CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-154/S-029, S-030
20-155/S-021
20-156/S-022

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

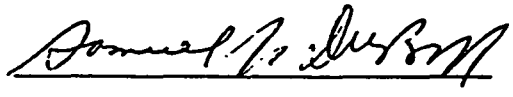
PATENT INFORMATION

1)	Patent No./Expiration:	U.S. Patent 4,861,759; expires August 29, 2006
	Type of Patent:	Method of use
	Patent Owner:	United States of America represented by Department of Human Services
2)	Patent No./Expiration:	U.S. Patent 5,254,539; expires August 29, 2006
	Type of Patent:	Method of use
	Patent Owner:	United States of America represented by Department of Human Services
3)	Patent No./Expiration:	U.S. Patent 5,616,566; expires August 29, 2006
	Type of Patent:	Method of use
	Patent Owner:	United States of America represented by Department of Human Services
4)	Patent No./Expiration:	U.S. Patent 5,880,106; expires July 22, 2011
	Type of Patent:	Composition
	Patent Owner:	Bristol-Myers Squibb Company

Bristol-Myers Squibb Company is the exclusive licensee of U.S. Patents 4,861,759, 5,254,539 and 5,616,566 by virtue of an agreement with NTIS dated February 1, 1988.

DECLARATION

The undersigned declares that U.S. Patents 4,861,759, 5,254,539, 5,616,566 and 5,880,106 cover the use of 2',3'-dideoxyinosine (ddI) which is the subject of the present Supplemental New Drug Application.



Signature of Authorized Person

Samuel J. DuBoff

Name of Authorized Person

Patent Counsel-International

Title of Authorized Person

April 13, 1999

Date

Exclusivity Checklist

NDA: 20-154/S-029, 20-155/S-021, 20-156/S-022				
Trade Name: Videx chewable tablets, powder for oral solution, pediatric powder for oral solution				
Generic Name: didanosine				
Applicant Name: Bristol-Myers Squibb				
Division: Division of Antiviral Drug Products, HFD-530				
Project Manager: Dotty Sullivan				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	X
b. Is it an effectiveness supplement?	Yes	X	No	
c. If yes, what type? (SE1, SE2, etc.)	SE2			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	X	No	

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Explanation: NA				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation: NA				
d. Did the applicant request exclusivity?	Yes		No	X
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	—			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes	X	No	
If yes, NDA # 20-154, 20-155, 20-156				
Drug Name: VIDEX				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE				

BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes	X	No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product VIDEX: Chewable/Dispersable Tablets	
NDA # 20-154	
Drug Product VIDEX: Powder for Oral Solution	
NDA # 20-155	
Drug Product VIDEX: Pediatric Powder for Oral Solution	
NDA # 20-156	

2. Combination product.	Yes		No	X
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any</u> <u>one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	
NDA #	
Drug Product	
NDA #	
Drug Product	
NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY

TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. Yes No

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? Yes No

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? Yes No

1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

If yes, explain:

2) If the answer to 2 b) is "no," are you aware of published				

studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
If yes, explain:				

c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:	
Investigation #2, Study #:	
Investigation #3, Study #:	

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1	
Investigation #2	

Investigation #3	

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may				

not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes	No
If yes, explain:		

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Signature of PM/CSO /S/
Date: 28 October 1999

Signature of Division Direct /S/
Date: October 28, 1999

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20154	**Trade Name:**	VIDEX CHEWABLE TABLETS
Supplement Number:	29	**Generic Name:**	DIDANOSINE
Supplement Type:	SE2	**Dosage Form:**	Capsule; Tablet; Tablet, Chewable; Oral
Regulatory Action:	AP	**Proposed Indication:**	VIDEX once daily dosing is indicated for the treatment of HIV-1 infection.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are submitted and under review

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

VIDEX once daily dosing is not adequetely labeled for pediatric patients. DAVDP has issued a written request for pediatric studies in HIV-1 infected neonates up to 6 months in age. August 5, 1999

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DESTRY SILLIVAN

(S)

Signature

22 September, 1999

Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20155	**Trade Name:**	VIDEX POWDER FOR ORAL SOLUTION
Supplement Number:	21	**Generic Name:**	DIDANOSINE
Supplement Type:	SE2	**Dosage Form:**	Powder For Reconstitution; Oral
Regulatory Action:	AP	**Proposed Indication:**	VIDEX once daily dosing is indicated for the treatment of HIV-1 infection.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are submitted and under review

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

VIDEX once daily dosing is not adequetely labeled for pediatric patients. DAVDP has issued a written request for pediatric studies in HIV-1 infected neonates up to 6 months in age. August 5, 1999

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DESTRY SILLIVAN

/S/ _____ 22 September, 1999

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20156	**Trade Name:**	VIDEX POWDER FOR ORAL SOLUTION
Supplement Number:	22	**Generic Name:**	DIDANOSINE
Supplement Type:	SE2	**Dosage Form:**	Powder For Reconstitution; Oral
Regulatory Action:	AP	**Proposed Indication:**	VIDEX once daily dosing is indicated for the treatment of HIV-1 infection.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
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This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DESTRY SULLIVAN

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22 September 1999
Date

CERTIFICATION: DEBARRED PERSONS

Bristol-Myers Squibb certifies that it has not used and will not use the services of any person listed as debarred as of the September 28, 1998 Debarment List under Section 306 (a) or (b) of the Federal Food and Drug Cosmetic Act [21 U.S.C. 355 (a) or (b)] in any capacity, in connection with this Application for VIDEX® (didanosine) Chewable/Dispersible Tablets.

