CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-906

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter			X	
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI			X	
Pharmacology Review(s)			X	
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)			X	
Bioequivalence Review(s)			X	
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-906

Trade Name: ETOPOPHOS FOR INJECTION

Generic Name:(etopophos phosphate)

Sponsor: Bristol-Myers Squibb

Approval Date: February 27, 1998

Indication: Provides for pharmacy bulk packaging

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-906

APPROVAL LETTER

DEPARTMENT OF HEAL & HUMAN SERVICES

Public Health Service

VIU. file

Food and Drug Administration
Rockville MD 20857

NDA 20-906

Bristol-Myers Squibb
P.O. Box 5400
Princeton, New Jersey 08543-5400

FEB 27 1998

Attention: Linus N. Igwemezie, Ph.D.
Associate Director, Oncology Products

Dear Dr. Igwemezie:

Please refer to your new drug application dated February 25, 1997, received February 28, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ETOPOPHOS (etoposide phosphate) for INJECTION.

We acknowledge receipt of your submissions dated September 11, 1997 and January 29, 1998. The User Fee goal date for this application is February 28, 1998.

This new drug application provides for pharmacy bulk packaging.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-906. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Amy Chapman, Consumer Safety Officer, at (301) 594-5768.

Sincerely yours,

/S/ 2/27/98

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 20-906
HFD-150/Div. files
HFD-150/Chapman
HFD-150/Barron/Wood
HFD-160/D. Hussong
HFD-710/R. Kelly
HFD-002/ORM (with labeling)
HFD-101/Office Director
HFD-810/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)
HFD-150/Pease
R/D by: Chapman-02-25-98 c:\wpfiles\n20906\ap1.ltr
R/D init by: RWood-02-26-98/JSimmons-02-26-98/Pease-02-25-98
F/T by: Chapman-02-26-98

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-906

CHEMISTRY REVIEW(S)

CHAPMAN

DEC 2 3 1997

DIVISION OF ONCOLOGIC DRUG PRODUCTS/HFD-150
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-906

DATE REVIEWED: 9-DEC-1997
Revised 23 DEC-1997

REVIEW #: Chemistry #1

REVIEWER: Robert P. Barron

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	25-FEB-1997	28-FEB-1997	3-MAR-1997
AMENDMENT	11-SEP-1997	12-SEP-1997	12-SEP-1997

NAME & ADDRESS OF APPLICANT:

Bristol-Myers Squibb
Pharmaceutical Research Institute
P. O. Box 4000
Princeton, NJ 0853-4000

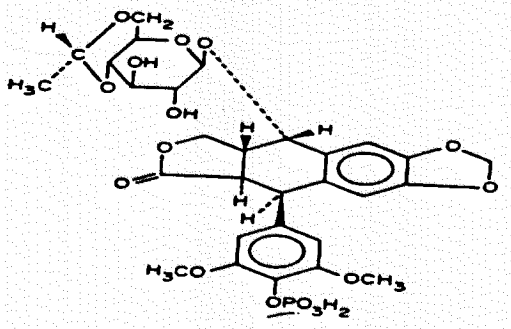
DRUG PRODUCT NAME

Proprietary:	Etopophos for Injection
Established:	Etoposide phosphate
Code Name/#:	
Chem.Type/Ther.Class:	1-S
PHARMACOL. CATEGORY/INDICATION:	antineoplastic agent
DOSAGE FORM:	sterile lyophilized powder
STRENGTHS:	100, 500 and 1000 mg/vial
ROUTE OF ADMINISTRATION:	IV
Rx/OTC:	XX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-[3,5-dimethoxy-4-(phosphonooxy)phenyl]-9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-furo [3', 4':6,7]naphthol[*2,3-d*]-1,3-dioxol-6(5a*H*)-one

$C_{29}H_{33}O_{16}P$ MW = 668.55



SUPPORTING DOCUMENTS:

DMF

RELATED DOCUMENTS (if applicable): NONE

CONSULTS:

1. Request for Statistical Review and Evaluation dated February 25, 1997 for review of stability data on the two new presentations of product. Initial review was completed with deficiencies faxed to the firm on July 17, 1997. The response was received and classed as Amendment BS on September 11, 1997. A review of this amendment was completed and found acceptable.

2. Request for microbiological review of sterility aspects of the pharmacy bulk pack was issued February 25, 1997. The review remains pending as of the date of this review.

REMARKS:

1. The applicant is currently approved to market ETOPOPHOS for Injection, equivalent to 100 mg of etoposide, manufactured and packaged at Bristol Caribbean, Inc., (a subsidiary of Bristol-Myers Squibb Co.) in Mayaguez PR.

2. The NDA was originally submitted as a supplement to approved NDA #20-457 as a "line extension" to the currently approved product line. This supplement was determined to be a pharmacy bulk pack (PBP) requiring the filing of a new NDA with the payment of user fees. The firm was accordingly notified of this decision in the Agency letter of 27-AUG-1997 and the supplement assigned the current NDA number. Due to the time frames involved in this determination, an expedited review clock was established.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is considered approved with a commitment and timeframe to the satisfactorily answer the minor CMC deficiencies

