CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 18768/S041

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 18768/S041

Trade Name: VePesid Capsules

Generic Name:(etoposide)

Sponsor: Bristol-Myers Squibb Company

Approval Date: April 2, 1999

Indication: Provides for minor editorial changes, and revisions as mandated by the Modernization Act of 1997.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18768/S041

APPROVAL LETTER

~~NDA 18-768/~~
NDA 19-557/ S-023 ~~S-041~~ APR - 2 1999

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

Attention: Joseph S. Sonk, Ph.D.
Director, Marketed Products

Dear Dr. Sonk:

We acknowledge your supplemental new drug applications dated October 28, 1998, received November 3, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VePesid (etoposide) For Injection and VePesid (etoposide) Capsules.

We also acknowledge receipt of the following submissions:

NDA Number	Supplement	Date of Submission	Date Received
18-768		June 30, 1988	July 1, 1988
18-768		June 2, 1994	June 9, 1994
18-768		October 8, 1996	October 15, 1996
18-768		June 27, 1997	July 2, 1997
18-768		July 18, 1997	July 23, 1997
19-557		June 2, 1994	June 9, 1994
19-557		October 8, 1996	October 15, 1996
19-557		July 18, 1997	July 23, 1997

Please note that NDA 18-768/S-041 and NDA 19-557/S-023 supersede the supplements listed above, all of which will be retained with your files.

Supplemental application NDA 18-768, provides for the addition of a statement regarding polysorbate 80 to the package insert which changes the **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections. The supplement also provides for the removal of from the product name as requested in FDA letter dated January 25, 1988. Special Supplements Changes Being Effected NDA 18-768 and NDA 19-557 provide for strengthening the **WARNINGS** and **ADVERSE REACTIONS** sections of the package insert due to recent entries of reactions in the company's safety database and recent publications. Special Supplements Changes Being Effected NDA 18-768 and NDA 19-557 provide for changes made to the **DESCRIPTION, ADVERSE REACTIONS**, and **References** sections and to the carton and vial labels. Additionally, the supplements provide for updated information regarding etoposide which provides consistency with the approved package insert

for Etopophos for Injection. Special Supplements Changes Being Effected NDA 18-768 and NDA 19-557 provide for changes made to the **WARNINGS, ADVERSE REACTIONS, DESCRIPTION, CLINICAL PHARMACOLOGY, INDICATION AND USAGE, PRECAUTIONS, DOSAGE AND ADMINISTRATION**, and **References** sections. These changes are based on events identified from ongoing postmarketing safety surveillance and to maintain consistency with the approved package insert for Etopophos for Injection. Special Supplements Changes Being Effected NDA 18-768/S-041 and NDA 19-557/S-023 provide for additions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the package insert based on events identified from ongoing post-marketing safety surveillance. The new **Drug Interactions** subsection included in the **PRECAUTIONS** section provides consistency with the approved package insert for Etopophos for Injection. These supplements also provide for minor editorial changes, and revisions as mandated by the Modernization Act of 1997.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling submitted on October 28, 1998. Accordingly, these supplemental applications (NDA 18-768/S-041 and NDA 19-557/S-023) are approved effective as of the date of this letter.

Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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/ 4/2/99

Robert Justice, M.D.
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18768/S041

FINAL PRINTED LABELING

Reviewed by: Durant for
4-2-99

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS

Rx only

VePesid®
(etoposide)
For Injection and Capsules

WARNINGS

VePesid (etoposide) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

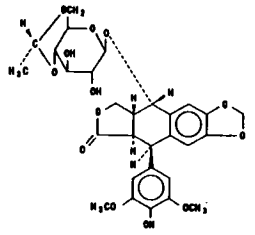
DESCRIPTION

VePesid® (etoposide) (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4'-demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D-glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.58 and a molecular formula of $C_{29}H_{32}O_{13}$.

VePesid may be administered either intravenously or orally. VePesid For Injection is available in 100 mg (5 mL), 150 mg (7.5 mL), 500 mg (25 mL), or 1 gram (50 mL), sterile, multiple dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/Tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen.