Cynthia F. Piccirillo

Cynthia F Piccirillo
Associate Director
Regulatory Science
Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492
(203) 677-7625

Group Leader Memorandum

NDA:	20-154, SE1-029
Drug:	Didanosine (Videx®)
Dose:	400 mg QD
Indication:	Treatment of HIV infection in combination with other antiretroviral agents.
Applicant:	Bristol-Meyers Squibb
Submission received:	April 29, 1999
Date of Memorandum:	September 23, 1999

In this application, Bristol-Meyer Squibb requests approval of a once daily dosing regimen that will utilize a new 200 mg strength tablet of didanosine. We believed that a once daily regimen of didanosine would significantly improve patient compliance by allowing flexibility in incorporating didanosine into combination antiretroviral regimens. The additional flexibility in dosing with a single daily dose of didanosine could also minimize possible drug and food interactions. For these reasons, we felt that a six month priority review time was appropriate for this application.

In support of this request, the applicant has submitted the results of three studies. Two of these studies were small (about 80 patients in each), of limited duration (12 weeks) and compared dual nucleoside regimens. However, each study provided evidence that 400 mg of didanosine taken as a daily dose had similar short-term effects on viral load and CD4 counts as the currently approved regimen of 200 mg BID. The most convincing efficacy data was provided by interim results from 24 week data in 325 treatment-naïve patients enrolled in Study AI454-148. This is an ongoing, 48 week, open label comparison of once daily didanosine, plus stavudine and nelfinavir to zidovudine plus lamivudine and nelfinavir. These data showed that both treatment arms produced similar proportions of patients whose viral load became undetectable by 24 weeks, and that similar increases in CD4 cell counts were obtained. As a phase 4 commitment, the sponsor has agreed to provide the 48 week results from this study as soon as they become available.

Of concern was a death due to pancreatitis in a patient receiving didanosine, stavudine and nelfinavir in Study AI 454-148. Deaths due to pancreatitis in patients receiving the combination of didanosine and stavudine have been reported from other clinical trials as

well as from post-marketing reports. Because several of these deaths have occurred individuals with preserved immune function and without other obvious factors that would put them at risk for this adverse event, and because there appears to be an increased risk for other toxicities shared in common by these two agents (peripheral neuropathy, increases in liver function tests), it is plausible that the risk of pancreatitis which may result in death could be associated with use of these two nucleosides together. The didanosine label will be revised to represent these concerns, and the applicant will be requested to submit similar label revisions for the stavudine label. In addition, the applicant will be requested to conduct and submit a comprehensive risk-benefit analysis of this serious adverse event as a phase 4 commitment.

The use of a once daily didanosine has not been studied in pediatric patients. The applicant has agreed to study both a once daily regimen in pediatric patients, as well as use of the new 200 mg tablet in pediatric patients able to take solid formulations as a phase 4 commitment. Based on this commitment, a deferral to submit pediatric data to support this indication has been granted.

I concur with the recommendation of the primary medical reviewer, Mr. R. Fleischer, that this application should be approved.

Therese Cvetkovich, M.D.
Medical Team Leader
Division of Antiviral Drug Products, HFD-530

CC:
NDA 20-154
NDA 20-155
NDA 20-156
HFD-530/Div Dir/HJolson
HFD-530/MO/RFleischer

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID NUMBER: #99319

DATE: November 23, 1999 DEC - 1 1999

FROM: Debra E. Boxwell, Pharm.D.
Judy A. Staffa, Ph.D., R.Ph.
Division of Drug Risk Evaluation II (DDRE II)

/S/

THROUGH: Evelyn M. Rodriguez, M.D., M.P.H., Director 12/1/99
DDRE II, HFD-440

TO: Heidi M. Jolson, M.D., M.P.H., Director
Division of Antiviral Drug Products, HFD-530

SUBJECT: Consult—Didanosine (Videx®)-associated pancreatitis: Emphasis on combination nucleoside reverse transcriptase inhibitor (NRTI) therapy with didanosine

Executive Summary

This document is in response to a request by Russ Fleischer, the medical officer for didanosine (Videx®), for reports of pancreatitis associated with didanosine when used as monotherapy and in combination therapy with other nucleoside reverse transcriptase inhibitors (NRTIs). There was particular interest in the combination of didanosine and stavudine (Zerit®).

Didanosine is manufactured by Bristol Myers Squibb and was approved for use in the U.S. on October 9, 1991. At the time of approval, pancreatitis was a well-known side effect and documented in the label. Of particular concern at this time is whether there is an above average number of pancreatitis cases when didanosine is used in combination with stavudine, another product of Bristol Myers Squibb and approved on June 24, 1994. A search was done of the Adverse Event Reporting System (AERS) database using the HLT term, Pancreatitis (all forms), for didanosine reports received up through 10/7/99. Of the 277 reports retrieved, 145 reports listed didanosine as the only NRTI, and 111 unduplicated reports documented combination NRTI therapy with didanosine.

The most commonly used NRTI in combination with didanosine up through 1995 was zidovudine. In 1997, there was a large jump in the number of cases of didanosine-associated pancreatitis, and starting in 1997, stavudine became the most commonly used NRTI in those combination cases. This trend continued through 1999. However, IMS prescription use data shows that didanosine use has been increasing since 1996, and stavudine use has steadily increased since 1995.

The percentage of death reports received in patients receiving NRTI combination therapy with didanosine was 36% (9/25) for 1997, 42% (14/33) for 1998, and 35% (11/31) for 1999.

Nearly all of these reports (32/34) have involved stavudine. In addition, many patients were also taking concomitant medications and/or had medical conditions associated with pancreatitis.

A conclusion cannot be made from these data as to whether patients are more likely to develop or die from pancreatitis with combination didanosine/stavudine use. However, our spontaneous reporting system does clearly show an increase in the number of reports of pancreatitis with combination didanosine/stavudine therapy since 1997, which parallels prescribing trends, as well as a substantial number of these reports resulting in death.

