CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74983

APPROVAL LETTER

ANDA 74-983

SEP 30

Applied Analytical Industries, Inc.
Attention: Jennifer Hutchison
1206 North 23rd Street
Wilmington, NC 28405

Dear Madam:

This is in reference to your abbreviated new drug application dated October 11, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etoposide Injection USP, 20 mg/mL (5 mL, 25 mL and 50 mL multiple dose vials).

Reference is also made to your amendments dated August 13 and September 3, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etoposide Injection USP, 20 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (VePesid® 20 mg/mL of Bristol Laboratories, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

9-25-95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74983

DRAFT FINAL PRINTED LABELING

Fujisawa USA, Inc.

45636/Issued: March 1998

ETOPOSIDE INJECTION

Must be diluted before IV infusion

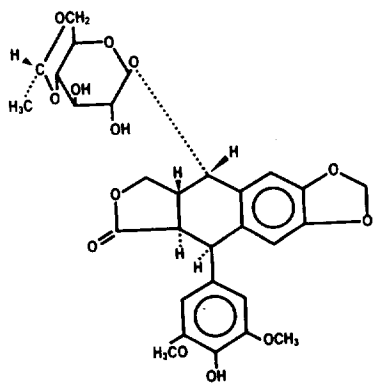
WARNINGS

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:

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-[4,6-0-(R)-ethylidine-ß-D-glucopryano-side]. 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.

Etoposide Injection is available for intravenous use as a 20 mg/mL solution in 100 mg (5 mL), 500 mg (25 mL), or 1 gram (50 mL) sterile, multiple dose vials. The pH of the clear yellow solution is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. The structural formula is:



$C_{29}H_{32}O_{13}$ M.W. 588.56

CLINICAL PHARMACOLOGY:

Etoposide 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 mcg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 mcg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of etoposide appears to be DNA synthesis inhibition.

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/m^2 and, like the terminal elimination half-life, are independent of dose over a range 100 to 600 mg/m^2. Over the same dose range, the areas under the plasma concentration vs time curves (AUC) and the maximum plasma concentration (C_{max}) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m^2 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/m^2. 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]

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.

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/m^2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m^2. 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-(4,6-0-(R)-ethylidene-ß-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.

After intravenous infusion, the C_{max} and AUC values exhibit marked intra- and inter-subject variability.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal 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.

INDICATIONS AND USAGE:

Etoposide Injection is indicated in the management of the following neoplasms:

Refractory Testicular Tumors

Etoposide 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.

Small Cell Lung Cancer

Etoposide Injection and/or Capsules in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.

CONTRAINDICATIONS:

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

WARNINGS:

Patients being treated with etoposide must be frequently observed for myelosuppression both during and after therapy. Dose-limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent dose of etoposide: 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. (See **ADVERSE REACTIONS**.) 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.

Etoposide Injection 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: *Pregnancy Category D.*

Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Etoposide is teratogenic and embryocidal in rats and mice at doses of 1 to 3% of the recommended clinical dose based on body surface area.

In a teratology study in SPF rats, etoposide was administered intravenously at doses of 0.13, 0.4, 1.2, and 3.6 mg/kg/day on days 6 to 15 of gestation. Etoposide caused dose-related maternal toxicity, embryotoxicity, and teratogenicity at dose levels of 0.4 mg/kg/day and higher. Embryonic resorptions were 90 and 100% at the 2 highest dosages. At 0.4 and 1.2 mg/kg, fetal weights were decreased and fetal abnormalities including decreased weight, major skeletal abnormalities, exencephaly, encephalocele, and anophthalmia occurred. Even at the lowest dose tested, 0.13 mg/kg, a significant increase in retarded ossification was observed.

Etoposide administered as a single intraperitoneal injection in Swiss-Albino mice at dosages of 1, 1.5 and 2 mg/kg on days 6, 7, or 8 of gestation caused dose-related embryotoxicity, cranial abnormalities, and major skeletal malformations.

PRECAUTIONS:

General

In all instances where the use of etoposide 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 etoposide 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.

Laboratory Tests

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity tests with etoposide have not been conducted in laboratory animals. Etoposide should be considered a potential carcinogen in humans. The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

The mutagenic and genotoxic potential of etoposide has been established in mammalian cells. Etoposide caused aberrations in chromosome number and structure in embryonic murine cells and human hematopoietic cells; gene mutations in Chinese hamster ovary cells; and DNA damage by strand breakage and DNA-protein cross-links in mouse leukemia cells. Etoposide also caused a dose-related

increase in sister chromatid exchanges in Chinese hamster ovary cells.

Treatment of Swiss-Albino mice with 1.5 mg/kg IP of etoposide 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.

Treatment of pregnant SPF rats with 1.2 mg/kg/day IV of etoposide for 10 days led to a prenatal mortality of 92%, and 50% of the implanting fetuses were abnormal.

Pregnancy: *Pregnancy Category D.*
See **WARNINGS**.

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 etoposide, 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.

Etoposide 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.

ADVERSE REACTIONS:
The following data on adverse reactions are based on both oral and intravenous administration of etoposide 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.

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

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. 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 etoposide 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 etoposide 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 etoposide.

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: aftertaste, fever, pigmentation, abdominal pain, constipation, dysphagia, transient cortical blindness, optic neuritis, 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 etoposide. Metabolic acidosis has also been reported in patients receiving these higher doses.