VePesid is also available as 50 mg pink capsules. Each liquid filled, soft gelatin capsule contains 50 mg of etoposide in a vehicle consisting of citric acid, glycerin, purified water, and polyethylene glycol 400. The soft gelatin capsules contain gelatin, glycerin, sorbitol, purified water, and parabens (ethyl and propyl) with the following dye system: iron oxide (red) and titanium dioxide; the capsules are printed with edible ink.

The structural formula is:



CLINICAL PHARMACOLOGY

VePesid has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the G_2 portion of the cell cycle in mammalian cells. Two different dose-dependent responses are seen. At high concentrations (10 μg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 μg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of etoposide appears to be the induction of DNA strand breaks by an interaction with DNA topoisomerase II or the formation of free radicals.

Pharmacokinetics

On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m² and, like the terminal elimination half-life, are independent of dose over a range 100-600 mg/m². Over the same dose range, the areas under the plasma concentration vs time curves (AUC) and the maximum plasma concentration (Cmax) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m² for 4 to 5 days.

The mean volumes of distribution at steady state fall in the range of 18 to 29 liters or 7 to 17 L/m² . Etoposide enters the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lower than in extracerebral tumors and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and are similar in primary tumors and normal tissues of the myometrium. *In vitro*, etoposide is highly protein bound (97%) to human plasma proteins. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. In a study determining the effect of other therapeutic agents on the *in vitro* binding of carbon-14 labeled etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and aspirin displaced protein-bound etoposide at concentrations achieved *in vivo*.[1]

Etoposide binding ratio correlates directly with serum albumin in patients with cancer and in normal volunteers. The unbound fraction of etoposide significantly correlated with bilirubin in a population of cancer patients.[2,3] Data have suggested a significant inverse correlation between serum albumin concentration and free fraction of etoposide. (See **PRECAUTIONS** section).

After intravenous administration of ^{3}H-etoposide (70–290 mg/m²), 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.

In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and nonrenal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known.

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 hydroxy acid [4'-demethylepipodophyllic acid-9-(4,6-O-(R)-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, presumably as the **trans** isomer. Glucuronide and/or sulfate conjugates of etoposide are excreted in human urine and represent 5 to 22% of the dose. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

After either intravenous infusion or oral capsule administration, the Cmax and AUC values exhibit marked intra- and inter-subject variability. This results in variability in the estimates of the absolute oral bioavailability of etoposide oral capsules.

Cmax and AUC values for orally administered etoposide capsules consistently fall in the same range as the Cmax and AUC values for an intravenous dose of one-half the size of the oral dose. The overall mean value of oral capsule bioavailability is approximately 50% (range 25–75%). The bioavailability of etoposide capsules appears to be linear up to a dose of at least 250 mg/m².

There is no evidence of a first-pass effect for etoposide. For example, no correlation exists between the absolute oral bioavailability of etoposide capsules and nonrenal clearance. No evidence exists for any other differences in etoposide metabolism and excretion after administration of oral capsules as compared to intravenous infusion.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and a lower volume of distribution at steady state. (See **PRECAUTIONS** section). Use of cisplatin therapy is associated with reduced total body clearance. In children, elevated serum SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.

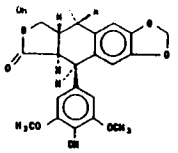
Although some minor differences in pharmacokinetic parameters between age and gender have been observed, these differences were not considered clinically significant.

INDICATION AND USAGE

VePesid is indicated in the management of the following neoplasms:

Refractory Testicular Tumors—VePesid For Injection in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic, and radiotherapeutic therapy.

Adequate data on the use of VePesid Capsules in the treatment of testicular



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INDICATION AND USAGE

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Refractory Testicular Tumors—VePesid For Injection in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic, and radiotherapeutic therapy.

Adequate data on the use of VePesid Capsules in the treatment of testicular cancer are not available.

Small Cell Lung Cancer—VePesid For Injection and/or Capsules in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.

CONTRAINDICATIONS

VePesid is contraindicated in patients who have demonstrated a previous hypersensitivity to etoposide or any component of the formulation.