I. LABELING

The didanosine labeling contains a boxed warning for pancreatitis that states:

> *Pancreatitis, which has been fatal in some cases, has occurred during therapy with Videx. Videx use should be suspended in patients with signs or symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis (see Warnings).*

The Warnings section continues to state:

> *When treatment with other drugs known to cause pancreatic toxicity is required, suspension of Videx (didanosine) therapy is recommended. In patients with risk factors for pancreatitis, Videx should be used with extreme caution and only if clearly indicated. Patients with advanced HIV infection are at increased risk of pancreatitis and should be followed closely. Patients with renal impairment may be at greater risk for pancreatitis if treated without dose adjustment.*
>
> *The frequency of pancreatitis is dose related. In phase 3 studies, incidence ranged from 1% to 7% with recommended dose.*
>
> *In pediatric studies, pancreatitis occurred in 3% (2/60) of patients treated at entry doses below 300 mg/m2/day and in 13% (5/38) of patients treated at higher doses. Videx use should be suspended in pediatric patients with signs or symptoms of pancreatitis and discontinued in pediatric patients with confirmed pancreatitis.*

II. SELECTION OF CASES FROM AERS

A search of the AERS database was done using the HLT term, Pancreatitis (all forms), for didanosine reports received up through 10/7/99. A total of 277 reports were retrieved. A line listing was printed for each of these reports, and narratives were also printed if available. Of these 277 reports, 145 reports listed didanosine as the only nucleoside reverse transcriptase inhibitor (NRTI); 132 reports documented combination NRTI therapy.

The line listings and available narratives of combination NRTI therapy with didanosine were examined and there is believed to be a total of 111 unduplicated reports. Because the focus of this consult is on combination therapy with didanosine, narratives were not provided on most of the didanosine monotherapy reports, and due to time constraints, the NRTI monotherapy with didanosine reports did not receive as close an examination as the combination NRTI therapy. Duplicate and follow-up reports may be included in the 145 total reports.

A. NRTI MONOTHERAPY WITH DIDANOSINE (n = 145)

A total of 145 reports of NRTI monotherapy with didanosine were retrieved. These reports were broken down by year and the number of reported deaths, as follows:

Table 1. Reports in AERS of pancreatitis associated with NRTI monotherapy (didanosine only) by year*

Year of Report	Number of Reports	Deaths
1991	2	1
1992	58	27
1993	37	8
1994	12	3
1995	8	0
1996	8	2
1997	5	2
1998	7	5
1999	8	0

* Duplicate and follow-up reports may be included in the 145 total reports

B. NRTI COMBINATION THERAPY WITH DIDANOSINE (n = 111)

A total of 111 reports of NRTI combination therapy with didanosine were retrieved. These reports were broken down by year and the number of reported deaths, as follows:

Table 2. Reports in AERS of pancreatitis associated with NRTI combination therapy (with didanosine) by year

Year of Report	Number of Reports	Deaths
1991	1	1
1992	5	3
1993	4	1
1994	7	3
1995	3	1
1996	2	1
1997	25	9
1998	33	14
1999	31	11

The specific NRTI that was taken in combination with didanosine is listed below. Again, the reports are broken down by year and deaths.

Table 3. Reports in AERS of pancreatitis associated with NRTI combination therapy (with didanosine): By year and specific combination

Year of Report	NRTI Taken in Combination With Didanosine	Number of Reports	Deaths
1991	Zidovudine	1	1
1992	Zidovudine	4	2
	Zidovudine/Zalcitabine	1	1
1993	Zidovudine	4	1
1994	Zidovudine	7	3
1995	Zidovudine	2	0
	Stavudine	1	1
1996	Stavudine	1	0
	Zidovudine/Lamivudine	1	1
1997	Stavudine	15	7
	Stavudine/Lamivudine	3	1
	Lamivudine	3	0
	Stavudine/Zidovudine	2	0
	Zidovudine	1	1
	Zidovudine/Lamivudine	1	0
1998	Stavudine	27	13
	Zidovudine	3	0
	Stavudine/Lamivudine	2	1
	Stavudine/Abacavir	1	0
1999	Stavudine	26	10
	Zidovudine	2	0
	Lamivudine	1	0
	Zalcitabine	1	0
	Abacavir	1	1

C. Clinical Description of Cases: Combination NRTI therapy with didanosine

1991-1996: Documented Possible Confounding Factors/Complications in Death Cases

1991 (1 death)—None documented
1992 (3 deaths)—Pentamidine (n=1)
1993 (1 death)—Pentamidine and renal failure (n=1)
1994 (3 deaths)—Cotrimoxazole, history of alcohol abuse (n=1); furosemide (n=1); fatty liver (n=1).
1995 (1 death)—Acidosis (n=1)
1996 (1 death)—None documented

Although fatty liver (1994) and acidosis (1995) are not predisposing factors for pancreatitis, these diagnoses may be evidence that these patients were possibly experiencing another type of mitochondrial toxicity in the form of acidosis/lactic acidosis and/or fatty liver. Pentamidine, furosemide, and cotrimoxazole are documented to contribute to the development of pancreatitis.

