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

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

CSO Label Review

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

Date submitted: May 31, 2002 (20-154/ S-040, 20-155/ S-030, 20-156/ S-031)
July 11, 2002 (20-154/ S-041, 20-155/ S-031, 20-156/ S-032)

Date received: June 3, 2002 (20-154/ S-040, 20-155/ S-030, 20-156/ S-031)
July 12, 2002 (20-154/ S-041, 20-155/ S-031, 20-156/ S-032)

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway
Wallingford, CT 06492

Products: VIDEX® (didanosine) Buffered Tablets
VIDEX ® (didanosine) Buffered Powder for Oral Solution
VIDEX ® (didanosine) Pediatric Powder for Oral Solution

Materials Reviewed: BMS submissions dated July 25, 2002, August 30, 2002, and September 19, 2002; Medical Officers review dated September 16, 2002.

Background:

On May 31, 2002, Bristol-Myers Squibb (BMS) submitted a "Prior Approval Labeling Supplement", to add precautionary information about the potential risk of didanosine-related adverse events when VIDEX® and ribavirin are co-administered.

On July 11, 2002, Bristol-Myers Squibb (BMS) submitted a "Prior Approval Labeling Supplement", to provide revisions to the VIDEX® labeling as requested by the Division during the May 20, 2002 teleconference, to reflect the recent pharmacokinetic data that have been generated in a study conducted in partnership between Gilead Sciences and BMS, demonstrating that co-administration of tenofovir disoproxil fumarate and VIDEX® resulted in significant increases in didanosine exposures. This interaction is sufficiently significant to warrant inclusion in the VIDEX® labeling.

This review outlines only what was submitted to the NDAs mentioned above, and incorporates the labeling revisions made by both supplements.

Label Revisions to the package insert:

1. Deletion of the following words in the Special Populations, Pediatric Patients Section:

   -PRECAUTIONS, Pediatric Use and **Clinical Studies**.

and replacement with the following:

   INDICATIONS AND USAGE: Clinical Studies and **PRECAUTIONS: Pediatric Use**.

2. In Table 3 in the **CLINICAL PHARMACOLOGY** section, the added text for tenofovir appears underlined and highlighted, as shown below:

Table 3: Results of Drug Interaction Studies: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{MAX} Values

Drugs With Clinical Recommendations Regarding Coadministration *(see* **PRECAUTIONS: Drug Interactions***)*

Drug	Didanosine Dosage	n	AUC of Didanosine (95% CI)	C_{MAX} of Didanosine (95% CI)
[redacted]				

↑ indicates increase.
↓ indicates decrease.
↔ indicates no change, or mean increase or decrease of <10%.
[a] HIV-infected patients.
[b] 90% CI.
[c] Parallel-group design; entries are subjects receiving combination and control regimens, respectively.

[redacted]

NA Not available.

3. In Table 4 in the **CLINICAL PHARMACOLOGY** section, the added text for tenofovir appears underlined and highlighted, as shown below:

Table 4: Results of Drug Interaction Studies: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{MAX} Values

Drugs With Clinical Recommendations Regarding Coadministration *(see* **PRECAUTIONS: Drug Interactions***)*				
Drug	Didanosine Dosage	n	AUC of Coadministered Drug (95% CI)	C_{MAX} of Coadministered Drug (95% CI)
ciprofloxacin 750 mg q12h for 3 days, 2 h before didanosine	200 mg q12h for 3 days	8[a]	↓26%	↓16%
750 mg single dose	buffered placebo tablet	12	↓98%	↓93%
No Clinically Significant Interaction Observed				
Drug	Didanosine Dosage	n	AUC of Coadministered Drug (95% CI)	C_{MAX} of Coadministered Drug (95% CI)
stavudine, 40 mg q12h for 4 days	100 mg q12h for 4 days	10[a]	↔	↑17%
sulfamethoxazole, 1000 mg single dose	200 mg single dose	8[a]	↓11% (-17, -4%)	↓12% (-28, 8%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trimethoprim, 200 mg single dose	200 mg single dose	8[a]	↑10% (-9, 34%)	↓22% (-59, 49%)

↑ indicates increase.
↓ indicates decrease.
↔ indicates no change, or mean increase or decrease of <10%.
[a] HIV-infected patients.
[redacted]
NA Not available.