WARNINGS

Patients being treated with VePesid must be frequently observed for myelosuppression both during and after therapy. Myelosuppression resulting in death has been reported. Dose-limiting bone marrow suppression is the most significant toxicity associated with VePesid therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent cycle of VePesid: platelet count, hemoglobin, white blood cell count, and differential. The occurrence of a platelet count below 50,000/mm^3 or an absolute neutrophil count below 500/mm^3 is an indication to withhold further therapy until the blood counts have sufficiently recovered.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. Higher rates of anaphylactic-like reactions have been reported in children who received infusions at concentrations higher than those recommended. The role that concentration of infusion (or rate of infusion) plays in the development of anaphylactic-like reactions is uncertain. (See **ADVERSE REACTIONS** section.) Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

For parenteral administration, VePesid should be given only by slow intravenous infusion (usually over a 30 to 60 minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection.

Pregnancy

VePesid can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats.

In rats, an intravenous etoposide dose of 0.4 mg/kg/day (about 1/20th of the human dose on a mg/m^2 basis) during organogenesis caused maternal toxicity, embryotoxicity, and teratogenicity (skeletal abnormalities, exencephaly, encephalocele, and anophthalmia); higher doses of 1.2 and 3.6 mg/kg/day (about 1/7th and 1/2 of human dose on a mg/m^2 basis) resulted in 90 and 100% embryonic resorptions. In mice, a single 1.0 mg/kg (1/16th of human dose on a mg/m^2 basis) dose of etoposide administered intraperitoneally on days 6, 7, or 8 of gestation caused embryotoxicity, cranial abnormalities, and major skeletal malformations. An I.P. dose of 1.5 mg/kg (about 1/10th of human dose on a mg/m^2 basis) on day 7 of gestation caused an increase in the incidence of intrauterine death and fetal malformations and a significant decrease in the average fetal body weight.

Women of childbearing potential should be advised to avoid becoming pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be warned of the potential hazard to the fetus.

VePesid should be considered a potential carcinogen in humans. The occurrence of acute leukemia with or without a preleukemic phase has been reported in rare instances in patients treated with etoposide alone or in association with other neoplastic agents. The risk of development of a preleukemic or leukemic syndrome is unclear. Carcinogenicity tests with VePesid have not been conducted in laboratory animals.

PRECAUTIONS

General

In all instances where the use of VePesid is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of VePesid therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

Patients with low serum albumin may be at an increased risk for etoposide associated toxicities.

Laboratory Tests

Periodic complete blood counts should be done during the course of VePesid treatment. They should be performed prior to each cycle of therapy and at appropriate intervals during and after therapy. At least one determination should be done prior to each dose of VePesid.

Renal Impairment

In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance:

Measured Creatinine Clearance	> 50 mL/min	15–50 mL/min
etoposide	100% of dose	75% of dose

Subsequent VePesid dosing should be based on patient tolerance and clinical effect.

Data are not available in patients with creatinine clearances <15 mL/min and further dose reduction should be considered in these patients.

Carcinogenesis, (see WARNINGS section), Mutagenesis, Impairment of Fertility

Etoposide has been shown to be mutagenic in Ames assay.

Treatment of Swiss-Albino mice with 1.5 mg/kg I.P. of VePesid on day 7 of gestation increased the incidence of intrauterine death and fetal malformations as well as significantly decreased the average fetal body weight. Maternal weight gain was not affected.

Irreversible testicular atrophy was present in rats treated with etoposide intravenously for 30 days at 0.5 mg/kg/day (about 1/16th of the human dose on a mg/m^2 basis).

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VePesid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

VePesid for Injection contains polysorbate 80. In premature infants, a life-threatening syndrome consisting of liver and renal failure, pulmonary deterioration, thrombocytopenia, and ascites has been associated with an injectable vitamin E product containing polysorbate 80. Anaphylactic reactions have been reported in pediatric patients. (See **WARNINGS** section.)

Drug Interactions
High-dose cyclosporine resulting in concentrations above 2000 ng/mL administered with oral etoposide has led to an 80% increase in etoposide exposure with a 38% decrease in total body clearance of etoposide compared to etoposide alone.