Description of Cases – by calendar year

1997 (n=25)

Demographics

Age:	11-63 years (mean 39.2 years, median 40 years), n=20
Sex:	Male 15, female 6, unknown 4
Location:	US 20, foreign 1, unknown 4
Outcome:	Death 9, life-threatening 1, hospitalized 12, required intervention 2, unk 1

Table 4. Documented Possible Confounding Factors/Complications in Death Cases (n=9) for 1997

NRTI Taken in Combination With Didanosine	Concomitant drugs associated with pancreatitis	Concomitant disease states associated with pancreatitis	Other medical conditions
Stavudine	--	Renal failure	Lactic acidosis/fatty liver; hepatic failure
Stavudine/lamivudine	Cotrimoxazole	--	Multiple sclerosis, hypotension, acute respiratory failure
Stavudine	--	--	Lactic acidosis/fatty liver; multiorg failure
Stavudine	--	--	Lactic acidosis
Zidovudine	Steroids, cyclosporine	--	Acidosis, acute circulatory failure
Stavudine	--	--	--
Stavudine	Cotrimoxazole	--	Acidosis
Stavudine	Cotrimoxazole	--	--
Stavudine	--	--	--

1998 (n=33)

Demographics

Age:	3-64 years (mean 36.4 years, median 36 years), n=32
Sex:	Male 21, female 11, unknown 1
Location:	US 20, foreign 12, unknown 1
Outcome:	Death 14, life-threatening 2, hospitalized 14, unknown 3

Table 5. Documented Possible Confounding Factors/Complications in Death Cases (n=14) for 1998

NRTI Taken in Combination With Didanosine	Concomitant drugs associated with pancreatitis	Concomitant disease states associated with pancreatitis	Other medical conditions/concomitant hydroxyurea use
Stavudine	--	Gallstones	Acidosis, fatty liver
Stavudine	Cotrimoxazole	--	--
Stavudine	--	H/O Etoh abuse, renal failure, gallstones	--
Stavudine	--	--	Lactic acidosis, multiorgan failure
Stavudine	Cotrimoxazole	--	Lactic acidosis, hepatitis
Stavudine/lamivudine	Cotrimoxazole	--	--
Stavudine	Cotrimoxazole	--	Multiorgan failure
Stavudine		--	Cirrhosis
Stavudine	Cotrimoxazole	Renal failure	--
Stavudine	--	--	--
Stavudine	--	Renal failure	Lactic acidosis
Stavudine	--	--	Lactic acidosis, fatty liver; Hydroxyurea
Stavudine	--	--	--
Stavudine	--	--	Hydroxyurea

1999 (n=31)

Demographics

Age:	8-71 years (mean 38.3 years, median 38 years), n=30
Sex:	Male 22, female 9, unknown 0
Location:	US 23, foreign 8
Outcome:	Death 11, life-threatening 2, hospitalized 14, unknown 4

Table 6. Documented Possible Confounding Factors/Complications in Death Cases (n=11) in 1999

NRTI Taken in Combination With Didanosine	Concomitant drugs associated with pancreatitis	Concomitant disease states associated with pancreatitis	Other medical conditions/concomitant hydroxyurea use
Stavudine	--	Inc triglycerides, cholesterol	--
Abacavir	--	--	--
Stavudine	Cotrimoxazole, naproxen	Inc triglycerides	--
Stavudine	--	--	--
Stavudine	--	--	--
Stavudine	--	--	Lactic acidosis
Stavudine	Cotrimoxazole	--	Cirrhosis Hydroxyurea
Stavudine	Metronidazole	--	Lactic acidosis
Stavudine	Cotrimoxazole	--	Fatty liver
Stavudine	--	--	
Stavudine	--	--	Hydroxyurea

PREVALENCE OF USE DATA

A. Overall use of NRTIs

To understand the context of these events reported to occur in patients using didanosine alone and in combination with other NRTIs, exposure in the U.S. to this class of agents was examined using two different data sources. First, the total number of prescriptions dispensed annually for each NRTI since 1994 was determined from the National Prescription Audit (NPA) and is presented in Table 7. With the exception of zalcitabine and didanosine, the numbers of prescriptions for each of the NRTIs has increased steadily since marketing. While zalcitabine prescriptions have dropped off since 1995, the number of didanosine prescriptions has increased since 1997, subsequent to a slight decline in 1995 and 1996. This may indicate either additional patients initiating therapy or continuation of patients on the drug for longer periods of time.

Table 7. Projected Number of Total Prescriptions Dispensed by Retail Pharmacies (Chain, Independent, Food Stores, and Mail Order) in the U.S.
--Oral Products Only--
(in thousands; add three 0's to each figure)

	Date of Approval	1994	1995	1996	1997	1998	Jan-Sept 1999
Zidovudine	3/19/87						
Didanosine	10/9/91						
Zalcitabine	6/19/92						
Stavudine	6/24/94						
Lamivudine	11/17/95						
Abacavir	12/17/98						

Source: IMS Health, National Prescription Audit
*****NOT TO BE USED OUTSIDE OF FDA WITHOUT PRIOR CLEARANCE BY IMS HEALTH*****

A second source, the National Drug and Therapeutic Index (NDTI) was queried to estimate the frequency of concomitancy of didanosine prescription with other NRTIs. The NDTI surveys visits made to a sample of office-based physicians throughout the U.S. Figure 1 (see Attachment) shows the didanosine "market", the total number of mentions of didanosine during patient visits by calendar year from 1994, as well as the number of mentions of other NRTIs concomitantly during the same visit. Clearly, the overall number of mentions of didanosine during visits has declined from 1994 to 1999. Coupled with the increased volume of prescriptions dispensed for didanosine (Table 7), this suggests that patients with HIV/AIDS may be receiving treatment from non-office based sites, such as hospitals or clinics, which may be outside the sampling frame of the NDTI survey. Therefore, estimates of concomitancy of NRTI use with didanosine from this survey should be interpreted with caution since they may represent an unknown subgroup of the treated HIV/AIDS patient population.

It appears that zidovudine and stavudine are the NRTIs mentioned most commonly in

combination with didanosine within the last five years. Didanosine was mentioned concomitantly with zidovudine about half the time between 1994 and 1996, dropping off to no concomitant mentions in 1999. Concomitant therapy with zidovudine appears to have been replaced with stavudine. Prevalence of stavudine concomitancy with didanosine grew from under — in 1996 to — of all didanosine mentions in 1999. In this data source, stavudine is clearly the NRTI most commonly prescribed with didanosine.

