hypothesis:

"Maintaining the same extent of exposure (same AUC) is more important than changes in rate of absorption (different C_{max} and T_{max}), since this class of drugs must undergo intracellular metabolism to yield active metabolites"

The applicant presented findings from the literature and pharmacokinetic analyses to support their hypothesis (See Highlights from FDA-BMS Discussions, Page 12)

IV. SYNOPSIS

Can the new enteric-coated didanosine formulation (VIDEX EC) be used in place of the marketed didanosine tablet in once-daily didanosine containing regimens?

The pharmacokinetic evidence (bioequivalence, exposure-response) provided was insufficient to conclude that VIDEX EC can be used in place of VIDEX tablets. Thus, clinical safety and efficacy data must be used to determine whether VIDEX EC can be used in place of VIDEX tablets.

A. Bioequivalence

In healthy adults and HIV-infected subjects, VIDEX EC capsules were not bioequivalent to the VIDEX tablets. The pharmacokinetics of didanosine in healthy volunteers and HIV-infected subjects were determined following administration of 400 mg didanosine, as VIDEX EC capsules or VIDEX tablets.

Table 1: Geometric Mean Ratio, GMR (EC CAP: Tablets) and 90 % Confidence Intervals (CI) of Log Transformed AUC and C_{max} in HIV-infected patients

Exposure Measure	GMR (Capsule:Tablet)	
	Point Estimate	90 % CI
C_{max} (ng/mL)	0.635	0.557 - 0.723
AUC_{inf} (ng h/mL)	0.951	0.855 - 1.058

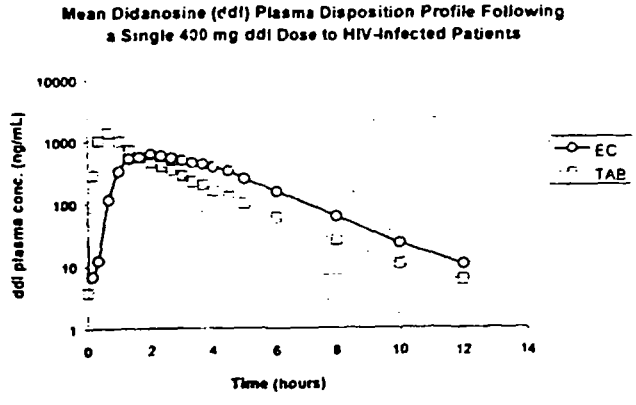

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Table II: Geometric Mean Ratio, GMR (EC capsule: Tablets) and 90 % Confidence Intervals (CI) of Log Transformed AUC and C_{max} in Healthy Volunteers

Exposure Measure	GMR (Capsule:Tablet)	
	Point Estimate	90 % CI
C_{max} (ng/mL)	0.579	0.524 - 0.639
AUC_{inf} (ng h/mL)	1.020	0.949 - 1.097

In both populations, the EC formulation (test) had comparable AUC to the tablets (reference), but had significantly lower C_{max} (~40 % less) than the tablets. These results indicated that the VIDEX EC capsules were not bioequivalent to VIDEX tablets. Thus exposure-response information or clinical efficacy data would be required for approval of VIDEX EC.

Didanosine T_{max} was prolonged when administered as the EC formulation (2.0 hr) relative to administration as tablet (0.67 hr), but didanosine $t_{1/2}$ were comparable for the two formulations. C_{max} and T_{max} were highly variable for EC formulation, as evidenced by the fairly wide range of T_{max} (1 –6 hr) and high CV in C_{max} (45 – 54 %). The source of this variability may be the inter-individual variability in GI motility and difference in absorption rates.

B. Exposure-Response Relationships

The applicant did not conduct exposure-response studies for purposes of this submission. However, the applicant indicates that AUC is a more important exposure measure than C_{max} in determining ddI efficacy, based on results from clinical efficacy studies (Study 148) and reports in the literature (See Highlights from FDA-BMS Discussions Background, Page 12). The FDA concluded that the applicant has not provided adequate exposure-response data.

C. Efficacy data supporting approval of once-daily VIDEX EC (Medical Officer Review)

Study 158

Study 158 is the only clinical efficacy study that directly compares the efficacy of VIDEX EC to VIDEX tablets in once-daily combination regimens. Due to the small number of patients who completed the study, the study results could not be interpreted.

Study 152

Based on an interim analysis, the ddI QD EC regimen is likely to have inferior activity to a comparable regimen. Study 152 was designed to support a marketing claim of equivalence. Approximately 65 % of the patients have completed 48 weeks of treatment. This study lends credence to the hypothesis that the QD regimen for ddI may not be optimal for treatment of HIV.