The incidences of adverse reactions in the table that follows are derived from multiple data bases from studies in 2,081 patients when etoposide 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 etoposide 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* Etoposide Injection.

The usual dose of Etoposide 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 Etoposide 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.

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

Dosage 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 etoposide. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Preparation for Intravenous Administration
Etoposide Injection must be diluted prior to use with either 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, 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 etoposide 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. **Etoposide should not be given by rapid intravenous injection.**

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

Stability
Unopened vials of Etoposide Injection are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 or 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.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-10] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED:
Etoposide Injection is supplied as follows:

Product No.	NDC No.	
100405	0469-1004-05	20 mg/mL in a 5 mL, Sterile Multiple Dose Vial, individually boxed in a package of 10.
100425	0469-1004-25	20 mg/mL in a 25 mL, Sterile Multiple Dose Vial, individually boxed.
100450	0469-1004-50	20 mg/mL in a 50 mL, Sterile Multiple Dose Vial, individually boxed.

Store at controlled room temperature 15° - 30°C (59° - 86°F).
Rx only

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, D.C. 20402.
5. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *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; Safe 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. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs, *Am J. Hosp Pharm.* 1986; 43:1193-1204.

Fujisawa USA, Inc.
Deerfield, IL 60015-2548

45636
Issued: March 1998

7K

(1 g/50 mL)

20 mg/mL

INJECTION

ETOPOSIDE

N 0469-1004-50 100450

Sterile

Each mL contains:
20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. pH 3 to 4.

Usual Dosage: See insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only

ETOPOSIDE

INJECTION

20 mg/mL

(1 g/50 mL)

Must be diluted before IV infusion.

50 mL

Multiple Dose Vial

N 0469-1004-50 8

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Fujisawa USA, Inc.

Fujisawa USA, Inc.

Fujisawa USA, Inc.

62511

Spec. No.: **7C**

N 0469-1004-25 100425

Sterile

Each mL contains: 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. pH 3 to 4.

Usual Dosage: See insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only

ETOPOSIDE

INJECTION

20 mg/mL

(500 mg/25 mL)

Must be diluted before IV infusion.

25 mL

Multiple Dose Vial

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62508

ETOPOSIDE

INJECTION

20 mg/mL

(500 mg/25 mL)

Spec. No.: **7A**

ETOPOSIDE
INJECTION
20 mg/mL
(100 mg/5 mL)

N 0469-1004-05 100405
Sterile
Each mL contains: 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. pH 3 to 4.
Usual Dosage: See insert.

Fujisawa USA, Inc.
Deerfield IL 60015-2548

Store at controlled room temperature 15°-30°C (59°-86°F).
Rx only

Fujisawa USA, Inc.

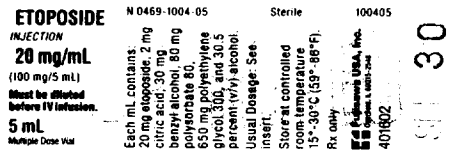
ETOPOSIDE
INJECTION
20 mg/mL
(100 mg/5 mL)
Must be diluted before IV infusion.
5 mL
Multiple Dose Vial

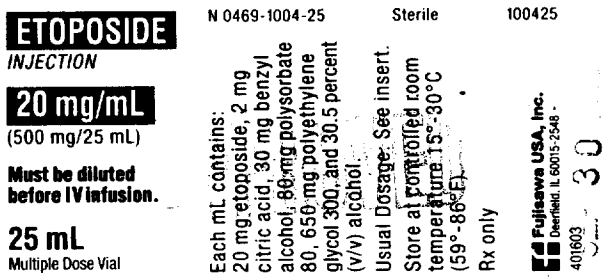
Fujisawa USA, Inc.

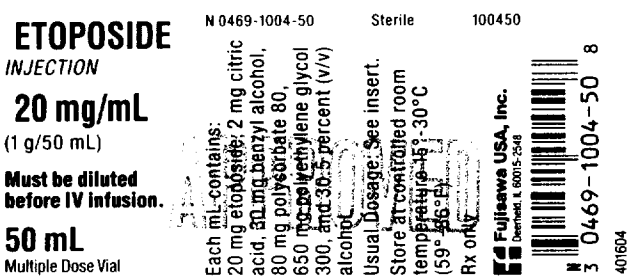
N 0469-1004-05 8

Fujisawa USA, Inc.

62510


ETOPOSIDE
INJECTION
20 mg/mL
(100 mg/5 mL)
Must be diluted before IV infusion.
5 mL
Multiple Dose Vial
N 0469-1004-05
Sterile
100405
Each mL contains: 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol.
Usual Dosage: See insert.
Store at controlled room temperature 15°-30°C (59°-86°F).
Rx only
Fujisawa USA, Inc.
Deerfield, IL 60015-2548
401602


ETOPOSIDE
INJECTION
20 mg/mL
(500 mg/25 mL)
Must be diluted before IV infusion.
25 mL
Multiple Dose Vial
N 0469-1004-25
Sterile
100425
Each mL contains: 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol.
Usual Dosage: See insert.
Store at controlled room temperature 15°-30°C (59°-86°F).
Rx only
Fujisawa USA, Inc.
Deerfield, IL 60015-2548
401603


ETOPOSIDE
INJECTION
20 mg/mL
(1 g/50 mL)
Must be diluted before IV infusion.
50 mL
Multiple Dose Vial
N 0469-1004-50
Sterile
100450
Each mL contains: 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol.
Usual Dosage: See insert.
Store at controlled room temperature 15°-30°C (59°-86°F).
Rx only
Fujisawa USA, Inc.
Deerfield, IL 60015-2548
3 0469-1004-50 8
401604

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74983

CHEMISTRY REVIEW(S)

ANDA NUMBER 74-983

FIRM: Applied Analytical Industries, Inc.