ADVERSE REACTIONS
The following data on adverse reactions are based on both oral and intravenous administration of VePesid as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Hematologic Toxicity
Myelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Fever and infection have also been reported in patients with neutropenia. Death associated with myelosuppression has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with VePesid in association with other antineoplastic agents. (See **WARNINGS** section.)

Gastrointestinal Toxicity
Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Mild to severe mucositis/esophagitis may occur. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

Hypotension
Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that VePesid be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to cessation of the infusion and administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

Allergic Reactions
Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension have been reported to occur in 0.7% to 2% of patients receiving intravenous VePesid and in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of VePesid.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely.

Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

Alopecia
Reversible alopecia, sometimes progressing to total baldness, was observed in up to 66% of patients.

Other Toxicities
The following adverse reactions have been infrequently reported: abdominal pain, aftertaste, constipation, dysphagia, asthenia, fatigue, malaise, somnolence, transient cortical blindness, optic neuritis, interstitial pneumonitis/pulmonary fibrosis, fever, seizure (occasionally associated with allergic reactions), Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation, and a single report of radiation recall dermatitis.

Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with VePesid. Metabolic acidosis has also been reported in patients receiving higher doses.

Reports of extravasation with swelling have been received postmarketing. Rarely extravasation has been associated with necrosis and venous induration.

The incidences of adverse reactions in the table that follows are derived from multiple data bases from studies in 2,081 patients when VePesid was used either orally or by injection as a single agent.

ADVERSE DRUG EFFECT	PERCENT RANGE OF REPORTED INCIDENCE
Hematologic toxicity	
Leukopenia (less than 1,000 WBC/mm³)	3–17
Leukopenia (less than 4,000 WBC/mm³)	60–91
Thrombocytopenia (less than 50,000 platelets/mm³)	1–20
Thrombocytopenia (less than 100,000 platelets/mm³)	22–41
Anemia	0–33
Gastrointestinal toxicity	
Nausea and vomiting	31–43
Abdominal pain	0–2
Anorexia	10–13
Diarrhea	1–13
Stomatitis	1–6
Hepatic	0–3
Alopecia	8–66
Peripheral neurotoxicity	1–2
Hypotension	1–2
Allergic reaction	1–2

OVERDOSAGE
No proven antidotes have been established for VePesid overdosage.

DOSAGE AND ADMINISTRATION
Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when used with *undiluted* VePesid For Injection.

VePesid For Injection
The usual dose of VePesid For Injection in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m²/day on days 1 through 5 to 100 mg/m²/day on days 1, 3, and 5.

In small cell lung cancer, the VePesid For Injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m²/day for 4 days to 50 mg/m²/day for 5 days.

For recommended dosing adjustments in patients with renal impairment see **PRECAUTIONS** section.

Chemotherapy courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity.

VePesid Capsules
In small cell lung cancer, the recommended dose of VePesid Capsules is two times the IV dose rounded to the nearest 50 mg.

The dosage, by either route, should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Administration Precautions
As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of VePesid. Skin reactions associated with accidental exposure to VePesid may occur. The use of gloves is recommended. If VePesid solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Preparation for Intravenous Administration
VePesid For Injection must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the VePesid solution be administered over a 30- to 60-minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. **VePesid should not be given by rapid intravenous injection.**

Parenteral drug products should be inspected visually for particulate matter and discoloration (see **DESCRIPTION** section) prior to administration whenever solution and container permit.

Stability
Unopened vials of VePesid For Injection are stable for 24 months at room temperature (25° C). Vials diluted as recommended to a concentration of 0.2 to 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25° C) under normal room fluorescent light in both glass and plastic containers.

VePesid Capsules must be stored under refrigeration 2°–8° C (36°–46° F). The capsules are stable for 24 months under such refrigeration conditions.

Reversible alopecia, sometimes progressing to total baldness, was observed in up to 66% of patients.

