

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-752

PHARMACOLOGY REVIEW

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

PHARMACOLOGIST'S REVIEW

NDA 21-752 (000)

Date Submitted: March 16, 2004

Date Assigned: March 18, 2004

Date Completed: March 22, 2004

Assigned Reviewer: Pritam Verma, Ph.D.

DAVDP

HFD-530

SPONSOR: Gilead Sciences, Inc.

333 Lakeside Drive

Foster City, CA 94404

INFORMATION TO SPONSOR: No

DRUG: VIREAD^R /EMTRIVATM (Tenofovir disoproxil fumarate/Emtricitabine) tablets

Each combination film coated tablet contains 300 mg of tenofovir disoproxil fumarate and 200 mg of emtricitabine.

Dosage and administration: The dose of VIREAD^R /EMTRIVATM is one tablet (containing 300 mg of tenofovir disoproxil fumarate and 200 mg of emtricitabine) once daily taken orally with or without food.

Patients with impaired renal function: The pharmacokinetics of VIREAD^R /EMTRIVATM are altered in patients with renal impairment. In patients with creatinine clearance <50 ml/min, the C_{max}, and AUCs of tenofovir and emtricitabine were increased. It is recommended that the dosing interval for the combination tablet be modified in patients with creatinine clearance <50 ml/kg. The combination tablet should not be used in patients with end-stage renal disease requiring dialysis.

PROPRIETARY NAME: To be determined.

1. VIREAD^R (Tenofovir disoproxil fumarate):

Dosage and administration: The recommended oral dose of VIREAD is 300 mg once daily taken orally, without regard to food.

Dose adjustment of renal impairment: Significantly increased drug exposures occurred when VIREAD was administered to patient with moderate to severe renal impairment. The dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 ml/min using the recommendations in Table 1.

**Table 1
Dosage adjustment for patients with altered creatinine clearance**

VIREAD	Creatinine clearance (ml/min) ¹			Hemodialysis patients
	>50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hr	Every 48 hr	Twice a week	Every 7 days or after a total of approx. 12 hr of dialysis ²

1. Calculated using ideal (lean) body weight.
2. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hr duration. VIREAD should be administered following completion of dialysis.

2. EMTRIVA™ (Emtricitabine)

Dosage and administration: For adults 18 years of age and older, the dose of EMTRIVA is 200 mg once daily taken with or without food.

Dose adjustment of renal impairment: Significantly increased drug exposures occurred when EMTRIVA was administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of EMTRIVA should be adjusted in patients with baseline creatinine clearance <50 ml/min using the recommendations in Table 2. The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

**Table 2
Dosage adjustment for patients with renal impairment**

EMTRIVA	Creatinine clearance (ml/min)			
	>50	30-49	15-29	<15
Recommended dose and dosing interval	200 mg every 24 hr	200 mg every 24 hr	200 mg every 72 hr	200 mg every 96 hr

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ROUTE OF ADMINISTRATION: Oral

RELATED INDs & NDAs: 21-356; 21-500; 53,971; 67,671; 52,849 and 44,487

INDICATION: Treatment of HIV infection.

INTRODUCTION AND DRUG HISTORY:

The sponsor is developing a fixed-dosage combination formulation consisting of VIREAD^R and EMTRIVATM in an oral tablet (trade name to be determined). The combination tablet has been shown to be effective antiretroviral therapy in the treatment of HIV patients. The steady state pharmacokinetics of VIREAD^R and EMTRIVATM were unaffected when these two drugs were administered together versus each agent dosed alone. The kidneys primarily excreted both drugs by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competitions for renal secretion were observed. The fixed-dosage tablet is to be administered as a once daily regimen that should offer a less complicated and more convenient dosing schedule for HIV-infected patients taking VIREAD^R and EMTRIVATM daily. Presently, the sponsor submitted a NDA for a fixed-dosage combination formulation consisting of VIREAD^R and EMTRIVATM tablet (trade name to be determined).

TOXICOLOGY, PHARMACLOGY AND PHARMACOKINETICS:

VIREAD^R and EMTRIVATM are approved drug products and have been reviewed in the division. For pharm/tox studies, please see the respective NDA and IND reviews.

LABEL:

The issue of label will be dealt with separately.

CONCLUSIONS:

There are no pharm/tox issues associated with this NDA.

Pritam S. Verma, Ph.D.
Reviewing Pharmacologist

Concurrences:

HFD-530/JFarrelly
HFD-530/PVerma

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