DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-768/S-045
NDA 19-557/S-028

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Steven J. Knapp, Executive Director
Life Cycle Management

Dear Mr. Knapp:

Please refer to your supplemental new drug applications dated August 23, 2000, received August 25, 2000, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for VePesid® (etoposide) for injection, 100 mg, 500 mg and 1gram.

These supplemental new drug applications provide for draft labeling for the Geriatric Use subsection.

We completed our review of these applications. These applications are approved, effective on the date of this letter, for use as recommended in the August 23, 2000 labeling text.

However, we have the following comments:

1. Reference items 1-3 should be deleted and the remaining references renumbered. It is the policy of the Office of Drug Evaluation I and the Division of Oncology Drug Products to include only those references which pertain to the handling of antineoplastic agents.

2. We remind you of the previously approved changes in NDA 18-768/S-042 and NDA 19-557/S-024 and that these changes should be incorporated into the package insert.

   a. **PRECAUTIONS** section, **Drug Interactions** subsection, the word "cyclosporine" has been changed to "cyclosporin A".

   b. **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, 4th paragraph:

      "After intravenous administration of ^{3}H-etoposide (70-290 mg/m^2), mean recoveries of radioactivity in the urine range from 42 to 67%, and fecal recoveries range from 0 to 16% of the dose. Less than 50% of an intravenous dose is excreted in the urine as etoposide with mean recoveries of 8 to 35% within 24 hours."

      has been changed to

"After intravenous administration of ^{14}C-etoposide (100-124 mg/m^2), mean recovery of radioactivity in the urine was 56% of the dose at 120 hours, 45% of which was excreted as etoposide: fecal recovery of radioactivity was 44% of the dose at 120 hours."

c. **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, 6th paragraph:

"Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the nonrenal clearance of etoposide. The major urinary metabolite of etoposide in adults and children is the hydroxyacid [4'-demethylepipodophyllic acid-9-(4,6-0-(R)-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, presumably as the transisomer. Glucuronide and/or sulfate conjugates of etoposide are excretedin human urine and represent 5 to 22% of the dose. In addition, 0-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol."

has been changed to

"Biliary excretion of unchanged drug and/or metabolites is an important route of etoposide elimination as fecal recovery of radioactivity is 44% of the intravenous dose. The hydroxy acid metabolite [4'-demethylepipodophyllic acid-9-(4,6-0-(R)-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring, is found in the urine of adults and children. It is also present in human plasma, presumably as the *trans* isomer. Glucuronide and/or sulfate conjugates of etoposide are also excreted in human urine. Only 8% or less of an intravenous dose is excreted in the urine as radiolabeled metabolites of ^{14}C-etoposide. In addition, 0-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol."

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted labeling (package insert submitted August 23, 2000). These revisions are terms of the approval of these applications.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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, these submissions should be designated "FPL for approved supplement NDA 20-457/S-006 AND NDA 20-906/S-002." Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 594-0490.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur

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