/S/

Robert P. Barron
Review Chemist 12/23/97

/S/ 12-23-97

Rebecca H. Wood, Ph.D.
Chemistry Team Leader, DNDC I

cc:
Org. NDA 20-906
HFD-150/Division File
HFD-150/RPBarron/4-DEC-1997
HFD-150/AChapman/CSO
HFD-150/RHWood, Ph.D.
R/D Init by:_____

filename: N20906a.rev

10. Request for Waiver of Environmental Assessment

Based on 21 CFR §25.24 (c) (2), Bristol-Myers Squibb Company requests waiver of the requirement for an environmental assessment. As a result of manufacturing and packaging two additional presentations of ETOPOPHOS® for Injection at Mayagüez, the drug (etoposide phosphate) will not be administered at higher dosage levels, for a longer duration, or for different indications than those previously in effect; and, at the expected levels of exposure, is not expected to be toxic to organisms in the environment.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF ONCOLOGIC DRUG PRODUCTS / HFD-150

CHEMISTRY TEAM LEADER REVIEW (R.H.WOOD 2-26-98)

NDA # 20-906: ETOPOPHOS FOR INJECTION (ETOPOSIDE PHOSPHATE)

DOCUMENT REVIEWED: CHEMIST'S (R. BARRON) REVIEW #2 (DATED 2-25-98) OF THE 1-29-98 NDA AMENDMENT.

COMMENTS:

The chemist's review dated February 25, 1998 proposes, , a revision of

In a team meeting on February 23, 1998 objections were raised to making revisions in the volumes of diluent, as stated in the package insert, to those values proposed by the review chemist. The objections were due to the fact that the proposed volumes were in fractional units (e.g. 5.25, 25.5) and others that would be difficult to measure out in a syringe and might result in errors.

Most important is the fact that the differences between the volumes of diluent specified in the package insert and those recommended by the review chemist (R. Barron) are quite small and result in insignificant concentration differences of etoposide phosphate, as shown in the table below:

Etoposide fill weight (mg/vial)	Vol. Diluent to add (PI)	Final Conc. (PI) (mg/ml)	Vol. Diluent to add (proposed)	Final Conc.
100mg vial				
105 mg (5% xs)	5.0 ml	21 mg/ml	5.25 ml	20 mg/ml
500 mg vial:				
510 mg (2 % xs)	25.0 ml	20.4 mg/ml	25.5 ml	20 mg/ml
1000 mg vial				
1018.2 mg (2% excess)	50.0 ml	20.4 mg/ml	51.0 ml	20 mg/ml

From the above table it can be seen that the package insert table for the reconstitution of each vial size need not be revised, since the actual resulting drug concentrations (21.0 mg/ml and 20.4 mg/ml) do not differ significantly from the stated value (20 mg/ml).

In summary, the chemist's recommended PI revisions of the reconstituting volumes are not necessary.

/S/

Rebecca H. Wood, Ph.D., Chemistry Team Leader

cc: Orig. NDA 20-906
HFD-150/Division File
HFD-150/RHWood
HFD-150/RBarron
HFD-150/Achapman
HFD-150/DPease
HFD-150/CHoiberg
HFD-150/JSimmons
DISTRICT OFFICE

DIVISION OF ONCOLOGIC DRUG PRODUCTS/HFD-150
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-906

DATE REVIEWED: 13-Feb-1998
Revised: 25-Feb-1998

REVIEW #: Chemistry #2

REVIEWER: Robert P. Barron

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	29-JAN-1998	2-FEB-1998	3-FEB-1998

NAME & ADDRESS OF APPLICANT:

Bristol-Myers Squibb
Pharmaceutical Research Institute
P. O. Box 4000
Princeton, NJ 0853-4000

DRUG PRODUCT NAME

Proprietary: Etopophos for Injection
Established: Etoposide phosphate
Code Name/#:
Chem.Type/Ther.Class: 1-S

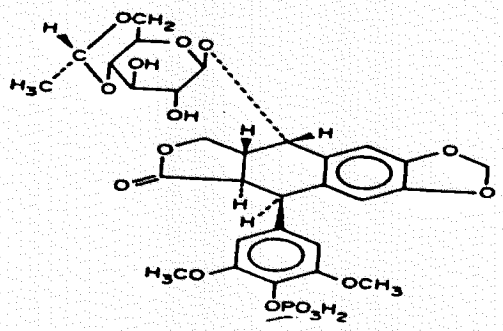
PHARMACOL. CATEGORY/INDICATION: antineoplastic agent

DOSAGE FORM: sterile lyophilized powder
STRENGTHS: 100, 500 and 1000 mg/vial
ROUTE OF ADMINISTRATION: IV
Rx/OTC: XX Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-[3,5-dimethoxy-4-(phosphonooxy)phenyl]-9-[(4,6-O-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-furo [3', 4':6,7]naphthol[2,3-d]-1,3-dioxol-6(5aH)-one

$C_{29}H_{33}O_{16}P$ MW = 668.55



SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS (if applicable): NONE

REMARKS:

Additional input may be necessary for the Drug Product Technical Committee on instructions for reconstitution of lyophilized products marketed as pharmacy bulk packages.

CONCLUSIONS & RECOMMENDATIONS:

The response to Deficiency in the amendment is considered inadequate. The supplement remains approvable until an adequate response is received on the dilution volumes are resolved by the applicant.

/S/

Robert P. Barron
Review Chemist

/S/ 2-26-98

Rebecca H. Wood, Ph.D.
Chemistry Team Leader, DNDC I

cc:
Org. NDA 20-906
HFD-150/Division File
HFD-150/RPBarron/13-FEB-1998
HFD-150/AChapman/CSO
HFD-150/RHWood, Ph.D.
R/D Init by:

filename: N20906bc.rev