Study 148

Once-daily administration of ddI was approved based on the results of a 24-week interim analysis of study AI454-148. This study compared the combination of once-daily didanosine (ddI tablet)+stavudine (d4T)+nelfinavir (NLF) to zidovudine (ZDV)+lamivudine (3TC)+NLF in 756 antiretroviral naïve HIV-infected adult patients. The 24-week analysis demonstrated that the two regimens produced similar antiviral and immunologic activity. However, the 48-week final analysis demonstrated that the regimen containing once-daily ddI tablet produced inferior antiviral activity compared to the ZDV+3TC+NLF regimen. Results from Study AI454-148 raise concerns about the utility of QD dosing as the preferred frequency for dosing ddI.

What are the possible pharmacokinetic explanations for lack of comparable efficacy between ddI BID and QD Regimens ?

Reasons for the long-term differences in efficacy between BID and QD ddI regimens are not clear, but may be related to the time ddI concentrations are maintained over a threshold in a 24 hour period. The different plasma concentration-time profiles of the two regimens clearly show that the BID regimen maintains ddI levels over the EC_{50} for a longer period of time than the QD regimens (Table III).

Table III: Duration of time and associated AUC for the interval over which a ddI treatment has ddI levels above a concentration threshold (EC)

	EC_{50} (113 ng/mL)		EC_{90} (566 ng/mL)	
Treatment	Interval (h)	AUC (ng hr/mL)	Interval (h)	AUC (ng hr/mL)
200 mg TAB BID	8.126	1842	1.528	244
400 mg TAB QD	5.154	2577	1.853	1240
400 mg EC QD	6.92	2648	3.026	633

It is possible that with long-term treatment, the activity of ddI in regimens with suboptimal concentrations may decrease. It is noted that the clinical significance of maintaining drug levels above an EC value is unknown. AUCs for the QD regimens are higher than those in the BID regimen over the defined interval: however, the significance of this finding is unknown.

Generally, for NRTIs such as ddI, the efficacy is assumed to be related to the intracellular concentration of the active triphosphate (TP), which has a longer half-life than the parent. However, the relationship between ddI concentrations and its putative active TP metabolite is unknown (See Highlights from FDA-BMS discussions, Page 12). No robust assays are available to measure ddI TP, therefore these hypotheses can not be tested or proved. With the present data, it is not possible to assess the significance of the different ddI exposure measures on efficacy. Blood samples were not collected during the clinical efficacy analyses and no exposure response relationships were determined.

Are there any significant advantages presented by VIDEX EC that are absent with VIDEX tablets?

Drug-drug Interactions

Pharmacokinetic drug-interactions between ddI, administered as VIDEX EC, and ciprofloxacin (CPX), ketoconazole (KTZ) and indinavir (IDV) were not clinically significant. These findings indicate that VIDEX EC and CPX, KTZ or IDV can be coadministered during therapy. Previous studies indicated that coadministration of ddI, as buffered formulations, with CPX, KTZ, or IDV, decreased the absorption and bioavailability of CPX, KTZ and IDV. The interaction between ddI and these coadministered drugs was due to the presence of buffer. Because Videx EC capsules do not contain buffer, no drug interaction was expected and none was observed.

A. In healthy subjects, coadministration of single doses of the fluoroquinolone antibiotic CPX (750 mg) and VIDEX EC (400 mg) resulted in 9 % and 8 % decreases (based on point estimates) in CPX AUC and C_{max}, respectively. These small changes in AUC and C_{max} are not clinically significant.

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Table IV : Geometric Mean Ratio (GMR) and Ninety Percent (90 %) Confidence Intervals (CI) of Log Transformed Ciprofloxacin AUC and C_{max}

Exposure Measure	GMR (CPX + ddI : CPX)	
	Point Estimate	90 % CI
C_{max} (ng/mL)	0.919	0.786 - 1.073
AUC_{inf} (ng h/mL)	0.909	0.763 - 1.083

B. In healthy subjects, coadministration of single dose of the antiretroviral agent IDV (800 mg) and VIDEX EC (400 mg) resulted in < 5 % decreases (based on point estimates) in IDV AUC and C_{max}. These changes in AUC and C_{max} are not clinically significant.

Table V : Geometric Mean Ratio (GMR) and Ninety Percent (90 %) Confidence Intervals (CI) of Log Transformed Indinavir AUC and C_{max}

Exposure Measure	GMR (IDV +ddI : IDV)	
	Point Estimate	90 % CI
C_{max} (ng/mL)	0.987	0.914 - 1.064
AUC_{inf} (ng h/mL)	0.960	0.905 - 1.017

C. In healthy subjects, coadministration of single doses of the antifungal agent, KTZ (200 mg) and VIDEX EC (400 mg) resulted in < 5 % decreases (based on point estimates) in KTZ AUC and C_{max}. These changes in AUC and C_{max} are not clinically significant.

