# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 75-635

# APPROVAL LETTER

ANDA 75-635

SEP 19 2001

King and Spalding
U.S. Agent for: Genpharm Inc.
Attention: Eugene Pfeifer
1730 Pennsylvania Ave., N.W.
Washington, DC 20006-4706

Dear Sir:

This is in reference to your abbreviated new drug application dated May 10, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Etoposide Capsules USP, 50 mg.

Reference is also made to your amendments dated November 22 and December 16, 1999; and July 30, August 14, and August 24, 2001.

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 Capsules USP, 50 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (VePesid® Capsules, 50 mg, of Bristol Laboratories Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, 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,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

9/19/01

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-635**

# APPROVED DRAFT LABELING

# ETOPOSIDE CAPSULES USP, 50 MG

**Rx only**

**WARNINGS**

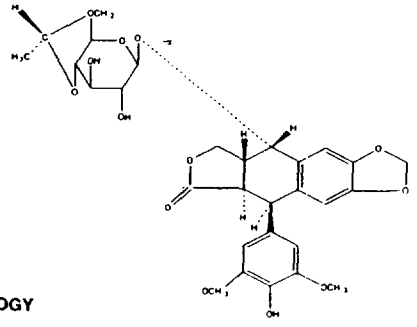
Etoposide should be administered under the supervision of a qualified physician experienced in the use of [illegible] chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

## ESCRIPTION

oposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin ed in the treatment of certain neoplastic diseases. It is 4'-Demethylepipodophyllotoxin 9-,6-*O*-*(R)*-ethylidene-β-D-glucopyranoside]. It is very soluble in methanol and chloroform, ghtly soluble in ethanol, and sparingly soluble in water and ether. It is made more miscible th water by means of organic solvents. It has a molecular weight of 588.56 and a olecular formula of $C_{29}H_{32}O_{13}$.

oposide may be administered either intravenously or orally. Etoposide is available as 50 g dark pink oblong capsules. Each liquid filled, soft gelatin capsule contains 50 mg of oposide in a vehicle consisting of citric acid anhydrous, glycerin, polyethylene glycol and rified water. The soft gelatin capsules contain anidrisorb, gelatin and glycerin with the llowing dye system: iron oxide and titanium dioxide; the capsules are printed with edible ack ink containing hydroxypropyl methylcellulose, propylene glycol and synthetic black on oxide.

ne structural formula is:





## LINICAL PHARMACOLOGY

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

### harmacokinetics

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

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

toposide binding ratio correlates directly with serum albumin in patients with cancer and in rmal volunteers. The unbound fraction of etoposide significantly correlated with bilirubin a population of cancer patients. Data have suggested a significant inverse correlation etween serum albumin concentration and free fraction of etoposide (see **PRECAUTIONS**).

fter intravenous administration of $^3$H-etoposide (70-290 mg/m²), mean recoveries of dioactivity in the urine range from 42 to 67%, and fecal recoveries range from 0 to 16% of e dose. Less than 50% of an intravenous dose is excreted in the urine as etoposide with ean recoveries of 8 to 35% within 24 hours.

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

iliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of n intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most f the nonrenal clearance of etoposide. The major urinary metabolite of etoposide in adults 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**). 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.

## INDICATIONS AND USAGE

Etoposide is indicated in the management of the following neoplasms:

### Small Cell Lung Cancer

Etoposide capsules in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.

## CONTRAINDICATIONS

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

## WARNINGS

Patients being treated with etoposide 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 etoposide therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent cycle of etoposide: platelet count, hemoglobin, white blood cell count, and differential. [illegible] an absolute neutrophil count below 500/mm³ is an indication to withhold further therapy until the blood counts have sufficiently recovered.

### Pregnancy

Etoposide 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/m² 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/m² basis) resulted in 90 and 100% embryonic resorptions. In mice, a single 1.0 mg/kg (1/16th of human dose on a mg/m² 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/m² 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.

Etoposide 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 etoposide have not been conducted in laboratory animals.

## 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 judgement 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.

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

hey should be performed prior to each cycle of therapy and at appropriate intervals during nd after therapy. At least one determination should be done prior to each dose of toposide.