DOSAGE FORM: Injection

STRENGTH: 20 mg/mL

DRUG: Etoposide

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable dated 3/30/98 by Ambrogio.

BIO STUDY: Pursuant to 21 CFR 320.22(b)(1), a waiver of the *in-vivo* bioequivalence study requirement for the drug product is granted. The review is dated February 28, 1997.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

N/A Drug Product is listed in the USP 23, Supplement 7.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Yes

5 mL: 6 cc, 20 mm molded, flint, Type I glass vial, USP

Closure: C1474 6720GC, 6TP gray bromobutyl rubber stopper, 20 mm

Seal: 20 mm aluminum/polypropylene Flip-off lacquer seal

25 mL: 30 cc, 20 mm molded, flint, Type I glass vial, USP

Closure: C1474 6720GC, 6TP gray bromobutyl rubber stopper, 20 mm

Seal: 20 mm aluminum/polypropylene Flip-off lacquer seal

50 mL: 50 cc, 20 mm molded, flint, Type I glass vial, USP

Closure: C1474 6720GC, 6TP gray bromobutyl rubber stopper, 20 mm

Seal: 20 mm aluminum/polypropylene Flip-off lacquer seal

udies:

1. Data (0, 1, 2, 3 months storage at 40° C/75% RH) for lot 0196028D packaged in all three container sizes are satisfactory.

2. Data (0, 3, 6, 9 and 12 months) for lots 0196028D (6 cc vial/5 mL fill), 0196028E (30 cc vial/25 mL fill) and 0196028F (50 cc vial/50 mL fill) stored at 25°C/60% RH are satisfactory.

Data support a tentative 24 month expiry date.

LABELING:

Satisfactory. 5/11/98 review per C. Holquist.

STERILIZATION VALIDATION (IF APPLICABLE):

Satisfactory. 5/8/98 review per J. McVey.

SIZE OF BIO BATCHES - (FIRM'S SOURCE OF NDS O.K.?):

Lot 0196028D (5 mL fill) - vials

Lot 0196028E (25 mL fill) - vials

Lot 0196028F (50 mL fill) - vials

Active ingredient by DMF is acceptable.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA SAME PROCESS):

Same.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? Yes

Proposed production batch sizes:

5 mL fill - L
25 mL fill - L
50 mL fill - L

Review Chemist: Shirley S. Brown/5/13/98
Supervisor: Michael Smela
Date: May, 13, 1998

/S/ 9/22/98

/S/ 9/22/98

1. CHEMISTRY REVIEW NO. 4

2. ANDA #74-983

3. NAME AND ADDRESS OF APPLICANT

Applied Analytical Industries, Inc.
5051 New Centre Drive
Wilmington, North Carolina 28405

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Etoposide

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original submission	October 11, 1996
March 28, 1997	NC (Acknowledgment of receipt of deficiencies in FAX dated March 4, 1997 and commitment to respond)
August 28, 1997	Major Amendment responding to March 4, 1997 FAX amendments.
March 19, 1998	FACSIMILE Amendment responding to FDA's February 17, 1998 FACSIMILE (deficiencies)
May 4, 1998	Labeling Amendment responding to FDA's April 6, 1998 communication
*August 13, 1998	Minor Amendment responding to FDA's June 8, 1998 FACSIMILE deficiency
August 20, 1998	NC regarding August 17, 1998 letter that the applicant sent to the Director of OGD

*September 3, 1998 Telephone Amendment

10. PHARMACOLOGICAL CATEGORY

Chemotherapeutic Agent to treat Refractory Testicular Tumors & Small Cell Lung Cancer

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF

DMF

13. DOSAGE FORM

Injection solution

14. POTENCY

20 mg/mL

(5 mL, 25 mL, 50 mL vials)

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

NA

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER:

/S/

Shirley S. Brown

DATE COMPLETED:

9/22/98

September 4, 1998

Supervisor: Michael Smela, Jr.

M Smela 9/22/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74983

MICROBIOLOGY REVIEW

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #1

November 14, 1996

A. 1. ANDA: **74-983**

APPLICANT: Applied Analytical Industries, Inc. (AAI)
5051 New Centre Drive
Wilmington, North Carolina 28405

MANUFACTURER:

2. PRODUCT NAMES: **Etoposide Injection, USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Sterile, non-aqueous solution contained in multiple dose vials for intravenous administration after dilution; packaged as follows:

5 mL fill in a 6 cc glass vial
25 mL fill in a 30 cc glass vial
50 mL fill in a 50 cc glass vial

4. METHOD(S) OF STERILIZATION:

5. PRINCIPLE INDICATIONS: Management of refractory testicular tumors and small cell lung cancer

6. PHARMACOLOGICAL CATEGORY: Antineoplastic agent

B. 1. DATE OF INITIAL SUBMISSION:

October 11, 1996 (Received by OGD on 11/15/96) - Subject of this Review

2. DATE OF AMENDMENTS: N/A; no amendments containing sterility assurance information were submitted by the time of this review

3. RELATED DOCUMENTS:

DMF

DMF

DMF

DMF

DMF

DMF

DMF

4. ASSIGNED FOR REVIEW: November 12, 1996

C. REMARKS: The applicant referred to DMF Number for sterility assurance validation data which supports processing of the subject drug product. However, to the best of our knowledge DMF was found deficient by James McVey on August 5, 1996 and no response to the Office's letter has been received. The information provided in the submissions [current ANDA & DMF was therefore insufficient to determine if the applicant is taking the necessary steps to ensure the sterility of the subject drug product (Etoposide Injection, USP). For example, enhancement/inhibition validation data was not provided for the LAL Kinetic-Turbidometric test using the subject drug product.

