

May 15, 2002

NIH DAIDS, MD
 Some Medical Institute
 1234 Main Street
 Anytown, NJ 12345-1234

Dear Dr. DAIDS:

Your inquiry concerning VIDEX[®] EC (didanosine) Delayed-Release Capsules Enteric-Coated Beadlets was forwarded to my attention.

You requested information regarding the potential interaction between didanosine and Viread[™] (tenofovir disoproxil fumarate, Gilead Sciences, Inc.).

The pharmacokinetics of once daily (QD) VIDEX Chewable Buffered Tablets (TABS) 400 mg (250 mg QD if < 60 kg) or VIDEX[®] EC 400 mg QD (all subjects ≥ 60 kg) have been studied in healthy subjects when administered with tenofovir disoproxil fumarate (DF) 300 mg QD. The results of these studies are summarized in the table below.¹⁻³

Changes in pharmacokinetic parameters for didanosine in the presence of tenofovir DF 300 mg once daily*

Ddl Dosage Form	ddl Dose	N	% Change of ddl Pharmacokinetic Parameters (90% CI)	
			C _{max}	AUC
Buffered Tablet ^{1,2}	250 mg† or 400 mg (ddl 1 hr prior to TDF; both fasting state)	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
EC Capsule ³	400 mg‡ (ddl fasting 2 hrs before TDF with a light meal [§])	14	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
	400 mg ‡ (ddl and TDF together with a light meal [§])	14	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)

* ddl indicates didanosine; TDF indicates tenofovir DF; CI indicates confidence interval; C_{max} indicates peak drug concentration; AUC indicates area under the curve; ? indicates increase; EC indicates Enteric Coated.

† Patients less than 60 kg.

‡ All patients greater than or equal to 60 kg.

§ 373 kcal; 8.2 grams fat.

Co-administration of didanosine either as chewable tablets or enteric coated beadlets had no effect on the area under the curve (AUC) of tenofovir DF. However, use of VIDEX EC or VIDEX TABS with tenofovir DF in various fasting and fed states results in a mean increase in the didanosine AUC ranging from approximately 44% to 60%.¹⁻³ Based on the results of these studies, the currently recommended doses of VIDEX EC or VIDEX TABS used in tenofovir DF-containing regimens may result in higher plasma levels of didanosine, with the potential for increased dose-related toxicities, including but not limited to peripheral neuropathy and pancreatitis. As such, patients taking tenofovir DF and standard doses of VIDEX EC or VIDEX

TABS concomitantly should be monitored for didanosine-associated adverse events.⁴ Details of these studies are summarized in greater detail below. Bristol-Myers Squibb will be evaluating the issue further, including considerations of dosage adjustments for VIDEX EC when administered with tenofovir DF.

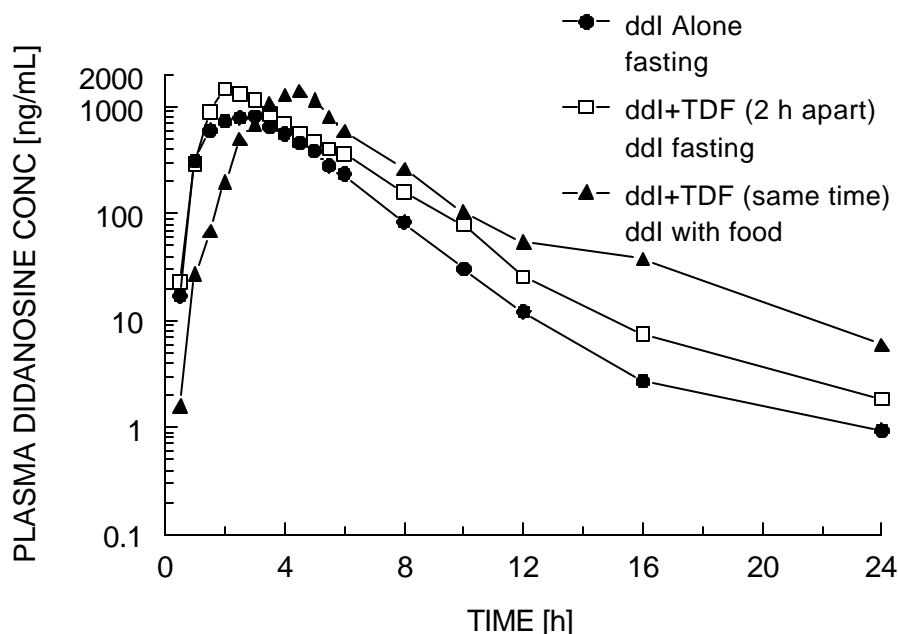
Detailed Background-Drug Interaction Data: Tenofovir DF with VIDEX TABS or VIDEX EC

Data from a Phase I pharmacokinetic (PK) study identified an increase in didanosine's (*chewable buffered tablet formulation*) C_{max} and area under the curve (AUC) by 28 % and 44%, respectively, when didanosine was administered one hour prior to tenofovir DF, both in the fasting state.^{1,2} The AUC of tenofovir DF remained unchanged in this fasting study. The package labeling for Viread™ contains this information and recommends in the Dosage and Administration section that "When administered with didanosine Viread™ should be administered 2 hours before or one hour after administration of didanosine."⁴