**tenal Impairment**

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

| leasured Creatinine Clearance | >50 mL/min | 15-50 mL/min |
|---|---|---|
| etoposide | 100% of dose | 75% of dose |

ubsequent etoposide dosing should be based on patient tolerance and clinical effect.

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

**arcinogenesis (see WARNINGS), Mutagenesis, Impairment of Fertility**

toposide has been shown to be mutagenic in Ames assay.

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

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

**regnancy**

regnancy "Category D" (see **WARNINGS**).

**ursing Mothers**

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

**ediatric Use**

afety and effectiveness in pediatric patients have not been established.

**rug Interactions**

igh-dose cyclosporine resulting in concentrations above 2000 ng/mL administered with ral etoposide has led to an 80% increase in etoposide exposure with a 38% decrease in otal body clearance of etoposide compared to etoposide alone.

**DVERSE REACTIONS**

he following data on adverse reactions are based on both oral and intravenous dministration of etoposide as a single agent, using several different dose schedules for eatment of a wide variety of malignancies.

**ematologic Toxicity**

yelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7 to 4 days after drug administration and platelet nadirs occurring 9 to 16 days after drug dministration. Bone marrow recovery is usually complete by day 20, and no cumulative oxicity has been reported. Fever and infection have also been reported in patients with eutropenia. Death associated with myelosuppression has been reported.

he occurrence of acute leukemia with or without a preleukemic phase has been reported (see **ARNINGS**).

**astrointestinal Toxicity**

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

**ypotension**

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

**llergic Reactions**

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

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

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

**pecia**

**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 etoposide. Metabolic acidosis has also been reported in patients receiving 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 | PERCE. RANGE OF REPORTED INCIDENCE |
|---|---|
| **Hematologic toxicity** | |
| Leukopenia (less than 1,000 WBC/mm$^3$) | 3-17 |
| Leukopenia (less than 4,000 WBC/mm$^3$) | 60-91 |
| Thrombocytopenia (less than 50,000 platelets/mm$^3$) | 1-20 |
| Thrombocytopenia (less than 100,000 platelets/mm$^3$) | 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**

**Etoposide Capsules**

In small cell lung cancer, the recommended dose of Etoposide Capsules is two times the IV dose rounded to the nearest 50 mg (i.e., Two times 35 mg/m$^2$/day for 4 days to 50 mg/m$^2$/day for 5 days).

The 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.

**Stability**

Etoposide capsules must be stored under refrigeration 2° to 8°C (36° to 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[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**HOW SUPPLIED**

Etoposide Capsules 50 mg are available as follows:

Dark pink oblong capsule with "E50" printed in black ink packaged in blisters of 10 in cartons of 20 (NDC 55567-050-02).

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

DO NOT FREEZE.

Dispense in child-resistant containers.

References:


1. Recommendations for the Safe Handling of Parental Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineo-plastics. JAMA; 253 (11):1590-1592, 1985.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffery, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts, 02115.
4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia; 1:426-428, 1983.
5. Jones RB, et al; Handling of Chemotherapeutic Agents: A report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians; (Sept/Oct) 258-263, 1983.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm; 47:1033-1049, 1990.
7. Controlling occupational exposure to hazardous drugs. (OSHA WORK PRACTICE GUIDELINES). Am J Health-Syst Pharm; 53:1669-1685, 1996.



Manufactured by:
R.P. Scherer Canada Inc.
Windsor, Ontario
Canada N8Y 4S2

Exp.: Lot No.:

**NDC 55567-050-02**

**20 Capsules Unit Dose**

006-431 Rev 800

# ETOPOSIDE

**Capsules USP**

**50 mg**

**Rx only**

APPROVED
SEP 19 2001

Store under refrigeration, 2° to 8°C (36° to 46°F).
Protect from freezing.

GENPHARM

**2 Blister Strips of 10 Capsules**

Manufactured by: R.P. Scherer Canada Inc., Windsor, Canada, N8Y 4S2.