D. CONCLUSIONS: The submissions are therefore not recommended for approval on the basis of sterility assurance. Specific comments are provided

/S/ 11/14/96
Kenneth H. Muhvich, Ph.D.

HFD-620/initialed by RPatel
drafted by: KHMuhvich, 11/15/96

Rec'd 11/15/96

OFFICE OF GENERIC DRUGS
Microbiologists Review #2
May 8, 1998

A. 1. ANDA: **74-983**

APPLICANT: Applied Analytical Industries, Inc.
Attention: Jennifer Hutchinson
5051 New Center Drive
Wilmington, NC 28405

2. PRODUCT NAME: **Etoposide Injection**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 20 mg/mL
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Cytotoxic Agent

B. 1. DATE OF INITIAL SUBMISSION: October 11, 1996 (received October 15, 1996), acknowledged December 27, 1996.
2. DATE OF AMENDMENT: **August 28, 1997- Subject of this review.**
3. RELATED DOCUMENTS: FAXed deficiencies dated March 4, 1997.
4. ASSIGNED FOR REVIEW: April 22, 1998.

C. REMARKS: The first microbiologist's review was done on November 14, 1996 and included original submission data dated October 11, 1996.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance.

/S/
James L. McVey 5/11/98

initialed by R. Patel

cc:
Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey 74983ap2.m

5/12/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74983

BIOEQUIVALENCY REVIEW(S)

FEB 28 1997

Etoposide
Injection solution
20 mg/ml
ANDA # **74-983**
Reviewer: Z.Z. Wahba
File# 74983w.o96

Applied Analytical Industries, In.
Wilmington, NC
Submission Date:
October 11, 1996

REVIEW OF A WAIVER REQUEST

BACKGROUND

1. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Etoposide injection solution, 20 mg/ml (5 ml, 25 mL and 50 mL vials) which contains drug ingredients in the same solvent and concentration as that approved in a new drug application manufactured by Bristol Laboratories under the trade name VePesid® injection 20 mg/ml (NDA #18768).

2. The drug is used in combination therapy with other approved chemotherapeutic agents in management of refractory testicular tumors and small cell lung cancer.

FORMULATION COMPARISON

Ingredients

	(TEST) mg/ml	(REFERENCE) mg/ml
Etoposide	20.0	20.0
Benzyl Alcohol, NF	30.0	30.0
Citric Acid	2.0	2.0
Polyethylene Glycol 300, NF	650.0	650.0
Polysorbate 80 (Tween 80)	80.0	80.0
Dehydrated Alcohol (100% alcohol, 200 proof)	30.5% v/v	30.5% v/v

COMMENTS

1. Both the test (Etoposide for injection solution, 20 mg/ml, manufactured by . for Applied Analytical Industries, Inc.) and reference (VePesid® for injection solution, 20 mg/ml, manufactured by products are identical in formulation.

2. The test drug product is a solution intended solely for intravenous administration.

3. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Applied Analytical Industries, Inc. on its drug product, Etoposide for injection solution, 20 mg/ml falls under 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems Etoposide for injection solution, 20 mg/ml, manufactured by for Applied Analytical Industries, Inc. to be bioequivalent to the reference drug product, Bristol's VePesid®.

The firm should be informed of the recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 2/27/97

Concur: /S/ Date: 2/28/97
Rabindra N. Pathaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA# 74-983, (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-658 (Mhatre, Wahba), Drug File, Division File.
ZZWahba/021297/022797/file#74983w.o96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74983

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

AND Number: **74-983** Date of Submission: **August 28, 1997**

Applicant's Name: **Applied Analytical Industries, Inc.**

Established Name: **Etoposide Injection, 20 mg/mL, 5 mL, 25 mL and 50 mL multiple dose vials**

Labeling Deficiencies:

1. CONTAINER (5 mL, 25 mL and 50 mL)

   Satisfactory in draft.

2. CARTON (1 x 5 mL and 10 x 5 mL, 1 x 25 mL and 1 x 50 mL)

   Satisfactory in draft.

3. INSERT

   a. WARNINGS

      Revise paragraph three to read as follows:

      Etoposide injection should be...

   b. PRECAUTIONS

      i. Impairment of Fertility - Revise the subsection heading to read as follows:

         Carcinogenesis, Mutagenesis, Impairment of Fertility

      ii. Paragraph three, first sentence - "Treatment of" rather than

c. DOSAGE AND ADMINISTRATION

Paragraph three - Dosage should...

[Note: Delete !

