CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-154/S-040, S-041
20-155/S-030, S-031
20-156/S-031, S-032

MEDICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

DATE: September 16, 2002

TO: NDA 20-154/SLR-040 (VIDEX® Chewable/dispersible Tablets)
NDA 20-155/SLR-030 (VIDEX® Buffered Powder for Oral Solution)
NDA 20-156/SLR-031 (VIDEX® Pediatric Powder for Oral Solution)
NDA 21-183/SLR-005 (VIDEX® Enteric-Coated)

FROM: Russell Fleischer, PA-C, MPH
Senior Clinical Analyst, DAVDP

THROUGH: Steve Gitterman, MD
Medical Team Leader, DAVDP

RE: Labeling Supplement: Interaction between VIDEX® and ribavirin

- **Background**

Bristol-Myers Squibb submitted a supplement to add precautionary information about the potential risk of didanosine-related adverse events when VIDEX® and ribavirin (RBV) are co-administered.

- **Review**

In Vitro Data

VIDEX is a purine nucleoside analogue. RBV is an IMPD inhibitor. RBV acts to block the utilization of IMP for guanine nucleotide biosynthesis, thus yielding a higher level of IMP to act as a phosphate donor for the reaction first step in the phosphorylation of ddI. The increased IMP concentration results in a downstream increase in the concentrations of the pharmacologically active metabolite of didanosine, ddATP. This reaction has been hypothesized to enhance the *in vitro* antiviral activity of 2'3'-dideoxyinosine, and the potency and therapeutic index of ddI *in vivo*. This reaction could also increase the risk of didanosine-related toxicities such as pancreatitis, peripheral neuropathy, and/or hepatic steatosis/failure.

Clinical Data

Published reports of outcomes of patients treated with VIDEX and RBV were reviewed. In addition, the AERS database was reviewed to identify possible cases of suspected toxicities in patients treated with VIDEX and RBV.

A letter in Lancet described two of 15 co-infected patients who experienced multiorgan dysfunction and lactic acedemia shortly after initiating RBV+IFN treatment for HCV. The first patient was on ZDV+ddI+SQV for three years. He started anti-HCV therapy with interferon alfa (3MIU TIW) and RBV (1000 mg/day). One month later the ZDV changed to d4T due to anemia. Over the ensuing months, the patient experienced progressive increase in GGT, alkaline phoshastase, and amylase. The lactate level increased to 9.7 mmol/L and the lactate/pyruvate ratio was 74. The patient lost 5 kg. An abdominal CT showed ascities and pancreatitis. Diabetes mellitus developed requiring insulin. At that time, the IFN+RBV was stopped and ddI replaced by 3TC. Two months later the amylase and lipase were normal, GGT was 8x ULN, and the lactate/pyruvate ratio was normal. IFN monotherapy was restarted without recurrence of toxicity.

The second patient was on d4T+ddI+3TC for four years. He started anti-HCV therapy with interferon alfa+RBV. Over the next six months, he lost 6 kilograms, his GGT increased from 90IU to 450 IU, his lactate concentrations increased to 9.3 mmol/L, his amylase increased 4-fold, and glucose intolerance developed. The RBV stopped and within two months the lactate concentrations decreased to normal.

The authors found that compared to patients infected with HCV alone, co-infected patients experienced more abnormalities in lactate/pyruvate ratio. In the other 13 patients, severe anemia occurred within a few weeks of RBV therapy; the anemia resolved after switching ZDV for d4T.

They concluded that the two patients were stable for more than three years on HAART and developed multiorgan dysfunction within 4-6 months following introduction of anti-HCV therapy. They suggest that RBV in patients on long-term HAART can increase the risk of mitochondrial toxicity, and that clinicians should be aware of the possible side effects and monitor markers of mitochondrial toxicity carefully (see Lafeuillade A, Hittinger G, Chadapaud S, The Lancet, Vol 357, Jan 27, 2001).

A second series reported on three patients with mitochondrial toxicity. Patients were 30-50 years of age and had received HAART therapy for median 21 months (ddI+d4T+FAM in 2 and ddI+ABC+NLF in 1). After median of 6 months of interferon alfa+RBV, all patients experienced increases in lipase concentrations with moderate hyperlactetemia; one patient experienced clinical pancreatitis. All three initially presented with asthenia and weight loss. The authors concluded that prospective studies are needed to determine the risk of mitochondrial toxicity when VIDEX and RBV are co-administered (see Salmon-Ceron D, Chauvelot-Moachon L, Abad S, et al., The Lancet, Vol 357, June 2, 2001).

An Office of Drug Safety (ODS) consult was obtained. Dr. Boxwell reviewed the AERS database and identified 24 reports of pancreatitis, hepatic steatosis/failure, and lactic acidosis among patients treated with VIDEX and RBV.

- **Assessment**

The *in vitro* data demonstrating that RBV increases the levels of ddATP, in conjunction with clinical data suggesting the potential for increased didanosine-related toxicities, support the addition of precautionary language in the VIDEX labels.

- **Label Review**

The following revisions will be made to the VIDEX labels:

Under **PRECAUTIONS: Drug Interactions**,

Ribavirin. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered

[ ]

- **Recommended Regulatory Action**

This supplement should be approved.

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/s/

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