Manufactured for: GENPHARM INC., Toronto, Canada M8Z 2S6 1-800-661-7134

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-635**

## CHEMISTRY REVIEW(S)

# Office of Generic Drugs

## Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.**: No. 5

2. **ANDA #** 75-635

3. **NAME AND ADDRESS OF APPLICANT:**

Genpharm Inc.
Attn: Mrs. Tirtho Uppal
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6
Telephone: (800)661-7134

US Agent: Mr. Eugene Pfiefer
Telephone: (202)737-0500

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s)**: N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Etoposide Capsules USP, 50 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

| | |
|---|---|
| 05/10/99 | Submission of ANDA (received on 05/14/99) |
| 08/03/99 | New name/address for US agent |
| 11/22/99 | Amendment-Bioequivalence |
| 12/06/99 | Major Amendment (CMC) |
| 12/16/99 | Telephone Amendment-Bioequivalence |
| 07/07/00 | Minor Amendment |
| 07/28/00 | NC (withdrawal of request of Minor to fax) |
| 11/14/00 | Minor Amendment |
| 03/12/01* | Minor Amendment |

* Subject of this review.

FDA:

| | |
|---|---|
| 06/10/99 | Acknowledgment (accept for filling: 05/14/99) |
| 06/10/99 | EERs were issued. |

| | |
|---|---|
| 09/28/99 | Bio review was completed with deficiencies. |
| 07/28/99 | Label review (1st round), w/ deficiencies. |
| 11/01/99 | CMC review (1st round), NA-Major |
| 12/23/99 | Label review (2nd round)-ACCEPTABLE |
| 12/23/99 | Bio Review-Acceptable |
| 06/22/00 | CMC review (2nd round), NA-Minor |
| 08/28/00 | CMC review (3rd round), NA-Minor |
| 08/28/00 | Review of EIRs-Acceptable, HFD-48 |
| 12/05/00 | CMC review (4th round), NA-Minor |

10. **PHARMACOLOGICAL CATEGORY**: Chemotherapeutic/Lung Cancer

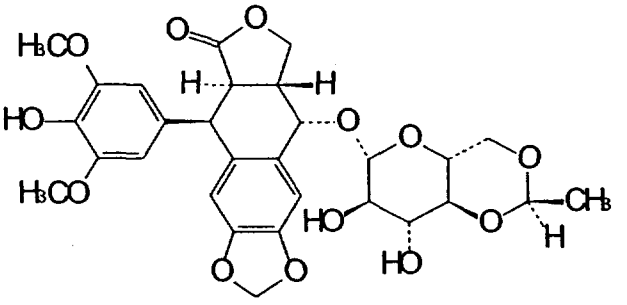
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
VePesid® (Bristol Laboratories)---Innovator
DMF: See DMF check list

13. **DOSAGE FORM**: Capsules

14. **POTENCY**: 50 mg

15. **CHEMICAL NAME AND STRUCTURE**:
Etoposide. $C_{29}H_{32}O_{13}$. 588.56. *33419-42-0*
Furo[3',4':6,7]naphtho[2,3-*d*]-1,3dioxol-6(5a*H*)-one-, 9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-[5α,5aβ,8aα,9β(*R**)]]-.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS:**

- EERs: Acceptable (12/12/00).
- Labeling review: Acceptable (12/23/99)
- Bio-review: Acceptable (12/23/99)
- Micro: N/A
- MV: Not required (USP DS/DP)
- *Minor CMC deficiencies could be found in item 38.*

18. **CONCLUSIONS AND RECOMMENDATIONS:**

Not approvable (**MINOR Amendment-DMF deficiency**).

| 19. **REVIEWER:** | **DATE COMPLETED:** | **DATE REVISED:** |
|---|---|---|
| Bing Cai, Ph.D. | 03/30/01 | |

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Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Ken Rev #5

3/30/01

# Office of Generic Drugs

**Chemistry, Manufacturing and Controls Review**

1. **CHEMIST'S REVIEW NO.**: No. 6

2. **ANDA #** 75-635

3. **NAME AND ADDRESS OF APPLICANT:**

Genpharm Inc.
Attn: Mrs. Tirtho Uppal
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6
Telephone: (800)661-7134

US Agent: Mr. Eugene Pfiefer
Telephone: (202)737-0500

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Etoposide Capsules USP, 50 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

| | |
|---|---|
| 05/10/99 | Submission of ANDA (received on 05/14/99) |
| 04/27/01* | Minor Amendment |
| 05/8/01 | Request for EA exclusion |

* Subject of this review.