B. NRTI use in relation to spontaneous reports in AERS

To understand whether the reporting of pancreatitis cases is commensurate with the extent of use of didanosine in the population, reporting rates are typically calculated. Reporting rates consist of the number of reported cases/number of prescriptions per year. Using the total number of reported cases mentioning didanosine/number of didanosine prescriptions, the following reporting rates can be estimated:

1994:
1995:
1996:
1997:
1998:
1999:

Clearly, these reporting rates have not changed over time. However, these overall reporting rates do not address the question of whether the combination of other NRTIs with didanosine, particularly stavudine, is associated with increased reports of pancreatitis. Such a calculation would require the number of didanosine prescriptions each year that are concomitantly taken with another NRTI, a quantity that is not known for the U.S. population.

Some effort can be made, however, to approximate the percentage of didanosine use that is in combination with other NRTIs using NDTI data on patient visits to office-based physicians (Figure 1). A side-by-side comparison was made between the percentage of pancreatitis reports where didanosine monotherapy had been used and the percentage of the didanosine market that appeared as monotherapy in the NDTI data yearly from 1994 through 1999 (Figure 2). The same comparison was made using the percentage of pancreatitis reports where didanosine had been used in combination with any other NRTI and the percentage of the didanosine market that was mentioned in combination with another NRTI (Figure 3).

These figures suggest that the pattern of NRTI use associated with the pancreatitis reports parallels rather closely the trend in prescribing over time – this is true for monotherapy with didanosine as well as for combined therapy with other NRTIs. Therefore, it cannot be determined from these data whether there is increased risk of pancreatitis when didanosine is combined with other NRTIs. Similar patterns are seen if one focuses solely on stavudine and zidovudine, the NRTIs most commonly used in combination with didanosine since 1994, but the numbers are smaller and thus less stable (data not presented). Some caution should be used when interpreting these data, as there may be duplicates and follow up reports among the 145 reports associated with didanosine monotherapy. The NDTI data may also represent only the subset of HIV/AIDS treatment occurring in office-based practice and may not be representative of all HIV/AIDS treatment.

DISCUSSION

It is very difficult to determine if the use of didanosine and stavudine combination is more likely to cause pancreatitis, and death, than other combinations of NRTIs with didanosine. One limitation is that didanosine has been labeled for pancreatitis since it was approved. This would greatly limit the number of cases that the FDA would receive since practitioners would be less likely to report a labeled event. In addition, if practitioners were to report a labeled event, they would probably be more likely to report cases of death.

In reviewing these reports, the most commonly used drug in combination with didanosine up through 1995 was zidovudine. In 1997, there was a large jump in the number of cases of didanosine-associated pancreatitis, and starting in 1997, stavudine was the most commonly used NRTI in those cases of pancreatitis. This trend continued through 1999. The percentage of death reports received in patients receiving NRTI combination therapy with didanosine was 36% (9/25) for 1997, 42% (14/33) for 1998, and 35% (11/31) for 1999. Nearly all of these reports (32/34) had stavudine as at least one of the concomitant NRTIs.

However, IMS prescription use data shows that didanosine use increased approximately —— between 1996 and 1997, and has increased approximately .— between 1996 and 1998. In addition, stavudine use has steadily increased, —— between 1995 and 1996, and again between 1996 and 1997. Use between 1997 and 1998 was up approximately — Because the increase in reports parallels the increase in prescription use data, an obvious trend toward a more toxic didanosine/stavudine combination cannot be determined. Moreover, the NDTI data suggests that the increasing trend for prescription of didanosine concomitantly with other NRTIs has also paralleled the increase in pancreatitis reports. This pattern is also seen when looking specifically at zidovudine and stavudine, which have constituted the majority of combination NRTI therapy combined with didanosine since 1994. It is not clear, however, whether these data on concomitancy represent the majority of treated HIV/AIDS patients or the subset treated in office-based practice.

In addition, many patients were also taking concomitant medications and/or had medical conditions associated with pancreatitis, such as cotrimoxazole, furosemide, gallstones, alcohol abuse, and renal failure. Also, there were 13 patients between 1997 and 1999 who had documented lactic acidosis, acidosis, and/or fatty liver. Because these events are believed to involve mitochondrial toxicity associated with NRTIs, as does pancreatitis, it could be argued that these pancreatitis cases are all part of a larger mitochondrial toxicity picture.

Four out of 25 patients who died between 1998-1999 were documented to be taking concomitant hydroxyurea. Two of the patients had no other documented risk factors for pancreatitis, one had developed lactic acidosis and fatty liver, and one patient had had documented cirrhosis. It is not known if hydroxyurea played any part in the development of pancreatitis based on so few cases. The NDTI data also showed little to no concomitance of didanosine and hydroxyurea mentioned during patient visits to office-based practices.

SUMMARY

In summary, starting in 1997 and continuing to the present, a large majority of the reported cases of pancreatitis involving combination NRTI use with didanosine involved stavudine. A substantial number of the cases from 1997 on were death reports (38% [34/89]). However, IMS prescription use data also showed a large increase in didanosine and stavudine use, starting in 1997 and 1996, respectively. IMS' NDTI survey of office-based practice also showed a large increase in concomitant mention of didanosine with stavudine during this same time period, suggesting an increase in the use of combination therapy. Therefore, it is not possible at this time to show an association between didanosine and stavudine use and an increased number of reports of pancreatitis.

/S/

Debra E. Boxwell, Pharm.D.

/S/

/S/

Judy A. Staffa, Ph.D, R.Ph.