Table VI: Geometric Mean Ratio (KTZ + ddI/KTZ alone) and 90 % Confidence Intervals (CI) of Log Transformed Ketoconazole AUC and C_{max}

Exposure Measure	GMR (KTZ + ddI : KTZ)	
	Point Estimate	90 % CI
C_{max} (µg/mL)	0.986	0.857 - 1.135
AUC_{inf} (µg h/mL)	0.969	0.852 - 1.102

What is the effect of food on absorption of ddI, administered as VIDEX EC?
A significant food effect was observed when the EC formulation was administered with a high fat meal. A single 400 mg dose of ddI, as VIDEX EC, was administered to fasted and fed subjects. The AUC and C_{max} in the fed state were approximately 50 and 20 % lower than in the fasted state. Median T_{max} and T_{lag} were increased by approximately 3 and 1.5 hours, respectively, in the presence of the high fat meal.

Table VII: Geometric Mean Ratio (GMR) Ninety Percent (90 %) Confidence Intervals (CI) of Log Transformed Didanosine AUC and C_{max}

Exposure Measure	GMR (Fed:Fasted)	
	Point Estimate	90 % CI
C_{max} (ng/mL)	0.543	0.457 - 0.644
AUC_{inf} (ng h/mL)	0.813	0.714 - 0.927

Overall, these findings indicate that ddI absorption is reduced and delayed in the presence of a high fat meal. Hence, VIDEX EC should not be administered with food. It is noteworthy that a food effect of a similar magnitude was observed with the VIDEX tablets.

Is the Manufacturing Site Change — BMS Comparison) Supported by Bioequivalence?
VIDEX EC beads coated at the — manufacturing site were comparable to those coated at the Evansville manufacturing site. Capsules containing beads coated at

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[redacted] and Bristol Myers-Squibb (Evansville, IN) were bioequivalent. All beads were manufactured at the Evansville site. [redacted] at either [redacted] or BMS.

Table VIII: Geometric Mean Ratio (GMR) Ninety Percent (90 %) Confidence Intervals (CI) of Log Transformed Didanosine AUC and C_{max}

Exposure Measure*	GMR (EC Glatt:BMS)	
	Point Estimate	90 % CI
C_{max} (ng/mL)	1.089	0.952 – 1.245
AUC_{inf} (ng h/mL)	1.073	0.994 – 1.157

* n = 43; one subject not included in analysis, because subject did not have any quantifiable levels for both treatments. Finding suggested that the subject did not follow the treatment protocol.

Are the pharmacokinetics of ddI in HIV infected patients comparable to those in Healthy subjects ?

Based on a cross-study comparison, the pharmacokinetics of didanosine in healthy individuals appeared to be significantly different from that in HIV-infected individuals. Mean ddI exposure tended to be higher in healthy subjects than in HIV-infected subjects, as shown in Table IX.

Table IX: Arithmetic Mean Pharmacokinetic Parameters of ddI in Healthy Volunteers and HIV-infected Subjects (Cross Study Comparison of ddI EC Formulations at 400 mg Dose)

Exposure Measure	Tablet Arithmetic Means		Capsule Arithmetic Means	
	Study #		Study #	
	151*	157^	151*	157^
C_{max} (ng/mL)	2321 ± 923	1475 ± 673	1427 ± 774	933 ± 434
AUC_{inf} (ng h/mL)	3489 ±1082	2516 ± 847	3587 ± 1296	2432 ± 919

* Study conducted in Healthy Volunteers
^ Study conducted in HIV-infected Subjects

How will VIDEX EC be used in Special Populations ?

A. Pediatric Development

[redacted]

B. Renal Impairment

VIDEX EC has not been evaluated in patients with impaired renal function; however, data are available for these patients following administration of buffered ddI formulations. Based on these data, recommendations were made for administration of VIDEX EC. Due to available VIDEX EC capsule strengths, the dosing recommendations for some patient groups will be different for the EC formulation compared to the tablet. The simulations conducted using PK data collected from subjects with renal impairment who received a buffered ddI formulation indicate the proposed dosing is acceptable.