Other Toxicities

The following adverse reactions have been infrequently reported: abdominal pain, aftertaste, constipation, dysphagia, asthenia, fatigue, malaise, somnolence, transient cortical blindness, optic neuritis, interstitial pneumonitis/pulmonary fibrosis, fever, seizure (occasionally associated with allergic reactions), Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation, and a single report of radiation recall dermatitis.

Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with VePesid. Metabolic acidosis has also been reported in patients receiving higher doses.

Reports of extravasation with swelling have been received postmarketing. Rarely extravasation has been associated with necrosis and venous induration.

The incidences of adverse reactions in the table that follows are derived from multiple data bases from studies in 2,081 patients when VePesid was used either orally or by injection as a single agent.

ADVERSE DRUG EFFECT	PERCENT RANGE OF REPORTED INCIDENCE
Hematologic toxicity	
Leukopenia (less than 1,000 WBC/mm³)	3–17
Leukopenia (less than 4,000 WBC/mm³)	60–91
Thrombocytopenia (less than 50,000 platelets/mm³)	1–20
Thrombocytopenia (less than 100,000 platelets/mm³)	22–41
Anemia	0–33
Gastrointestinal toxicity	
Nausea and vomiting	31–43
Abdominal pain	0–2
Anorexia	10–13
Diarrhea	1–13
Stomatitis	1–6
Hepatic	0–3
Alopecia	8–66
Peripheral neurotoxicity	1–2
Hypotension	1–2
Allergic reaction	1–2

OVERDOSAGE

No proven antidotes have been established for VePesid overdosage.

DOSAGE AND ADMINISTRATION

Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when used with *undiluted* VePesid For Injection.

VePesid For Injection

The usual dose of VePesid For Injection in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m²/day on days 1 through 5 to 100 mg/m²/day on days 1, 3, and 5.

In small cell lung cancer, the VePesid For Injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m²/day for 4 days to 50 mg/m²/day for 5 days.

For recommended dosing adjustments in patients with renal impairment see **PRECAUTIONS** section.

Chemotherapy courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity.

VePesid Capsules

In small cell lung cancer, the recommended dose of VePesid Capsules is two times the IV dose rounded to the nearest 50 mg.

The dosage, by either route, should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Administration Precautions

As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of VePesid. Skin reactions associated with accidental exposure to VePesid may occur. The use of gloves is recommended. If VePesid solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Preparation for Intravenous Administration

VePesid For Injection must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the VePesid solution be administered over a 30- to 60-minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. **VePesid should not be given by rapid intravenous injection.**

Parenteral drug products should be inspected visually for particulate matter and discoloration (see **DESCRIPTION** section) prior to administration whenever solution and container permit.

Stability

Unopened vials of VePesid For Injection are stable for 24 months at room temperature (25° C). Vials diluted as recommended to a concentration of 0.2 to 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25° C) under normal room fluorescent light in both glass and plastic containers.

VePesid Capsules must be stored under refrigeration 2°–8° C (36°–46° F). The capsules are stable for 24 months under such refrigeration conditions.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published [4-10]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

VePesid® (etoposide) For Injection

NDC 0015-3095-20—100 mg/5 mL Sterile, Multiple Dose Vial, 10's

NDC 0015-3084-20—150 mg/7.5 mL Sterile, Multiple Dose Vial

NDC 0015-3061-20—500 mg/25 mL Sterile, Multiple Dose Vial

NDC 0015-3062-20—1 gram/50 mL Sterile, Multiple Dose Vial

VePesid® (etoposide) Capsules

NDC 0015-3091-45—50 mg pink capsules with "BRISTOL 3091" printed in black in blisterpacks of 20 individually labeled blisters, each containing one capsule.

Capsules are to be stored under refrigeration 2°–8° C (36°–46° F).

DO NOT FREEZE.

Dispense in child-resistant containers.

For information on package sizes available, refer to the current price schedule.

