

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

**APPLICATION NUMBER: 20-154/S-028
20-155/S-020
20-156/S-021**

ADMINISTRATIVE DOCUMENTS

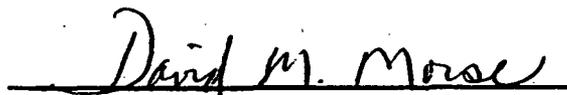
PATENT INFORMATION

- 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

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 and 5,616,566 cover the use of 2',3'-dideoxyinosine (ddI) which is the subject of the present Supplemental New Drug Application.



Signature of authorized person

DAVID M. MORSE

Name of authorized person

PATENT COUNSEL

Title of authorized person

March 26, 1998

Date

Exclusivity Checklist

NDA: 20-154/S-028	20-155/S-020	20-156/S-021
Trade Name: VIDEX chewable/dispersible tablets, powder for oral solution, pediatric powder for oral S		
Generic Name: didanosine		
Applicant Name: Bristol-Myers Squibb		
Division: HFD-530		
Project Manager: MELISSA M TRUFFA		
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	<input checked="" type="checkbox"/>
b. Is it an effectiveness supplement?	Yes	<input checked="" type="checkbox"/>	No	
c. If yes, what type? (SE1, SE2, etc.)	SE8			
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	<input checked="" type="checkbox"/>	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	<input checked="" type="checkbox"/>
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	NA			

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		No	<input checked="" type="checkbox"/>
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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	
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IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

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 #:			
<p>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.</p>			
<p>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.")</p>			
Investigation #1	Yes	No	
Investigation #2	Yes	No	
Investigation #3	Yes	No	
<p>If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:</p>			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
<p>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?</p>			
Investigation #1	Yes	No	
Investigation #2	Yes	No	
Investigation #3	Yes	No	
<p>If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:</p>			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
<p>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"):</p>			
Investigation #1			
Investigation #2			
Investigation #3			
<p>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.</p>			
<p>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?</p>			

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:				



Signature of PM/CSO

Date: 6-29-99

LSI

Signature of Division Dir

Date:

LSI

cc:

Original NDA

Division File

HFD-93 Mary Ann Holovac



PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20154 **Trade Name:** VIDEX CHEWABLE TABLETS
Supplement Number: 28 **Generic Name:** DIDANOSINE
Supplement Type: SEB **Dosage Form:** Tablet, Chewable; Oral
Regulatory Action: AP **Proposed Indication:** Videx in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) X Children (25 months-12 Years)
 X Infants (1-24 Months) X Adolescents (13-16 Years)

Label Adequacy Adequate for SOME pediatric age groups
Formulation Status NO NEW FORMULATION is needed
Studies Needed _____
Study Status _____

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

COMMENTS:

VIDEX in combination is adequately labeled for pediatrics 6 month and above in age. _____

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

Signature MS

Date 6-28-99

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20155 **Trade Name:** VIDEX POWDER FOR ORAL SOLUTION
Supplement Number: 20 **Generic Name:** DIDANOSINE
Supplement Type: SE8 **Dosage Form:** Powder For Reconstitution; Oral
Regulatory Action: AP **Proposed Indication:** VIDEX in combination with other antiretroviral agents 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) X Children (25 months-12 Years)
 X Infants (1-24 Months) X Adolescents (13-16 Years)

Label Adequacy Adequate for SOME pediatric age groups
Formulation Status NO NEW FORMULATION is needed
Studies Needed _____
Study Status _____

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

COMMENTS:

VIDEX in combiantion is adaquately labeled for pediatric patients 6 month and above in age.

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

Signature LSI

Date 6-28-99

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20156 **Trade Name:** VIDEX POWDER FOR ORAL SOLUTION
Supplement Number: 21 **Generic Name:** DIDANOSINE
Supplement Type: SEB **Dosage Form:** Powder For Reconstitution; Oral
Regulatory Action: AP **Proposed Indication:** VIDEX in combination with other antiretroviral agents is indicated for the treatment 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) X Children (25 months-12 Years)
X Infants (1-24 Months) X Adolescents (13-16 Years)

Label Adequacy Adequate for SOME pediatric age groups
Formulation Status NO NEW FORMULATION is needed
Studies Needed _____
Study Status _____

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

COMMENTS:

VIDEX in combination is adequately labeled for pediatric patients 6 months and above in age

This Page was completed based on information from a **PROJECT MANAGER/CONSUMER SAFETY OFFICER, MELISSA TRUFFA**

LS

 Signature

6-28-99

 Date

CERTIFICATION: DEBARRED PERSONS

Bristol-Myers Squibb certifies that to the best of its knowledge, information, and belief, it has not used and will not use the services of any person listed as debarred as of the November 12, 1997 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® Chewable/Dispersible Buffered Tablets and VIDEX® Buffered and non-Buffered Powders for Oral Solution.

Cynthia F. Piccirillo

**Cynthia F. Piccirillo, Manager
Worldwide Regulatory Affairs
Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492
(203) 677-7625**

Group Leader Memorandum

NDA: 20-154

Drug: Didanosine (Videx®)

Dose: 200 mg BID (adults)
120 mg/m² BID (pediatrics)

Indication: Treatment of HIV infection in combination with other antiretroviral agents.

Applicant: Bristol-Meyers Squibb

Submission received: June 30, 1998

Date of Memorandum: June 24, 1999

In this application, the applicant requests approval of didanosine (a nucleoside analogue reverse transcriptase inhibitor of HIV) for use in combination with other antiretroviral agents. The indication for use as a single therapeutic agent, as currently reflected in the label, would be removed from the revised label.

In support of this request, the applicant has submitted multiple studies of dual and triple antiretroviral combinations which include didanosine. Based upon the results of these studies, as well as the current treatment recommendations that include in most triple combinations the use of two nucleoside analogues, I concur with the recommendation of the primary medical reviewer, R. Fleischer, that this application should be approved.

Both the didanosine and stavudine labels will be modified to reflect the increased frequency of peripheral neuropathy and liver enzyme abnormalities that were noted in association with the combination use of these two nucleosides.

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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