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Table X: Proposed Recommended Dosing Regimens of Didanosine in Subjects with Normal or Impaired Renal Function

	Patient Body Weight					
	≥ 60 kg			< 60		
$CL_{creatinine}$ (mL/min)	Tablet	Solution*	Capsule	Tablet	Solution*	Capsule
≥ 60	400 QD or 200 BID	250 BID	400 QD	250 BID or 125 BID	167 BID	250 QD
30-59	200 QD or 100 BID	100 BID	200 QD	150 QD or 75 BID	100 BID	125 QD
10-29	150 QD	167 QD	125 QD	100 QD	100 QD	125 QD
< 10	100 QD	100 QD	125 QD	75 QD	100 QD	a

* Solution is obtained by dissolving Videx powder

a: not suitable with VIDEX EC. An alternative ddI formulation should be used

Dissolution

The proposed dissolution methodology and specification are acceptable. Due to the enteric coating, a two stage method in two media is required for VIDEX EC.

Methodology:

Apparatus: USP Apparatus 1 (Basket) at 100 rpm
Medium A: 1000 mL of 0.1 M HCl for 120 minutes
Medium B: 1000 mL phosphate buffer, pH 6.8
Assay: UV absorption

Specifications:

Medium A no more than 1 — dissolved
Medium B Q = — in 45 minutes

V. LABELING

VIDEX EC will have a separate label from the buffered didanosine formulations; however, information for VIDEX tablets will be incorporated in the VIDEX EC label. This cross-referencing is acceptable because the inherent pharmacokinetic properties of ddI are not expected to change based on administration of didanosine via this modified release product or buffered didanosine products. Specific areas of interest with respect to VIDEX EC that are different from buffered ddI formulations are present in the drug interaction and renal impairment sections.

Drug-Drug Interactions

In the drug interaction section, no significant interaction will be reported for ddI administered as VIDEX EC with indinavir, ciprofloxacin and ketoconazole. Additionally, ddI, administered as Videx EC can be administered simultaneously with other fluoroquinolone antibiotics undergoing chelation based reactions like ciprofloxacin. Itraconazole, which has similar pH characteristics as ketoconazole, may be coadminstered with VIDEX EC.

Recommended Dosage of VIDEX EC in Renal Impairment

Differences between the buffered formulations and VIDEX EC in dosing of patients with renal impairment are presented in Table X.

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Phase IV Commitment
The applicant will be asked to conduct clinical efficacy studies and pharmacokinetic studies using VIDEX EC capsules administered in a twice daily regimen.

VI. RECOMMENDATIONS

1) This submission has adequately addressed the requirements of the Office of Clinical Pharmacology and Biopharmacuetics. However, due to the lack of bioequivalence between VIDEX EC and VIDEX tablets and the lack of exposure-response data for didanosine, clinical efficacy studies with VIDEX EC were required.

2) *In vivo* bioavailability studies are not required for the four strengths (125, 200, 250 and 400 mg) of EC capsules, because the highest strengths were used in the clinical trials, all proposed capsule strengths are compositionally similar, and adequate dissolution data were provided for all to-be-marketed strengths.

/S/ 11/20/2000

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Concurrence:

/S/ 11/22/2000

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cc:
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/MO/Fleischer
/PM/Sillivan
HFD-880 /Kumi, R.
/TL/Reynolds
HFD-340 /Viswanathan

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VII. VIDEX EC FORMULATION

The applicant intends to market EC capsules as 125, 200, 250 and 400 mg didanosine/capsule strengths. Capsules of different strength are made from the same batch of EC beads. With the exception of the 125 mg strength capsule, all proposed VIDEX EC capsule strengths were administered during clinical trials. Dissolution data were provided for all strengths and are acceptable.

Table XI : Composition of VIDEX EC Capsules

Ingredients	125 mg	200 mg	250 mg	400 mg
	Amount in g/ capsule			
Uncoated Beads				
Didanosine	0.1250	0.2000	0.25000	0.40000
Sodium Starch Glycolate, NF				
Carboxymethylcellulose Sodium 12, NF				
Purified Water , USP or Water for Injection, USP [1]				
Film Coat[2]				
Methacrylic Acid Copolymer				
Diethyl Phthalate, NF				
Sodium Hydroxide, NF [3]				
Purified Water, USP or Water for Injection, USP[1]				
Talc Addition				
Talc, USP				
Net Capsule Weight (g)				
Encapsulation				
White, Opaque, Two Piece, Hard Gelatin Capsule, Size				

[1] Water is used f

[2] Quantities for 18 % w/w film coat

[3] Film coat suspension adjusted to pH 5 ± 0.1 using Sodium Hydroxide

[4] Actual fill weight adjusted based on associated potency of bulk beads

Table XII: EC Capsule Formulations used in Clinical Trials

Capsule Strength (mg)	Batch Number (DOM)	Batch Size	Study Number AI454-
200	M96038		136
250	8MBN156 (Jan-98)		152
	8MCN178 (Jan-98)		152, 158
	8MLN376 (Nov-98)		152
400	8MAN109 (Jan-98)		151, 152, 158, 153, 157, 161
	8MAN113 (Jan-98)		152, 159, 160
	8MAN112 (Jan-98)		164
	8MAN108 (Jan-98)		152,
	8MAN110 (Jan-98)		152

Dissolution data for all the EC capsule strengths are provided.