References:

1. Gaver RC; Deeb G; "The effect of other drugs on the *in vitro* binding of 14C-etoposide to human serum proteins." *Proc Am Assoc Cancer Res*;30:A2132, 1989.
2. Stewart CF; Pieper JA; Arbuck SG; Evans WE; "Altered protein binding of etoposide in patients with cancer." *Clin Pharmacol Ther;* 45:49-55, 1989.
3. Stewart CF; Arbuck SG; Fleming RA; Evans WE; "Prospective evaluation of a model for predicting etoposide plasma protein binding in cancer patients." *Proc Am Assoc Cancer Res;* 30:A958, 1989.
4. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
5. AMA Council Report. Guidelines for Handling Parenteral Antineo-plastics. *JAMA* 1985;253(11): 1590-1592.
6. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
7. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983;1:426-428.
8. Jones RB, et al; Handling of Chemotherapeutic Agents: A report from the Mount Sinai Medical Center. *CA–A Cancer Journal for Clinicians* 1983;(Sept/Oct) 258-263.
9. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990;47:1033-1049.
10. Controlling occupational exposure to hazardous drugs. (OSHA WORK PRACTICE GUIDELINES). *Am J Health-Syst Pharm* 1996;53:1669-1685.

Capsules:
Manufactured by:
R.P. Scherer GmbH
Eberback/Baden, Germany

Distributed by:
BRISTOL LABORATORIES
Oncology Products
A Bristol-Myers Squibb Co.
Princeton, New Jersey 08543 USA

Injection:
BRISTOL LABORATORIES
Oncology Products
A Bristol-Myers Squibb Co.
Princeton, New Jersey 08543 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18768/S041

ADMINISTRATIVE DOCUMENTS

DIVISION OF ONCOLOGY DRUG PRODUCTS
LABELING REVIEW

NDA: ~~18-768/SLR-041~~
19-557/SLR-023

DEC - 9 1998

SPONSOR: Bristol-Myers Squibb Company

DRUG: VePesid® (etoposide) For Injection
VePesid® (etoposide) Capsules

DATES OF SUBMISSION: **NDA 18-768:** October 28, 1998 (S-041);

NDA 19-557: October 28, 1998 (S-023);

BACKGROUND:

Special Supplements Changes Being Effected NDA 18-768/S-041 and NDA 19-557/ S-023 provide for additions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the package insert. These additions are based on events identified from ongoing post-marketing safety surveillance. The new **Drug Interactions** subsection included in the **PRECAUTIONS** section is the same text the agency required for the ETOPOPHOS package insert (NDA 20-457). This change was made to assure consistency between the labels. These supplements also provide for minor editorial changes, and revisions as mandated by the Modernization Act of 1997.

NDA 18-768 and NDA 19-557 provide for revisions to the **CLINICAL PHARMACOLOGY, Pharmacokinetics** subsection of the package insert based on new findings on the disposition of etoposide. Supportive documentation for the revision is enclosed.

A labeling review was recently completed for the following VePesid supplements:
NDA 18-768:
NDA 19-557:
It was determined that the following letters would issue:

- APPROVAL for Special Supplements Changes Being Effected NDA 18-768 and NDA 19-557 with a note that these supplements supersede Special Supplements Changes Being Effected NDA 18-768 and NDA 19-557/
- APPROVABLE for NDA 18-768/ and NDA 19-557

Comparisons were done between the proposed package inserts for Special Supplements Changes Being Effected NDA 18-768/S-041and NDA 19-557/S-023 and the latest labeling for Special Supplements Changes Being Effected NDA 18-768 and NDA 19-557 NDA 18-768/ and NDA 19-557 were also compared to the latest labeling for Special Supplements Changes Being Effected NDA 18-768 and NDA 19-557 , with the understanding that all changes requested by the Division for NDA 18-768 and NDA 19-557 also be made to

these supplements at the next printing. Differences between the proposed and approved package inserts are noted below.

I. Special Supplements Changes Being Effected NDA 18-768/S-041 and NDA 19-557/S-023

1. The prescription legend has been changed to "**Rx only**".

   Comment: This change is acceptable per the Modernization Act of 1997.

2. **DESCRIPTION** section, 1st sentence, the symbol "®" has been added after the word "VePesid".

   Comment: This editorial change is acceptable.