Concurrence: Toni Piazza-Hepp, Pharm.D.
HFD-440 SE Team Leader

cc:
HFD-400 Honig
HFD-440 Rodriguez / Williams / Dempsey
HFD-440 Boxwell / Piazza-Hepp / Bacsanyi / Staffa
HFD-400 Chron / Consult file
HFD-002 Lumpkin
HFD-400 Garry
HFD-530 Division File (NDA 20-154)
HFD-530 NDA 20-154
HFD-530 Project Manager
HFD-530 Medical Officer
HFD-530 Team Leader
HFD-530 Division Director

Attachment

Figures 1, 2 and 3

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 29, 1999

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, M.S., Regulatory Management Officer, HFD-530

Through: Russell Fleischer, PA-C, Medical Officer, HFD-530
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530

Subject: VIDEX® once daily dosing supplement to NDA 20-154, NDA 20-155, and NDA 20-156. Please respond to the following requests:

The following requests are made on behalf of Dr. Therese Cvetkovich and Russell Fleischer. Please provide the following:

1. Your plans for informing investigators and patients enrolled in clinical trials in which ddI with d4T with or without hydroxyurea are components of a combination regimen about the potential increased risk for pancreatitis.

2. A draft Dear Healthcare Provider letter informing clinicians about the potential increased risk for pancreatitis in patients treated with ddI with d4T with or without hydroxyurea.

3. Proposed revisions to the ddI PPI to inform patients being treated with ddI with d4T with or without hydroxyurea about the potential increased risk for pancreatitis.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Please feel free to contact me if you have any questions regarding the contents of this transmission.

Destry M. Sillivan, MS
Regulatory Management Officer
Division of Antiviral Drug Products

Concurrence:
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/RPM/Sillivan

cc:
Original NDA 20-154, 20-155, 20-156
Division File
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/Sillivan

NDA 20-154, 20-155, 20-156

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 23, 1999

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, MS, Regulatory Management Officer, HFD-530

Through: Russell Fleischer, PA-C, Medical Officer, HFD-53 /S/
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530 /S/

Subject: VIDEX® once daily dosing supplement to NDA 20-154, NDA 20-155, and NDA 20-156. Please respond to the following request:

The following request is made on behalf of Dr. Therese Cvetkovich and Russell Fleischer:

1. We request that you agree to provide a comprehensive risk assessment for fatal and non-fatal pancreatitis in patients treated with the combination of VIDEX® plus STAVUDINE®, with a report of the findings submitted within 60 days.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Destry M. Sillivan, MS
Regulatory Management Officer
Division of Antiviral Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 22, 1999

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, MS, Regulatory Management Officer, HFD-530

Through: Russell Fleischer, PA-C, Medical Officer, HFD-530
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530

Subject: Videx® once daily dosing supplement to NDA 20-154, NDA 20-155, and NDA 20-156. Please respond to the following request:

The following request is made on behalf of Dr. Therese Cvetkovich and Russell Fleischer:

1. We request that you agree to conduct studies adequate to support the efficacy of a once daily dosing interval, as well as assessing the use of the 200 mg tablet in the appropriate pediatric populations as part of your phase IV commitments for these VIDEX™ supplements.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Destry M. Sillivan, MS
Regulatory Management Officer
Division of Antiviral Drug Products

Concurrence:
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/RPM/Sillivan

cc:
Original NDA 20-154, 20-155, 20-156
Division File
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/Sillivan

NDA 20-154, 20-155, 20-156

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 9, 1999

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, MS, Regulatory Management Officer, HFD-530 /S/ 08/09/99

Through: Girish Aras, Ph.D., Statistical Team Leader, HFD-530 /S/ 8/9/99
Greg Soon, Ph.D., Statistical Reviewer, HFD-530 /S/ 8/9/99
Stephen Miller, Ph.D., Chemistry Team Leader, HFD-530 /S/ 8/9/99
Ko-Yu Lo, Ph.D., Chemistry Reviewer, HFD-530 /S/ 8/9/99
Russell Fleischer, PA-C, Medical Officer, HFD-530 8/9/99
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530 /S/ 08/09/99

Subject: Please respond to the following comments

Statistics:

In reference to Study 148:

1) Please re-run your randomization program 10,000 times and submit the results in a dataset.

2) Please use the following procedure to generate an ad hoc 95% confidence interval for the difference of the proportions with HIV RNA <400 copies/mL. This procedure is based on an inversion of the permutation test.

a) For each arm, classify subjects into three groups: Group I, consisting of subjects who were on the original randomized therapy at Week 24 with Week 24 HIV RNA <400 copies/mL, Group II, consisting of subjects who were on the original randomized therapy at Week 24 with Week 24 HIV RNA >400 copies/mL, and Group III, consisting of subjects who discontinued the randomized therapy or lost to follow-ups by Week 24. For subjects who were on the original randomized therapy at Week 24 but were missing Week 24 HIV RNA values, the Week 24 HIV RNA values can be imputed using the worst of pre and post HIV RNA values.

b) Find the largest l in the interval (0,1) such that for any number p in the interval $(0, l)$ the p-value based on the following procedure is <0.05.

   i) Let m= p x {# of subjects in the experimental arm}. Re-classify m subjects from Group II with the smallest HIV RNA values in the experimental arm as "successes". For all other subjects only those in Group I will be regarded as "successes".

   ii) Calculate the p-value based on this new classification using the permutation test with the original randomization procedure.

c) Similarly, find the largest u in the interval (0, 1) such that for any number p in the interval $(0, u)$ the p-value based on the following procedure is <0.05

   i) Let m= p x {# of subjects in the control arm}. Re-classify m subjects from Group II with the smallest HIV RNA values in the control arm as "successes." For all other subjects, only those in Group I will be regarded as "successes."

   ii) Calculate the p-value based on this new classification using the permutation test with the original randomization procedure.

Please report the 95% confidence interval as $(-l,u)$.

) Please identify the subject who was randomized twice.