FDA:

| | |
|---|---|
| 06/10/99 | Acknowledgment (accept for filling: 05/14/99) |
| 06/10/99 | EERs were issued. |
| 09/28/99 | Bio review was completed with deficiencies. |
| 07/28/99 | Label review (1st round), w/ deficiencies. |
| 11/01/99 | CMC review (1st round), NA-Major |
| 12/23/99 | Label review (2nd round)-ACCEPTABLE |
| 12/23/99 | Bio Review-Acceptable |
| 06/22/00 | CMC review (2nd round), NA-Minor |
| 08/28/00 | CMC review (3rd round), NA-Minor |

| | |
|---|---|
| 08/28/00 | Review of EIRs-Acceptable, HFD-48 |
| 12/05/00 | CMC review (4th round), NA-Minor |
| 04/06/01 | CMC review (5th round), NA-Minor |
| 04/20/01 | TelCon: re EA |

10. **PHARMACOLOGICAL CATEGORY**: Chemotherapeutic/Lung Cancer

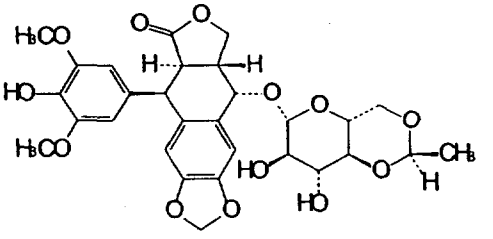
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
VePesid® (Bristol Laboratories)---Innovator
DMF: See DMF check list

13. **DOSAGE FORM**: Capsules

14. **POTENCY**: 50 mg

15. **CHEMICAL NAME AND STRUCTURE**:
Etoposide. $C_{29}H_{32}O_{13}$. 588.56. *33419-42-0*
Furo[3',4':6,7]naphtho[2,3-*d*]-1,3dioxol-6(5a*H*)-one-, 9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-[5α,5aβ,8aα,9β(*R**)]]-.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

- EERs: Acceptable (12/12/00).
- Labeling review: Acceptable (12/23/99)
- Bio-review: Acceptable (12/23/99)
- Micro: N/A

- MV: Not required (USP DS/DP)
- EA: Pending
- NA, Minor: Need EA

18. **CONCLUSIONS AND RECOMMENDATIONS:**

As their DS is manufactured from wild plants (based on the information cited in their reference DMF), their ANDA must contain a complete Environmental Assessment. Their agent was notified of this by telephone on April 20, 2001.

NA, Minor (Pending EA submission/review)

| 19. **REVIEWER:** | **DATE COMPLETED:** | **DATE REVISED:** |
|---|---|---|
| Bing Cai, Ph.D. | 05/18/01 | 05/23/01 |

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Chem Rev 6

5/18/01

5/23/01

# Office of Generic Drugs

## Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.**: No. 4

2. **ANDA #** 75-635

3. **NAME AND ADDRESS OF APPLICANT:**

Genpharm Inc.
Attn: Mrs. Tirtho Uppal
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6
Telephone: (800)661-7134

US Agent: Mr. Eugene Pfiefer
Telephone: (202)737-0500

4. **LEGAL BASIS FOR ANDA SUBMISSION**: 505 j

5. **Supplement(s)**: N/A

6. **PROPRIETARY NAME**: None

7. **NONPROPRIETARY NAME**: Etoposide Capsules USP, 50 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

| | |
|---|---|
| 05/10/99 | Submission of ANDA (received on 05/14/99) |
| 08/03/99 | New name/address for US agent |
| 11/22/99 | Amendment-Bioequivalence |
| 12/06/99 | Major Amendment (CMC) |
| 12/16/99 | Telephone Amendment-Bioequivalence |
| 07/07/00 | Minor Amendment |
| 07/28/00 | NC (withdrawal of request of Minor to fax) |
| *11/14/00 | Minor Amendment |

* Subject of this review.