Please revise your insert labeling, as instructed above, and submit final printed container labels, carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-983** Date of Submission: **March 19, 1998**

Applicant's Name: **Applied Analytical Industries, Inc.**

Established Name: **Etoposide Injection, 20 mg/mL, 5 mL, 25 mL and 50 mL multiple dose vials**

Labeling Deficiencies:

1. CONTAINER (5 mL, 25 mL and 50 mL)

   Satisfactory in draft.

2. CARTON (1 x 5 mL and 10 x 5 mL, 1 x 25 mL and 1 x 50 mL)

   Satisfactory in draft.

3. INSERT

   Satisfactory in draft.

Please submit final printed container labels, carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-983** Date of Submission: **October 11, 1996**

Applicant's Name: **Applied Analytical Industries, Inc.**

Established Name: **Etoposide Injection, 20 mg/mL, 5 mL, 25 mL and 50 mL multiple dose vials**

Labeling Deficiencies:

1. CONTAINER (5 mL, 25 mL and 50 mL)

   Revise the secondary expression of strength to read "per mL" rather than "per vial". For example:

   (100 mg/5 mL)

2. CARTON (1 x 5 mL and 10 x 5 mL, 1 x 25 mL and 1 x 50 mL)

   See comment under CONTAINER.

3. INSERT

   a. DESCRIPTION

      i. Revise the first sentence of paragraph two to read as follows:

         ...for intravenous use as a 20 mg/mL solution in 100 mg...

      ii. To be in accord with USP 23, revise the molecular weight to read "588.56" rather than

   b. CLINICAL PHARMACOLOGY

      Revise to read "children" rather than throughout this section.

c. INDICATIONS AND USAGE

i. Etoposide injection is indicated...

ii. Small Cell Lung Cancer - Etoposide Injection and/or Capsules in combination...

[Note: Insert "and/or Capsules".]

d. WARNINGS

i. We note your comments on including the second and third sentences of paragraph two. However, this text does not appear in the most recent approved labeling of the reference listed drug's product. Therefore, you must delete these sentences.

ii. Revise paragraph three to read as follows:

Etoposide injection should be given...

e. PRECAUTIONS

Pediatric Use - Delete the last sentence of paragraph two. See comment i. under WARNINGS.

f. ADVERSE REACTIONS

i. Hematologic Toxicity - Delete the last sentence of paragraph one. See comment i. under WARNINGS.

ii. Other Toxicities - Delete that appears prior to "optic neuritis" in paragraph one.

g. DOSAGE AND ADMINISTRATION

Preparation for Intravenous Administration

i. Delete in two places.

ii. Revise the first sentence to read "...concentration of 0.2 to 0.4 mg/mL." rather than

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed container labels, carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74983

CORRESPONDENCE

ANDA 74-983

Applied Analytical Industries, Inc
Attention: Michael Barbush
5051 New Centre Drive
Wilmington NC 28405

MAR 13 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Etoposide Injection Solution 20 mg/mL.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AAI

1206 North 23rd Street
Wilmington, NC 28405
910.763.4536
Telefax: 910.251.6755

NEW CORRESP. NC

noted Standafe 4/3/97

March 28, 1997

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
HFD-630, Document Control Room, 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ANDA No. 74-983
Etoposide injection, 20 mg/mL
5 mL, 25 mL & 50 mL Vials

RE: MAJOR CHEMISTRY DEFICIENCY FACSIMILE DATED MARCH 4, 1997

Dear Dr. Patel:

Reference is made to Applied Analytical Industries, Inc.'s (AAI) pending Abbreviated New Drug Application for Etoposide Injection, 20 mg/mL, filled into 5 mL, 25 mL and 50 mL vials, submitted on October 11, 1996 and found acceptable for filing on October 15, 1996. Reference is also made to your facsimile dated March 4, 1997, detailing deficiencies in this application with regard to chemistry, microbiology and labeling issues.

This letter is to inform the Agency that AAI acknowledges the deficiencies outlined in the March 4 facsimile and is currently in the process of preparing a full response to all of the Agency's queries. We plan to file an amendment to the ANDA with the Office of Generic Drugs in the very near future and we are confident that the information which will be provided in the amendment will resolve all remaining chemistry, microbiology, and labeling deficiencies in ANDA No. 74-983. Should you have any questions related to the attached, please contact the undersigned at (910) 392-1606, ext. 299 or FAX (910) 350-6954.

Sincerely,

Michael Barbush
Regulatory Affairs, AAI

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Nadine 4-2-97

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September 3, 1998

TELEPHONE AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-983
Etoposide Injection, 20 mg/mL
Telephone Amendment

Dear Mr. Sporn:

Applied Analytical Industries (AAI), Inc. is submitting an amendment to our pending Abbreviated New Drug Application for Etoposide Injection, 20 mg/mL. Reference is made to your telephone communication on September 2, 1998.

As requested in a telephone conversation with Ms. Denise Huie, FDA-OGD, the specifications for the inactive ingredient Polysorbate 80, NF have been revised to USP23/NF18, Supplement 8. The revised specifications are attached.

This amendment is being provided to the Office of Generic Drugs in duplicate: oneArchival copy and one Review copy. In addition, AAI certifies that a true copy of this amendment has been forwarded to the FDA District Office in Chicago, Illinois. Please incorporate this information into the application.

If you have any additional questions, please feel free to contact the undersigned at (910) 392-1606, ext. 304 or FAX (910) 350-6954.