4. In the last sentence of the **Lactic Acidosis/Severe Hepatomegaly with Steatosis** subsection of the **WARNINGS** section, the following deleted text is reflected as a ~~strike-thru~~ and new text is underlined:

   Treatment with VIDEX should be suspended in any patient who develops clinical or laboratory findings suggestive of ~~lactic acidosis~~ symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5. Insertion of the words "**INDICATIONS AND USAGE**" in the PRECAUTIONS, Frequency of Dosing section, as follows (changes underlined):

   The preferred dosing frequency of VIDEX is twice daily because there is more evidence to support the effectiveness of this dosing frequency. Once-daily dosing should be considered only for adult patients whose management requires once-daily dosing of VIDEX (see **INDICATIONS AND USAGE: Clinical Studies**).

6. In the **PRECAUTIONS, Frequency of Dosing** section, the following words were inserted at the end of the first paragraph, before the words "**Clinical Studies.:**"

   INDICATIONS AND USAGE

7. In Table 7 in the **PRECAUTIONS, Drug Interactions** section, the added text for tenofovir appears underlined and highlighted in green, as shown below:

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Table 7: Established Drug Interactions with VIDEX

Coadministration Not Recommended Based on Drug Interaction Studies *(see* **CLINICAL PHARMACOLOGY: Drug Interactions** *for Magnitude of Interaction)*

Drug	Effect	Clinical Comment
allopurinol	↑ didanosine concentration	Coadministration not recommended.

Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies *(see* **CLINICAL PHARMACOLOGY: Drug Interactions** *for Magnitude of Interaction)*

Drug	Effect	Clinical Comment
ciprofloxacin	↓ ciprofloxacin concentration	Administer VIDEX at least 2 hours after or 6 hours before ciprofloxacin.
delavirdine	↓ delavirdine concentration	Administer VIDEX 1 hour after delavirdine.
ganciclovir	↑ didanosine concentration	Appropriate doses for this combination, with respect to efficacy and safety, have not been established.
indinavir	↓ indinavir concentration	Administer VIDEX 1 hour after indinavir.
methadone	↓ didanosine concentration	Appropriate doses for this combination, with respect to efficacy and safety, have not been established.
nelfinavir	No interaction 1 hour after didanosine	Administer nelfinavir 1 hour after VIDEX.
[redacted]	[redacted]	[redacted]

↑ indicates increase.
↓ indicates decrease.

8. In Table 8 in the **PRECAUTIONS, Drug Interactions** section, in the section titled, **Use with Caution, Risk of Adverse Reactions May Be Increased**, the heading "Drug Class" was changed to "Drug or Drug Class."

9. In Table 8 in the **PRECAUTIONS, Drug Interactions** section, the added text for ribavirin appears underlined and highlighted, as shown below:

Table 8: Predicted Drug Interactions with VIDEX

Use with Caution, Risk of Adverse Reactions May Be Increased		
Drug or Drug Class	**Effect**	**Clinical Comment**
Drugs that may cause pancreatic toxicity	↑ risk of pancreatitis	Use only with extreme caution.[a]
Neurotoxic drugs	↑ risk of neuropathy	Use with caution.[b]
Antacids containing magnesium or aluminum	↑ side effects associated with antacid components	Use caution with VIDEX Chewable/Dispersible Buffered Tablets and Pediatric Powder for Oral Solution.
[redacted]	[redacted]	[redacted]
Use with Caution, Plasma Concentrations May Be Decreased by Coadministration with VIDEX		
Drug Class	**Effect**	**Clinical Comment**
Azole antifungals	↓ ketoconazole or itraconazole concentration	Administer drugs such as ketoconazole or itraconazole at least 2 hours before VIDEX.

10. Insertion of the following paragraph in the **PRECAUTIONS, Drug Interactions** section. The last three sentences are bolded as shown below:

Tenofovir disoproxil fumarate or ribavirin. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with either tenofovir (see Tables 3 and 7) or ribavirin (see Table 8). **Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. Coadministration of tenofovir or ribavirin with VIDEX should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities. VIDEX should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop** (see **WARNINGS**).