FDA:

| | |
|---|---|
| 06/10/99 | Acknowledgment (accept for filling: 05/14/99) |
| 06/10/99 | EERs were issued. |
| 09/28/99 | Bio review was completed with deficiencies. |

| | |
|---|---|
| 07/28/99 | Label review (1st round), w/ deficiencies. |
| 11/01/99 | CMC review (1st round), NA-Major |
| 12/23/99 | Label review (2nd round)-ACCEPTABLE |
| 12/23/99 | Bio Review-Acceptable |
| 06/22/00 | CMC review (2nd round), NA-Minor |
| 08/28/00 | CMC review (3rd round), NA-Minor |
| 08/28/00 | Review of EIRs-Acceptable, HFD-48 |

10. **PHARMACOLOGICAL CATEGORY**: Chemotherapeutic/Lung Cancer

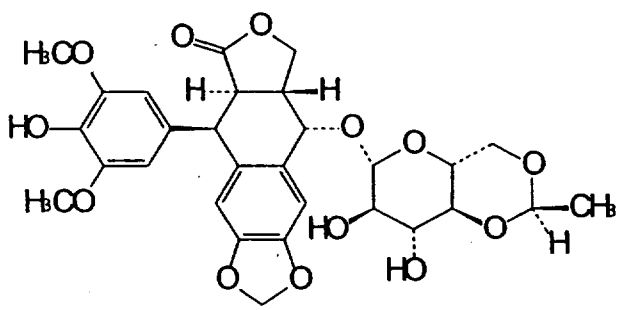
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
VePesid® (Bristol Laboratories)---Innovator
DMF: See DMF check list

13. **DOSAGE FORM**: Capsules

14. **POTENCY**: 50 mg

15. **CHEMICAL NAME AND STRUCTURE**:
Etoposide. $C_{29}H_{32}O_{13}$. 588.56. *33419-42-0*
Furo[3',4':6,7]naphtho[2,3-*d*]-1,3dioxol-6(5a*H*)-one-, 9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-[5α,5aβ,8aα,9β(*R**)]]-.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

- EERs: Pending (11/27/00).
- Labeling review: Acceptable (12/23/99)

- Bio-review: Acceptable (12/23/99)
- Micro: N/A
- MV: Not required (USP DS/DP)
- *Minor CMC deficiencies could be found in item 38.*

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (**MINOR Amendment-DMF deficiency**).

| 19. **REVIEWER:** | **DATE COMPLETED:** | **DATE REVISED:** |
|---|---|---|
| Bing Cai, Ph.D. | 11/27/00 | |

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Chem Review 4

11/27/00

# Office of Generic Drugs

## Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 3

2. **ANDA #:** 75-635

3. **NAME AND ADDRESS OF APPLICANT:**

Genpharm Inc.
Attn: Mrs. Tirtho Uppal
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6
Telephone: (800) 661-7134

US Agent: Dr. John O'Donnell
Telephone: 304-599-2595

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Etoposide Capsules USP, 50 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

| | |
|---|---|
| 05/10/99 | Submission of ANDA (received on 05/14/99) |
| 08/03/99 | New name/address for US agent |
| 11/22/99 | Amendment-Bioequivalence |
| 12/06/99 | Major Amendment (CMC) |
| 12/16/99 | Telephone Amendment-Bioequivalence |
| 07/07/00 | Minor Amendment |
| 07/28/00 | NC (withdrawal of rerquest of Minor to fax). |

FDA:

| | |
|---|---|
| 06/10/99 | Acknowledgment (accept for filling: 05/14/99) |
| 06/10/99 | EERs were issued. |
| 09/28/99 | Bio review was completed with deficiencies. |
| 07/28/99 | Label review (1st round), w/ deficiencies. |
| 11/01/99 | CMC review (1st round), NA-Major |
| 12/23/99 | Label review (2nd round)-ACCEPTABLE |

12/23/99 Bio Review–Acceptable
06/22/00 CMC review (2nd round), NA-Minor

10. **PHARMACOLOGICAL CATEGORY**: Chemotherapeutic/Lung Cancer

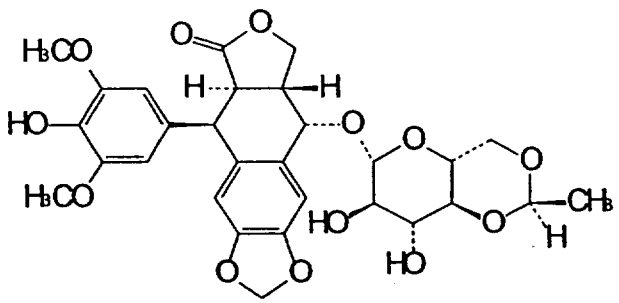
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
VePesid® (Bristol Laboratories)---Innovator
DMF: See DMF check list