3. **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, two places:

   "(See **PRECAUTIONS**)." has been changed to "(See **PRECAUTIONS** section)."

   Comment: This editorial change is acceptable.

4. **PRECAUTIONS** section, the following has been added as the last subsection:

   "**Drug Interactions**: High-dose cyclosporine resulting in concentrations above 2000 ng/mL administered with oral etoposide has led to an 80% increase in etoposide exposure with a 38% decrease in total body clearance of etoposide compared to etoposide alone."

   Comment: This has been reviewed and approved by the Medical Officer (see draft CSO labeling review).

5. **ADVERSE REACTIONS** section, **Gastrointestinal Toxicity** subsection, the following has been added as the 4th sentence:

   "Mild to severe mucositis/esophagitis may occur."

   Comment: This has been reviewed and approved by the Medical Officer (see draft CSO labeling review).

6. **ADVERSE REACTIONS** section, **Other Toxicities** subsection:

   "The following adverse reactions have been infrequently reported: abdominal pain, aftertaste, constipation, dysphagia, fever, transient cortical blindness, interstitial pneumonitis/pulmonary fibrosis, optic neuritis, pigmentation, seizure (occasionally associated with allergic reactions), and a single report of radiation recall dermatitis."

has been changed to (the items underlined have been added)

"The following adverse reactions have been infrequently reported: abdominal pain, aftertaste, constipation, dysphagia, asthenia, fatigue, malaise, somnolence, transient cortical blindness, optic neuritis, interstitial pneumonitis/pulmonary fibrosis, fever, seizure (occasionally associated with allergic reactions), Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation, and a single report of radiation recall dermatitis."

Comment: This has been reviewed and approved by the Medical Officer (see draft CSO labeling review).

7. **ADVERSE REACTIONS** section, **Other Toxicities** subsection, the following has been added as the 3rd paragraph:

"Reports of extravasation with swelling have been received post-marketing. Rarely extravasation has been associated with necrosis and venous induration."

Comment: This has been reviewed and approved by the Medical Officer (see draft CSO labeling review).

8. **DOSAGE AND ADMINISTRATION** section, **VePesid For Injection** subsection, 3rd paragraph:

"For recommended dosing adjustments in patients with renal impairment. (See **PRECAUTIONS**)."

has been changed to

"For recommended dosing adjustments in patients with renal impairment see **PRECAUTIONS** section."

Comment: This editorial change is acceptable.

9. **HOW SUPPLIED** section, the symbol "®" has been added after the word "VePesid".

Comment: This editorial change is acceptable.

10. **References** section, the journal names will be italicized.

Comment: This editorial change is acceptable.

II. **NDA 18-768/ and NDA 19-557/**

1. **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."

Comment: This has been reviewed and approved by the Medical Officer and Biopharmaceutist (see draft CSO labeling review).

2. **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 trans isomer. Glucuronide and/or sulfate conjugates of etoposide are excreted in 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."

Comment: This has been reviewed and approved by the Medical Officer and Biopharmaceutist (see draft CSO labeling review).

These supplements will be approved since the reviewing Medical Officer and Biopharmaceutist find the changes outlined in this review acceptable. Acceptability of these changes are indicated by the reviewers' concurrence on the draft CSO labeling review. With these concurrences, an APPROVAL letter will issue for Special Supplements Changes Being Effected NDA 18-768/S-041 and NDA 19-557/S-023 with a note that these supplements supersede Special Supplements Changes Being Effected NDA 18-768/ and NDA 19-557 Additionally, an APPROVABLE letter will issue for NDA 18-768 and NDA 19-557

/S/

Christy Wilson 12-9-98
Technical Information Assistant

concurrence: /S/ 12-9-98

Dotti Pease
Chief Project Management Staff

cc:
Original NDA 18-768/ S-041,
Original NDA 19-557/ S-023,
HFD-150/Div. File
HFD-150/Barron/Wood/McGuinn/Andrews/Cohen/JJohnson/Rahman/Chapman/CWilson
Drafted by: CWilson, 11-30-98
F/T by: CWilson, 12-9-98

HF-2/Medwatch