The package labeling for VIDEX TABS notes an approximate 55% decrease in the didanosine AUC when administered up to two hours after a meal. VIDEX TABS should be taken on an empty stomach, at least 30 minutes before or 2 hours after eating.⁵ The package labeling for VIDEX EC notes an approximate 19% decrease in the didanosine AUC when administered in the presence of food, leading to the recommendation that VIDEX EC should be taken on an empty stomach.⁶ Based on this initial Phase I study, it was hypothesized that the addition of food may have a counterbalancing effect on the AUC of didanosine if the two products are given concomitantly, and a PK study was designed to examine this possibility. The hypothesis did not hold true and, in fact, when VIDEX EC and tenofovir DF were administered together with food, the AUC of didanosine increased even more (~60%). The mean plasma concentration-time profiles of didanosine following administration of VIDEX EC with tenofovir DF in various fasting and fed states can be found in the figure provided below. As with the initial PK study, co-administration of VIDEX EC had no effect the AUC of tenofovir DF.

An analysis using pooled data sets from two 24-week, placebo-controlled, Phase II-III studies (GS-98-902 and GS-99-907), wherein 30% (n=197) of patients received didanosine as part of their antiretroviral background regimen, demonstrated no increased risk of didanosine-related adverse events or laboratory abnormalities (pancreatitis, neuropathy, paresthesia or elevations in serum amylase or lipase) when didanosine was administered in tenofovir DF-containing regimens.^{1,7} Despite these short-term safety data, patients should be monitored for long-term didanosine-associated adverse effects.

Mean plasma concentration-time profiles of didanosine following administration of VIDEX EC with tenofovir DF in various fasting and fed states.³



Summary

The pharmacokinetics of VIDEX TABS or VIDEX EC when administered with tenofovir DF 300 mg QD have been studied in healthy subjects.¹⁻³ Administration of VIDEX TABS 400 mg QD (250 mg QD if < 60 kg) one hour before tenofovir DF 300 mg QD results in an approximate 44% increase in didanosine exposure relative to the administration of VIDEX TABS 400 mg alone in the fasted state.

Administration of VIDEX EC 400 mg QD (all subjects \geq 60 kg) two hours before tenofovir DF 300 mg with a light meal, results in an approximate 48% increase in didanosine exposure relative to the administration of VIDEX EC alone in the fasted state. Co-administration of VIDEX EC 400 mg QD (all subjects \geq 60 kg) and tenofovir DF 300 mg with a light meal, results in an approximate 60% increase in didanosine exposure relative to the administration of VIDEX EC alone in the fasted state.

Bristol-Myers Squibb will be evaluating the issue further, including considerations of dosage adjustments for VIDEX EC when administered with tenofovir DF.

Reporting Adverse Reactions

If you have had a patient who experienced an adverse event following or coincident with the use of VIDEX EC or VIDEX TABS, please provide us with the information using the Adverse Event Reporting Form. You may order an Adverse Event Reporting Form by dialing 1-800-426-7644 and selecting document code number 2000, or you may contact a Bristol-Myers Squibb Global Pharmacovigilance and Labeling representative directly by dialing 1 (609) 818-3737 or via fax at 1 (609) 818-3804.

Current VIDEX EC Indication

VIDEX EC in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection.

VIDEX EC is available as 400 mg, 250 mg, 200 mg, and 125 mg capsules.

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VIDEX in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection.

This letter may contain information not found in the package insert(s). For full prescribing information and a complete list of Adverse Events, please consult the official package circular(s).

We appreciate your interest in Bristol-Myers Squibb Virology products. If we can be of further assistance, please do not hesitate to contact us.

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We appreciate your interest in Bristol-Myers Squibb Virology products. If we can be of further assistance, please do not hesitate to contact us.

Sincerely,

A handwritten signature in black ink that reads "Dan J. Halberstadt". The signature is written in a cursive, flowing style.

Dan J. Halberstadt, R.Ph.
Director, Virology Medical Services

Encl: VIDEX EC OPC, VIDEX OPC

REFERENCES

1. Flaherty JF, Kearney B, Wolf J, et al. Coadministration of tenofovir DF and didanosine: a pharmacokinetic and safety evaluation. Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, December 16-19, 2001 (Poster #1729).
2. Kearney BP, Flaherty JF, Sayre JR, et al. A multiple-dose randomized, crossover drug interaction study between tenofovir DF and lamivudine or didanosine. Presented at the 1st IAS Conference on HIV Pathogenesis and Treatment, Buenos Aires, Argentina, July 8-11, 2001 (Poster #337).
3. Data on file. Bristol-Myers Squibb Company, Princeton, NJ; 2002.
4. Viread™ (tenofovir disoproxil fumarate) Tablets Prescribing Information. Gilead Sciences, Inc., October 2001.
5. VIDEX (didanosine) chewable/dispersible buffered tablets, buffered powder for oral solution, pediatric powder for oral solution prescribing information. Bristol-Myers Squibb Company, Princeton, NJ; October 2001.
6. VIDEX EC (didanosine) Delayed-Release Capsules Enteric-Coated Beadlets Package Insert. Bristol-Myers Squibb Company, Princeton, NJ; January 2002.
7. Kearney BP, Flaherty JF, Wolf J, et al. Coadministration of tenofovir DF and didanosine: pharmacokinetic drug-drug interaction and safety evaluations (poster 172). Presented at the 8th European Conference on Clinical Aspects and Treatment of HIV Infection, Athens, Greece, October 28-31, 2001 (Poster #172).