) Please resubmit dataset FAILDAT in submission dated 7/21/99 to include a variable describing the reasons for the discontinuation of the randomized treatment. The number of discontinuations derived using variable DISCTI or DISCDT differs from that derived using variable DISCFL, and they differs from the number derived from the variable RNAWK24 in dataset DEMO. Please reconcile the differences.

) Please re-calculate TAD for CD4 using all CD4 measurements available, including those observed after discontinuation of the randomized therapy.

n reference to Study 143 and 146:

) Please follow comments 1 and 2 above for these two studies with Week 24 replaced by Week 12.

linical Pharmacology:

) Because mg/kg dosing is preferred for pediatric patients, please provide data to support the conversion of dosing recommended from mg/m^2 to equivalent doses in mg/kg.

C istry:

8) The master batch record indicates a typical batch size of — for the 200 mg tablets. However, the stability section stated that the commercial scale production for this product is — Please clarify the commercial batch size for the 200 mg tablets.

9) Please provide the COAs for the drug substance lots and the COAs for the 200 mg tablets.

10) Please provide comparative regression graphs for the 200 mg tablets vs. the 25 mg and 150 mg tablets.

11) Please clarify whether the 200 mg tablets will be packaged into a ——— so, please provide stability data in support of the blister configuration.

Clinical:

12) Please investigate and provide a discussion of the discrepancies in laboratory abnormalities between the START 2 and 148 trials in Tables 7 and 8 in the proposed label.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Desiry M. Sullivan, MS
Regulatory Management Officer
Division of Antiviral Drug Products

Concurrence:
HFD-530/STL/Aras
HFD-530/SR/Soon
HFD-530/BR/R. Kumi
HFD-530/BTL/P. Raja
HFD-530/CTL/Miller
HFD-530/MO/Fleisch
HFD-530/MTL/Cvetk
HFD-530/RPM/Silliv

cc:
Original NDA 20-154, 20-155, 20-156
Division File
HFD-530/Fleischer
HFD-530/Cvetkovich
HFD-530/Soon
HFD-530/Aras
HFD-530/Miller
HFD-530/Lo
HFD-530/R. Kumi
HFD-530/Sillivan

NDA 20-154, 20-155, 20-156

HFD-530/Sullivan

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-154/S-030

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

JUL 16 1999

Attention: Cynthia F. Piccirillo
Manager, Worldwide Regulatory Affairs

Dear Mr. Piccirillo:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Videx® (didanosine) Oral Tablets

NDA Number: 20-154

Supplement Number: S-030

Date of Supplement: April 30, 1999

Date of Receipt: April 30, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 29, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

/S/

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-154/S-030
HFD-530/Div. Files
HFD-530/CSO/Sillivan, D.

SUPPLEMENT ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 28, 1999

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, MS, Regulatory Management Officer, HFD-5

Through: Girish Aras, Ph.D., Statistical Team Leader, HFD-5
Greg Soon,Ph.D., Statistical Reviewer, HFD-530
Russell Fleischer, PA-C, Medical Officer, HFD-530
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530

Subject: Please respond to the following comments

The following comments are made on behalf of Dr. Greg Soon and Russell Fleischer:

Concerning study 148:

1. Please submit the following information used for the randomization: all the covariates used, the order of patient entry, the algorithms, and the SAS programs.

2. Please explain why some subjects started treatment long after they were being randomized. For example, at least four subjects started treatment more than 20 days after they were randomized. (In calculating study days, it is recommended that the day of randomization be regarded as "day one.")

3. A permutation-based analysis that takes into account the randomization procedure used should be applied to construct the 95% confidence intervals in the proportion analysis.

4. Please resubmit the results for the proportion analysis based on all subjects randomized, regardless of whether any medication was initiated after randomization. The randomized subjects who did not start medication should be regarded as "failures" for the proportion analysis.

5. Please provide data for "time to viral failure" and "time to first HIV RNA <400 copies/mL" as defined in the protocol. A subject who never started medication should be regarded as one who never achieved HIV RNA <400 copies/mL. Please provide a Week 24 proportion analysis in which subjects who achieved HIV RNA <400 copies/mL before or at Week 24 and were not a "viral failure" up to Week 24 are regarded as "successes" and all others as "failures."

6. Please incorporate variables that were used to derive the major efficacy endpoints into the dataset. For example, time to first AIDS-defining event, time to first drug switch/discontinuation (excluding switches between d4T and ZDV) and time to 'lost to follow-up'. Since switching between d4T and ZDV was treated differently from other treatment switches in the proportion analysis, please also provide 'time to first d4T to ZDV switch' and 'time to first ZDV to d4T switch.'

7. SAS programs for all efficacy analyses should be submitted and they should be able to reproduce the efficacy results based on the submitted data.

8. Please provide narratives explaining the reasons for premature study discontinuation for the following ddI-treated patients: 03-162, 17-215, 17-359, 17-363, 21-152, 22-135, 31-177, 40-353, 85-692, and 89-762, and for the following ZDV-treated patients: 08-451, 51-569, 51-645, 82-301, 85-370, and 103-485.