13. **DOSAGE FORM**: Capsules

14. **POTENCY**: 50 mg

15. **CHEMICAL NAME AND STRUCTURE**:
Etoposide. $C_{29}H_{32}O_{13}$. 588.56. *33419-42-0*
Furo[3',4':6,7]naphtho[2,3-*d*]-1,3dioxol-6(5a*H*)-one-, 9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-[5α,5aβ,8aα,9β(*R**)]]-.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

- EERs (issued on 06/10/99): Pending.
- Labeling review: Acceptable (12/23/99)
- Bio-review: Acceptable (12/23/99)
- Micro: N/A
- MV: Not required (USP DS/DP)
- *Minor CMC deficiencies could be found in item 38.*

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (**MINOR Amendment**).

| 19. **REVIEWER:** | **DATE COMPLETED:** | **DATE REVISED:** |
|---|---|---|
| Bing Cai, Ph.D. | 07/31/00 | |

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chem Rev # 3

7/13/00

# Office of Generic Drugs

## Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 2

2. **ANDA #** 75-635

3. **NAME AND ADDRESS OF APPLICANT:**

Genpharm Inc.
Attn: Mrs. Tirtho Uppal
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6
Telephone: (800) 661-7134

US Agent: Dr. John O'Donnell
Telephone: 304-599-2595

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Etoposide Capsules USP, 50 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

| | |
|---|---|
| 05/10/99 | Submission of ANDA (received on 05/14/99) |
| 08/03/99 | New name/address for US agent |
| 11/22/99 | Amendment-Bioequivalence |
| 12/06/99 | Major Amendment (CMC) |
| 12/16/99 | Telephone Amendment-Bioequivalence |

FDA:

| | |
|---|---|
| 06/10/99 | Acknowledgment (accept for filling: 05/14/99) |
| 06/10/99 | EERs were issued. |
| 09/28/99 | Bio review was completed with deficiencies. |
| 07/28/99 | Label review (1st round), w/ deficiencies. |
| 11/01/99 | CMC review (1st round), NA-Major |
| 12/23/99 | Label review (2nd round)-ACCEPTABLE |

10. **PHARMACOLOGICAL CATEGORY**: Chemotherapeutic/Lung Cancer

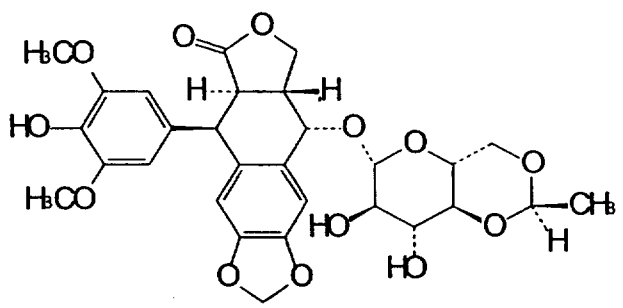
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
VePesid® (Bristol Laboratories)---Innovator
DMF: See DMF check list

13. **DOSAGE FORM**: Capsules

14. **POTENCY**: 50 mg

15. **CHEMICAL NAME AND STRUCTURE**:
Etoposide. $C_{29}H_{32}O_{13}$. 588.56. *33419-42-0*
Furo[3',4':6,7]naphtho[2,3-*d*]-1,3dioxol-6(5a*H*)-one-, 9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-[5α,5aβ,8aα,9β(*R**)]]-.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

- EERs (issued on 06/10/99): Pending.
- Labeling review: Acceptable (12/23/99)
- Bio-review: Pending?
- Micro: N/A
- MV: Not required (USP DS/DP)
- Consultation: Yes (PEG issue, see Section 20)
- *Minor CMC deficiencies could be found in item 38.*

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (**MINOR Amendment**).