11. In the **Observed during Clinical Practice** subsection of the **ADVERSE REACTIONS** section, the following deleted text is reflected as a ~~strike thru~~ and new text is underlined:

Liver – ~~lactic acidosis~~ symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see **WARNINGS**); hepatitis and liver failure.

12. Insertion of the words "**INDICATIONS AND USAGE**" in the **PRECAUTIONS, Pediatric Use** section, as follows (changes underlined):

    Use of VIDEX in pediatric patients from 2 weeks of age through adolescence is supported by evidence from adequate and well-controlled studies of VIDEX in adults and pediatric patients (see **INDICATIONS AND USAGE: Clinical Studies, CLINICAL PHARMACOLOGY, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION**).

13. Insertion of the word "(didanosine)" after the word "VIDEX" in the **ADVERSE REACTIONS, Adults** section, after Table 10.

14. Insertion of the words "**INDICATIONS AND USAGE**" in the **ADVERSE REACTIONS, Pediatric Patients** section, immediately preceding the words "**Clinical Studies**" at the end of the second paragraph.

15. Insertion of the words "**INDICATIONS AND USAGE**" in the **DOSAGE AND ADMINISTRATION, Adults** section, immediately preceding the words "**Clinical Studies**" the first paragraph.

16. Insertion of the words "**and PRECAUTIONS: Drug Interactions)**" in the **DOSAGE AND ADMINISTRATION, Dose Adjustment** section, at the end of the first paragraph.

Label Revisions to the patient information leaflet:

17. In the first sentence of the **How should I take VIDEX? How should I store it?** section, the following deleted text is reflected as a ~~strike thru~~ and new text is underlined:

    Your doctor will determine your dose based on your body weight, kidney and liver function, ~~and any side effects that you may have had with other medicines~~ other medicines you are taking, -… - VIDEX or other medicines

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/s/

Destry Sillivan
10/16/02 05:21:06 PM
CSO

Tony, this is the CSO review for VIDEX supplements 20-154/ S-040, S-041 20-155/ S-030, S-031 20-156/ S-031, S-032

Tony DeCicco
10/18/02 10:56:32 AM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-154/S-040
NDA 20-155/S-030
NDA 20-156/S-031
NDA 21-183/S-005

PRIOR APPROVAL SUPPLEMENT

Bristol Myers Squibb
Attention: Marie-Laure Papi
Senior Regulatory Associate, Regulatory Science
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Papi,

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Products:	VIDEX® (didanosine) Chewable/dispersible Tablets VIDEX® (didanosine) Buffered Powder for Oral Solution VIDEX® (didanosine) Pediatric Powder for Oral Solution VIDEX® (didanosine) Delayed-Release Capsules Enteric Coated
NDA Numbers:	20-154 20-155 20-156 21-183
Supplement number:	S-040 (NDA 20-154) S-030 (NDA 20-155) S-031 (NDA 20-156) S-005 (NDA 21-183)
Date of supplements:	May 31, 2002
Date of receipt:	Jun 3, 2002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 2, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room # N115
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, please call Destry M. Sillivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Anthony DeCicco, R.Ph.
Chief, Project Management
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Tony DeCicco
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-154/S-041
NDA 20-155/S-031
NDA 20-156/S-032
NDA 21-183/S-006

PRIOR APPROVAL SUPPLEMENTS

Bristol-Myers Squibb Company
Attention: Marie-Laure Papi
Sr. Regulatory Associate
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Papi:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Products:	VIDEX® (didanosine) Chewable/dispersible Tablets VIDEX® (didanosine) Buffered Powder for Oral Solution VIDEX® (didanosine) Pediatric Powder for Oral Solution VIDEX® (didanosine) Delayed-Release Capsules Enteric Coated
NDA Numbers:	20-154 20-155 20-156 21-183
Supplement numbers:	S-041 (NDA 20-154) S-031 (NDA 20-155) S-032 (NDA 20-156) S-006 (NDA 21-183)
Date of supplements:	July 11, 2002
Date of receipt:	July 12, 2002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 10, 2002, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

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Anthony DeCicco, R.Ph.
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Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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Tony DeCicco
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