Concerning studies 143 and 146:

9. Please conduct a Week 12 proportion analysis for studies 143 and 146, similar to the Week 24 proportion analysis for study 148. Follow comments 1-7 with Week 24 analysis replaced by Week 12 analysis for these two studies.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Destry M. Sillivan, MS
Regulatory Management Officer
Division of Antiviral Drug Products

Concurrence:
HFD-530/STL/Aras
HFD-530/SR/Soon /S/
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/RPM/Sillivan

cc:
Original NDA 20-154, 20-155, 20-156
Division File
HFD-530/Fleischer
HFD-530/Cvetkovich
HFD-530/Soon
HFD-530/Aras
HFD-530/Sillivan

NDA 20-154, 20-155, 20-156

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

45 DAY FILING MEETING MINUTES

NDA: 20-154, 20-155, 20-156
SE2 029, SE2 021, SE2 022

DATE: June 9, 1999

DRUG: Videx® (didanosine) Chewable/Dispersible Tablets
Videx® (didanosine) Buffered Powder for Oral Solution
Videx® (didanosine) Pediatric Powder for Oral Solution

SPONSOR: Bristol-Myers Squibb
Pharmaceutical Research Institute

PARTICIPANTS: Heidi Jolson, M.D., M.P.H., Division Director
Walla Dempsey, Ph.D., Associate Director
Anthony DeCicco, R.Ph., Chief, Project Management Staff
Therese Cvetkovich, M.D., Medical Team Leader
Russell Fleischer, PA-C, Clinical Reviewer
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader
Anita Bigger, Ph.D., Pharmacology/Toxicology Reviewer
Girish Aras, Ph.D., Statistical Team Leader (Acting)
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader
Robert Kumi, Ph.D., Clinical Pharmacology Reviewer
Lauren Connors, Ph.D., Microbiology Team Leader
Lalji Mishra, Ph.D., Microbiology Reviewer
Stephen Miller, Ph.D., Chemistry Team Leader
Ko-Yu Lo, Ph.D., Chemistry Reviewer
Destry Sillivan, MS, Regulatory Project Manager
Christine Kelly, RN, MS, MBA, Regulatory Project Manager

BACKGROUND: This SNDA is being made in support of a new 200 mg strength tablet, a change in dosing to once-daily administration in combination therapy to treat HIV-infected patients, and other revisions to relevant sections of the VIDEX® package insert. Submission date 30 April 1999.

CHEMISTRY:

- This submission is acceptable for filing.
- CMC would like to add an additional code, SCF, reflecting a change in formulation.

PHARMACOLOGY/TOXICOLOGY:

- This submission is acceptable for filing.

- No further issues.

BIOPHARMACEUTICS:

- This submission is acceptable for filing.
- Approval will be based on efficacy.
- Possible problem with buffering, as two tablets are necessary to achieve sufficient buffering with this dose.

CLINICAL:

- This submission is acceptable for filing, and will be given a "P" for priority review.
- DAVDP will ask for 48 week data from study 148 as a phase IV commitment.
- Bristol-Myers Squibb must request a waiver or a deferment for these SNDAs with regard to studies in pediatric patients, or submit those studies, in order to comply with the pediatric rule.

MICROBIOLOGY:

- This submission is acceptable for filing.
- Micro will provide a revised label.

STATISTICS:

- This submission is acceptable for filing.
- The SAS data sets are available.

DISCUSSION:

- There are no filing issues; these SNDAs are filable.
- The six month time line is acceptable, but DAVDP will attempt to complete the review before six months.

CONCURRENCE:

HFD-530/Dir/Jolson /S/
HFD-530/DepDir/Birnki
HFD-530/AscDir/Demp
HFD-530/C-RPM/DeCi
HFD-530/MTL/Cvetkov
HFD-530/MO/Fleischer /S/
HFD-530/PTTL/Farrell
HFD-530/PTR/Bigger
HFD-530/STL/Aras
HFD-530/BPTL/Rajago
HFD-530/BPR/Kumi /S/
HFD-530/MicroTL/Iacc
HFD-530/MicroR/Mish
HFD-530/CTL/Miller
HFD-530/CR/Lo
HFD-530/RPM/Sillivar

cc:

NDA 20-154
NDA 20-155
NDA 20-156

Division File
HFD-530/Dir/Jolson
HFD-530/DepDir/Birnkrant
HFD-530/AscDir/Dempsey
HFD-530/C-RPM/DeCicco
HFD-530/MTL/Cvetkovich
HFD-530/MO/Fleischer
HFD-530/PTTL/Farrelly
HFD-530/PTR/Bigger
HFD-530/STL/Aras
HFD-530/BPTL/Rajagopalan
HFD-530/BPR/Kumi
HFD-530/MicroTL/Iaconno-Connors
HFD-530/MicroR/Mishra
HFD-530/CTL/Miller
HFD-530/CR/Lo
HFD-530/RPM/Sillivan

45 Day Filing Meeting

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-154/S-029

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

MAY 20 1999

Attention: Cynthia F. Piccirillo
Manager, Worldwide Regulatory Affairs

Dear Mr. Piccirillo:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Videx® (didanosine) Oral Tablets

NDA Number: 20-154

Supplement Number: S-029

Date of Supplement: April 30, 1999

Date of Receipt: April 30, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 29, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

/S/

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

HFD-530/Sullivan, D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-155/S-021

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

MAY 20 1999

Attention: Cynthia F. Pirccirillo
Manager, Worldwide Regulatory Affairs

Dear Ms. Piccirillo:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Videx® (didanosine) Buffered Powder for Oral Solution

NDA Number: 20-155

Supplement Number: S-021

Date of Supplement: April 30, 1999

Date of Receipt: April 30, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 29, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

/S/

Anthony W. Pecicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-155/S-021
HFD-530/Div. Files
HFD-530/CSO/Sillivan, D.

SUPPLEMENT ACKNOWLEDGEMENT

HFD-530/Sullivan, D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-156/S-022

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

MAY 20 1999

Attention: Cynthia F. Pirccirillo
Manager, Worldwide Regulatory Affairs

Dear Ms. Piccirillo:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Videx® (didanosine) Pediatric Powder for Oral Solution

NDA Number: 20-156

Supplement Number: S-022

Date of Supplement: April 30, 1999

Date of Receipt: April 30, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 29, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

/S/

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-152/S-022
HFD-530/Div. Files
HFD-530/CSO/Sillivan, D.

SUPPLEMENT ACKNOWLEDGEMENT