Sincerely,

Jennifer Hutchison
Regulatory Affairs Associate

Attachment

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NAI DA 8/31/98

August 20, 1998

AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-983
Etoposide Injection, 20 mg/mL
Amendment – Concerns Regarding FDA Review

Dear Mr. Sporn:

Applied Analytical Industries (AAI), Inc. is submitting an amendment to our pending Abbreviated New Drug Application for Etoposide Injection, 20 mg/mL. Reference is made to our facsimile communication dated August 17, 1998.

Attached please find a copy of a letter sent to the Director of Office of Generic Drugs. AAI wished to bring to Mr. Sporn's attention our concern regarding recent review activities associated with this - as well as another - ANDA.

This amendment is being provided to the Office of Generic Drugs in duplicate: oneArchival copy and one Review copy. Please incorporate this information into the application.

If you have any additional questions, please feel free to contact the undersigned at (910) 392-1606, ext. 304 or FAX (910) 350-6954.

Sincerely,

Jennifer Hutchison
Regulatory Affairs Associate

Attachment

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August 17, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 75 – 154: Midazolam Injection
ANDA 74 – 983: Etoposide Injection

Dear Mr. Sporn:

I am writing to express Applied Analytical Industries' (AAI) concern about the review of two applications for which we are the regulatory agent. AAI is concerned because it seems that the ultimate approval of these applications will be delayed due to the lack of appropriate responsiveness within the Office of Generic Drugs (OGD). The applications in question are ANDA 75-154 for Midazolam Injection and ANDA 74-983 for Etoposide Injection. The particular concerns are outlined in the following paragraphs.

Midazolam

On August 20, 1997, FDA accepted ANDA 75-154 for Midazolam Injection, submitted on behalf of Aesgen, Inc., for filing. Since that date, the only communication has been a labeling deficiency letter dated March 10, 1998 to which AAI responded by amendment on May 26, 1998. Neither AAI nor Aesgen has received any further communication regarding Chemistry or Microbiology deficiencies associated with this ANDA even though the application has been accepted for filing for almost a full year.

This time period far exceeds the FDA review timeframe of 180 days. Repeated telephone calls to the OGD Project Manager since March, 1998, have only elicited the information that the ANDA may be the first generic filing. As such, it is undergoing additional review by the Division Director, Frank Holcombe. An indication that a Major deficiency letter is anticipated has also been communicated to AAI. However, we are told currently this ANDA remains under review by the Division Director.

1206 North 23rd Street, Wilmington, NC 28405 800.575.4AAI or 910.251.6700 Fax: 910.251.6755

We find this review process to be totally unacceptable, particularly if, in fact, this ANDA was the first generic application for Midazolam Injection to be filed. This situation is not due to any inaction or lack of responsiveness on the part of AAI or Aesgen, but the result of OGD's lack of timely communication to us about the pending application.

Etoposide

On December 27, 1996, FDA accepted ANDA #74-983 for Etoposide Injection for filing. During the review process, three deficiency letters have been issued. None of these letters raised any concern about the drug substance DMF referenced in our application. Responses to those three deficiency letters have been filed. The last Chemistry letter was a facsimile issued on February 17, 1998 to which a response was filed within thirty days on March 19, 1998. Following the March 19 amendment, the OGD Project Manager informed AAI that no further issues were outstanding except for the Final Printed Labeling. Once an amendment was filed in May, 1998 with the Final Printed Labeling, AAI believed a final approval to be imminent. However, to our dismay, on June 8, 1998, a Minor deficiency letter was issued regarding the drug substance DMF. We can only assume that during the entire process (covering 18 months) no review of this DMF was conducted. As with the Midazolam ANDA, it seems that an approval for AAI's Etoposide Injection will be delayed due to an error on the part of OGD.

On the whole, AAI's past experience and communication with OGD has been positive; however, the incidents with ANDA 75-154 and ANDA 74-983 have caused us to become seriously concerned regarding the ANDA review process involving these applications. AAI certainly hopes that these situations will be addressed appropriately within the Office of Generic Drugs and will be avoided in the future. If you have any questions, I can be reached at (910) 392 – 1606 x 233. I look forward to your prompt attention to this serious matter.

Sincerely,

APPLIED ANALYTICAL INDUSTRIES, INC.

Lois Q. Semmens
Director, Regulatory Affairs

-17-98
3.1

ORIG AMENDMENT
N/AM

AAI®

August 13, 1998

MINOR AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-983
Etoposide Injection, 20 mg/mL
Minor Amendment

Dear Mr. Sporn:

Applied Analytical Industries (AAI), Inc. is submitting an amendment to our pending Abbreviated New Drug Application for Etoposide Injection, 20 mg/mL. Reference is made to your communication dated June 8, 1998. A copy of this communication is provided for your convenience.

AAI acknowledges that Drug Master File (DMF) for the active ingredient has been found deficient. We have been informed by the holder of the DMF that they have responded to their deficiency letter on August 3, 1998 and confirmed receipt by CDER-OGD on August 7, 1998. A copy of coverletter is provided in **ATTACHMENT 1**.

We would also like to take this opportunity to report the transfer of ownership of Etoposide drug substance DMF from
A copy of the letter of notification and revised DMF Authorization Letter from is provided in **ATTACHMENTS 2** and **3**, respectively.

We are confident that the information provided herein completely and satisfactorily responds to your comments.

