

May 7, 2002

Dear HIV Treating Professional:

Bristol-Myers Squibb Virology would like to make HIV clinicians aware of new pharmacokinetic (PK) data concerning the co-administration of VIDEX® EC (didanosine) Delayed-Release Capsules Enteric Coated Beadlets and Viread™ (tenofovir disoproxil fumarate, Gilead Sciences, Inc.). A previous Gilead Study demonstrated an increase in didanosine exposure when VIDEX® Chewable Buffered Tablets (TABS) were administered with tenofovir disoproxil fumarate (DF).

In a recent study, conducted in partnership between BMS and Gilead Sciences, the pharmacokinetics of VIDEX EC were investigated when co-administered with tenofovir DF in two dosing approaches: 1) VIDEX EC administered *without* food two hours prior to administration of tenofovir DF *with* food and, 2) both drugs administered together *with* food. The results of this recent study showed that administration of once daily (QD) VIDEX EC 400 mg (all subjects ≥60 kg) two hours before tenofovir DF 300 mg with a light meal, resulted in an approximate 46% 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 ≥60 kg) and tenofovir DF 300 mg with a light meal, resulted in an approximate 60% increase in didanosine exposure relative to the administration of VIDEX EC alone in the fasted state. Summarized below are the results from both the initial and new PK studies.

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	↑49 (↑24 to ↑78)	↑46 (↑29 to ↑66)
	400 mg [†] (ddl and TDF together with a light meal [§])	14	↑64 (↑41 to ↑90)	↑60 (↑43 to ↑78)

* 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

Summary

- Administration of VIDEX[®] TABS (didanosine) 400 mg QD (250 mg QD if <60 kg) one hour before tenofovir DF 300 mg QD (both in the fasting state) 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 (didanosine) 400 mg QD (all subjects ≥60 kg) two hours before tenofovir DF 300 mg with a light meal, results in an approximate 46% 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 ≥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. Patients taking tenofovir DF and standard doses of VIDEX EC or VIDEX TABS concomitantly should continue to be monitored for didanosine-associated adverse events.

Fatal and non-fatal pancreatitis have occurred with didanosine. Didanosine should be suspended in suspected cases of pancreatitis and discontinued in confirmed cases. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fatal lactic acidosis has occurred in pregnant women receiving the combination of didanosine and stavudine. This combination should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.

Important toxicities include retinal changes, optic neuritis and peripheral neuropathy. The risk for pancreatitis, peripheral neuropathy and hepatotoxicity may be increased for patients treated with didanosine in combination with stavudine.

Frequent side effects reported in VIDEX EC-containing triple combination regimens are diarrhea (57%), peripheral neurologic symptoms (25%), nausea (24%), headache (22%), rash (14%), and vomiting (14%).

[‡] VIDEX EC 400 mg Capsule (≥60 kg) or 250 mg Capsule (<60 kg)

Frequent side effects reported in VIDEX-containing regimens are diarrhea (70%), nausea (53%), headache (46%), rash (30%), vomiting (30%) and neuropathy (26%).

All didanosine formulations should be administered on an empty stomach.^{5,6} VIDEX® EC should only be administered once daily.

We appreciate your interest in Bristol-Myers Squibb Virology products and hope you find this information helpful. If you would like to receive additional information on this issue, please contact our Medical Department at 1-800-426-7644.

Please see the enclosed VIDEX® EC (didanosine) and VIDEX® (didanosine) full prescribing information.

Sincerely,



Michael R. Stevens, PharmD
Vice President, Virology Medical Affairs

Encl: VIDEX EC P.I.
VIDEX P.I.

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® EC (didanosine) Delayed-Release Capsules Enteric-Coated Beadlets Package Insert. Bristol-Myers Squibb Company, Princeton, NJ; January 2002.
6. VIDEX® (didanosine) Chewable/Dispersible Buffered Tablets, Buffered Powder for Oral Solution, Pediatric Powder for Oral Solution Package Insert. Bristol-Myers Squibb Company, Princeton, NJ; October 2001.