DOM- date of manufacture

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VIII. BIOANALYTICAL METHODS

[redacted]

IX. HIGHLIGHTS FROM FDA-BMS DISCUSSIONS

Discussions held between FDA and BMS in December 1998 and September 1999 covered similar topics. The key topics are summarized in the following section.

1. Comparison of Absorption Rate:

Applicant

In most BE studies, the rate of absorption is assessed by C_{max}; however, C_{max} depends on both rate and extent of absorption. Rate of absorption measures that are less dependent on the extent of absorption include partial AUCs and C_{max}/AUC. VIDEX EC had absorption rates that were comparable to VIDEX tablets for the 0-6 hour post dose interval using partial AUCs, but the absorption rates were unequal using the C_{max}/AUC ratio and for the 0-2 and 0-4 hour post dose intervals partial AUCs.

Agency

The conclusion from the comparison of the EC and tablet formulations is that there is a difference in the rate of absorption. These analyses do not address the relevance of the observed differences in rate of absorption.

2. Assumed Site of Action: Peripheral Compartment:

Applicant

A two-compartment model, comprising a central compartment and a peripheral compartment (the presumed site of action), was used to model ddI PK following administration of VIDEX EC and VIDEX tablets. Results from the analyses indicated that the C_{max} in the central compartment after VIDEX EC administration was 45 % lower than with VIDEX tablets; however, differences in the C_{max} of the peripheral compartment were < 13 %.

Agency

Analyses support the applicant's hypothesis, but do not provide sufficient evidence to conclude that the two formulations will provide similar efficacy. The results are not conclusive because the modeling approach was theoretical and not supported by clinical data.

3. Reduced C_{max} with other NRTIs: Role of intracellular concentrations of active triphosphate

Applicant

Intracellular concentrations of the active triphosphate forms of NRTIs are more dependent on systemic exposure (measured by AUC) to the parent compound than by a single peak value

(C_{max}). Hence the reduction in ddI C_{max} will not appreciably affect active triphosphate levels; subsequently, efficacy of a NRTI will not be diminished. Food-drug interaction with other approved NRTIs lead to significant decreases in rate of absorption and minimal changes in extent of absorption. Package inserts for these NRTIs indicate that the drugs may be taken without regard to meals, despite the observed food effects.

Agency
No counter argument was made by the Agency regarding the triphosphate levels. However, it is noted that [redacted] indicated that the relationship between plasma C_{max} and intracellular concentrations of the active triphosphate have not been established for ddI. The food effect argument was not considered acceptable because clinical studies for the NRTIs were conducted without regard for the timing of meals. Consequently, efficacy data are available for these drugs when C_{max} is decreased. No such efficacy or clinical data are available for ddI administered once daily with VIDEX EC (lower C_{max}).

4. Relevance of C_{max}: Clinical Data

Applicant
The applicant indicated that they have clinical data indicating that C_{max} is not a critical determinant of antiviral efficacy. Clinical data from AI454-143 and AI454-146 show 200 mg BID and 400 mg QD dosing of the tablet formulation result in similar HIV RNA suppression, although C_{max} is lower for the 200 mg BID regimen. Thus, C_{max} is not critical for antiviral efficacy.

Agency
The pharmacokinetic profiles of the two regimens are clearly different: BID regimen produces a lower C_{max} and has two peaks in the 24 hour period, whereas the QD regimen produces a higher C_{max} and has a single peak. However, the efficacy of a QD regimen with a lower C_{max}, as would be obtained with VIDEX EC, has not been demonstrated.

5. Requirements for filing NDA 21,183

Applicant
The applicant indicated that safety and efficacy of VIDEX EC was assured by PK data and clinical data from trials with VIDEX tablets and that the medical need for VIDEX EC warrants its approval.

Agency
Upper FDA management informed the Applicant that supporting clinical efficacy data would be required for filing of the NDA. The management indicated that clinical data from Study 158 would provide a suitable comparison of VIDEX EC activity, safety and efficacy relative to the currently approved formulation.

At the end of the discussions, the Agency concluded that the evidence supporting the applicant's hypothesis was not definitive, therefore a clinical efficacy trial would be required to approve VIDEX EC.