This amendment is being provided to the Office of Generic Drugs in duplicate: one Archival copy and one Review copy. Please incorporate this information into the application. AAI certifies that a Field copy has also been forwarded to the FDA District Office in Chicago, Illinois.

1206 North 23rd Street, Wilmington, NC 28405 800.575.4AAI or 910.251.6700 Fax: 910.251.6755

If you have any additional questions, please feel free to contact the undersigned at (910) 392-1606, ext. 304 or FAX (910) 350-6954.

Sincerely,

Jennifer Hutchison
Regulatory Affairs Associate

Attachments

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ORIG AMENDMENT
N/FA

May 4, 1998

TELEPHONE AMENDMENT

F.O.L. satisfactory
C. Hulquist
5/14/98

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-983
Etoposide Injection, 20 mg/mL
Labeling Amendment

Dear Mr. Phillips:

Applied Analytical Industries (AAI), Inc. is submitting a TELEPHONE amendment to our pending Abbreviated New Drug Application for Etoposide Injection, 20 mg/mL. Reference is made to your communication dated April 6, 1998. A copy of this communication is provided for your convenience.

AAI ackowledges that container labels, carton, and insert labeling for the above referenced drug product have been found satisfactory in draft. As requested, AAI is submitting twelve (12) copies of final printed container labels (**ATTACHMENT 1**), cartons (**ATTACHMENT 2**), and insert labeling (**ATTACHMENT 3**).

This amendment is being provided to the Office of Generic Drugs in duplicate: oneArchival copy and one Review copy. Please incorporate this information into the application.

We are confident that the information provided completely and satisfactorily responds to your comments. If you have any additional questions, please feel free to contact the undersigned at (910) 392-1606, ext. 304 or FAX (910) 350-6954.

Sincerely,

Jennifer Hutchison
Regulatory Affairs Associate

Attachments

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AAI®

Draft labeling review
C. Hufgard
4/6/98

March 19, 1998

FACSIMILE AMENDMENT

NEW CORRESP
NC / FAX - [illegible]

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-983
Etoposide Injection, 20 mg/mL
Chemistry and Labeling Amendment

Dear Dr. Patel:

Applied Analytical Industries (AAI), Inc. is submitting a FACSIMILE amendment to our pending Abbreviated New Drug Application for Etoposide Injection, 20 mg/mL. Reference is made to your communication dated February 17, 1998 and received by AAI on February 19, 1998. A copy of this communication is provided for your convenience.

For ease of review, the information has been organized in a comment-response format, i.e., FDA comment followed by AAI's written response for each comment.

CHEMISTRY DEFICIENCIES:

FDA 1. The specifications for the active ingredient must be updated per Supplement 7 to the USP 23.

- ***(a) Delete the Loss on Drying test, if desired.***
- ***(b) Add the test for Water.***
- ***(c) Add the Related compounds test method per the current USP or demonstrate that the proposed ANDA test method is equivalent.***
- ***(d) Related compounds specifications should continue to include limits for all identified and unidentified impurities.***

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Response: The specifications for the active ingredient have been updated per USP 23, Supplement 7. The revised specifications are provided in **ATTACHMENT 1.**

1206 North 23rd Street, Wilmington, NC 28405 800.575.4AAI or 910.251.6700 Fax: 910.251.6755

FDA 2. ***The release specifications for the drug product must be revised to include the USP thin layer chromatography identification test.***

Response: The release specifications for the drug product have been revised to include the USP TLC Identification test. The revised specifications are provided in **ATTACHMENT 2**.

FDA 3. ***The proposed drug product release specification for color of seems high. Please comment.***

Response: The color test is performed by

FDA 4. ***Release and stability testing for Related compounds should be added per the current USP test method or demonstrate that the ANDA test method is equivalent. In any case, your specifications should continue to include limits for all identified and unidentified impurities.***

Response: The release and stability specifications have been revised to include Related Substances testing per the current USP. The revised specifications are provided in **ATTACHMENTS 2 and 3**, respectively.

The AAI Related Substances method and a crossover study to demonstrate equivalency to the USP method are provided in **ATTACHMENT 4**.

FDA 5. ***The stability specifications on page 69 (8/97 amendment) do not include the following tests which were included initially and are included on pages 66-67 for the post-approval protocol:***

> ***Sterility: Sterile (meets USP <71> requirements)***
> ***Bacterial Endotoxins: NMT 2 USP Endotoxin Units/mg of Etoposide***
> ***Antimicrobial Preservative Effectiveness: Meets USP.***
> ***Headspace Analysis: Oxygen – NMT %***

The specifications on pages 66-67 do not include the following tests which are included on page 69:

> ***Color: of the Standards***
> ***Assay – Ethyl Alcohol: % of***

Stability specifications must be clarified and an updated document provided.

Response: We have corrected the stability specifications and post approval protocols so that both documents reflect the same testing, with the exception of Bacterial Endotoxins (MBE). We confirm that the drug product conforms to MBE specifications at the time of initial release. Because we continue to monitor for sterility at later timepoints in the stability studies, we feel further MBE testing past the initial timepoint is unnecessary. The stability specifications reflect this change. The revised specifications and post approval protocols are provided in **ATTACHMENTS 3 and 5,** respectively.

FDA 6. ***Stability data for the studies at 40°C/75% RH are incomplete. Results are not provided for the following tests: sterility, bacterial endotoxins, antimicrobial preservative effectiveness and headspace analysis. These tests are included in the post approval protocol (pages 66-67). Please clarify.***

Response: We inadvertently forgot to include the following test results in our 40°C/75% RH stability studies at the initial (0) time point: Sterility, bacterial endotoxins, antimicrobial preservative effectiveness, GC headspace analysis, Volume in Container, and Specific Gravity. The complete stability tables are provided in **ATTACHMENT 6**.

Additional analysis for the above tests beyond the initial (0) timepoint was deemed unnecessary unless needed to support extending the expiration dating past 24 months. The post approval protocols reflect this necessity. Etoposide for Injection contains two excipients, 30 mg/mL benzyl alcohol and 30.5% ethyl alcohol, 95%, that will deter microbial growth. The benzyl alcohol is at a level that far exceeds levels required to reduce or prevent microbial growth. The reason for the excess benzyl alcohol is believed to be because the innovator wanted the ingredient to serve as both a preservative and a solubilizing aid. Benzyl alcohol is used as a preservative at concentrations up to 2% and is known to be bacteriostatic. Ethyl alcohol is used

as both a solvent and antimicrobial preservative. Ethanol is bactericidal in aqueous mixtures at concentrations between % v/v. Although the etoposide formula does not contain ethyl alcohol at this level, the combination of both ethanol and benzyl alcohol contribute to an environment less likely to stimulate or support microbial growth. A study to support this was conducted at in which 1.6×10^7 organisms Pseudomonas diminuta per mL of Etoposide for Injection were charged and zero growth was observed over a 24 hour time period (see the table provided by in **ATTACHMENT 7**). Based upon this data, concluded that Etoposide for Injection is bactericidal to Pseudomonas diminuta since no viable organisms were recovered.

AAI is monitoring the potency levels for benzyl alcohol and ethyl alcohol, along with the active ingredient etoposide, at release and ongoing stability studies.

FDA 7. ***The post approval protocol (page 65) states that "each fill size" will be tested. Testing of each "size and type of container/closure system" should be indicated to cover possible post approval changes.***

Response: The post approval stability commitment has been revised to state each "size and type of container/closure system". The revised commitment is provided in **ATTACHMENT 8**.

ACKNOWLEDGEMENTS:

1. AAI acknowledges that our initial proposed specification for assay of % is acceptable.

2. AAI acknowledges that USP methods are the officially recognized methodology. Results obtained from these methods shall prevail in event of a dispute.

3. AAI acknowledges that stability testing for Antimicrobial Preservative Effectiveness is only necessary for the first three batches initially and at expiry.

4. AAI acknowledges that our response must also address the labeling deficiencies.

5. AAI acknowledges that the microbiological information is pending review, and any deficiencies will be communicated separately.

6. AAI acknowledges that a clearance from the Office of Compliance for the firms referenced in the ANDA is necessary before the application may be approved.

LABELING:

AAI acknowledges that the Container and Carton labels have been found satisfactory. However, we would like to take this opportunity to incorporate the recent FDA "Rx only" requirement into our proposed labeling. Four copies of draft container and carton labeling are provided in **ATTACHMENT 9**.

The insert has been revised based on your comments in item 3. Again, we have also incorporated the "Rx only" requirement into our proposed insert. Four copies of the draft insert are provided in **ATTACHMENT 10**.

We have provided a side-by-side comparison of our proposed labeling with our last submission (8/28/97) with all differences annotated and explained. The side-by-side comparison is provided in **ATTACHMENT 11**.

This amendment is being provided to the Office of Generic Drugs in duplicate: oneArchival copy and one Review copy. Please incorporate this information into the application. In addition, the Atlanta District Office has instructed AAI to forward a field copy of the amendment to the district which covers the contract manufacturer's site . Therefore, AAI certifies that a Field copy has been forwarded to the FDA District Office in Chicago, Illinois.

We are confident that the information provided completely and satisfactorily responds to your comments. If you have any additional questions, please feel free to contact the undersigned at (910) 392-1606, ext. 304 or FAX (910) 350-6954.

Sincerely,

Jennifer Hutchison
Regulatory Affairs Associate

Attachments

AAI®

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August 28, 1997

MAJOR AMENDMENT

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-983
Etoposide Injection, 20 mg/mL
Chemistry, Labeling and Microbiology Amendment

Dear Dr. Patel:

Applied Analytical Industries (AAI), Inc. is submitting a MAJOR amendment to our pending Abbreviated New Drug Application for Etoposide Injection, 20 mg/mL. Reference is made to your communication dated March 4, 1997. A copy of this communication is provided for your convenience.

For ease of review, the information has been organized in a comment-response format, i.e., FDA comment followed by AAI's written response for each comment.

This amendment is being provided to the Office of Generic Drugs in duplicate: one Archival copy and one Review copy. Please incorporate this information into the application. In addition, the Atlanta District Office has instructed AAI to forward a field copy of the amendment to the district which covers the contract manudacturer's site – Chicago. Therefore, AAI certifies that a Field copy has been forwarded to the FDA District Office in Chicago, Illinois.

We are confident that the information provided completely and satisfactorily responds to your comments. If you have any additional questions, please feel free to contact the undersigned at (910) 392-1606, ext. 304 or FAX (910) 350-6954.

Sincerely,

Jennifer Hutchison
Regulatory Affairs

Encls.

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