| 19. **REVIEWER:** | **DATE COMPLETED:** | **DATE REVISED:** |
|---|---|---|
| Bing Cai, Ph.D. | 05/31/00 | 06/12/00 |

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Chem Review

6/12/00

# Office of Generic Drugs

## Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 7

2. **ANDA #** 75-635

3. **NAME AND ADDRESS OF APPLICANT:**

Genpharm Inc.
Attn: Mrs. Bonnie Southorn
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6
Telephone: (800)661-7134

King & Spalding
U.S. Agent for Genpharm Inc.
US Agent: Mr. Eugene Pfiefer
Telephone: (202)737-0500

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Etoposide Capsules USP, 50 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

| | |
|---|---|
| 05/10/99 | Submission of ANDA (received on 05/14/99) |
| 1999-2000 | See CR#5 |
| 04/27/01 | Minor Amendment |
| 05/08/01 | Request for EA exclusion |
| 06/28/01* | NC |
| 07/30/01* | Minor Amendment (EA) |
| 08/14/01* | NC (EA) |
| 08/24/01* | NC (EA) |

* Subject of this review.

FDA:

| | |
|---|---|
| 06/10/99 | Acknowledgment (accept for filling: 05/14/99) |
| 09/28/99 | Bio review was completed with deficiencies. |

| | |
|---|---|
| 07/28/99 | Labeling review (1st round), w/deficiencies. |
| 11/01/99 | CMC review (1st round), NA-Major |
| 12/23/99 | Label review (2nd round)-ACCEPTABLE |
| 12/23/99 | Bio Review–Acceptable |
| 06/22/00 | CMC review (2nd round), NA-Minor |
| 08/28/00 | CMC review (3rd round), NA-Minor |
| 12/05/00 | CMC review (4th round), NA-Minor |
| 04/06/01 | CMC review (5th round), NA-Minor |
| 05/31/01 | CMC review (6th round), NA-Minor |

10. **PHARMACOLOGICAL CATEGORY**: Chemotherapeutic/Lung Cancer

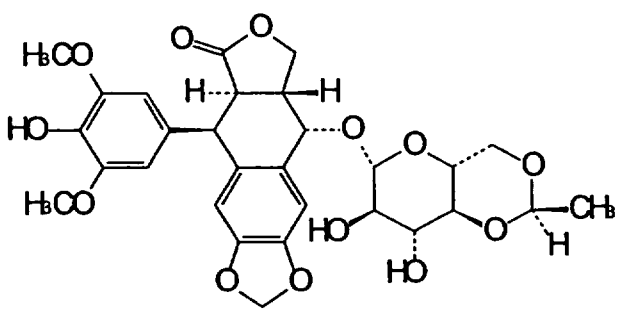
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
VePesid® (Bristol Laboratories)---Innovator
DMF: See DMF check list

13. **DOSAGE FORM**: Capsules

14. **POTENCY**: 50 mg

15. **CHEMICAL NAME AND STRUCTURE:**
Etoposide. $C_{29}H_{32}O_{13}$. 588.56. *33419-42-0*
Furo[3',4':6,7]naphtho[2,3-*d*]-1,3dioxol-6(5a*H*)-one-, 9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-[5α,5aβ,8aα,9β(*R**)]]-.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS:**

- EERs: Acceptable (07/09/01).
- Labeling review: Acceptable (12/23/99)
- Bio-review: Acceptable (12/23/99)
- Micro: N/A
- MV: Not required (USP DS/DP)
- EA: Acceptable per 08/29/01 (per N. Sager's E-mail)
- Chemistry: Adequate

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Approvable

| 19. **REVIEWER:** | **DATE COMPLETED:** | **DATE REVISED:** |
|---|---|---|
| Bing Cai, Ph.D. | 08/29/01 | |

Page(s) 7

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Chem Rev 7
8/29/01

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-635**

## CORRESPONDENCE

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-635**

# BIOEQUIVALENCE

| | |
|---|---|
| Etoposide Soft Gelatin Capsules | Genpharm Inc. |
| 50 mg | Etobicoke, Canada |
| ANDA #75-635 | Submission Date: |
| Reviewer: Moheb H. Makary | November 22, 1999 |
| W 75635SD.N99 | December 16, 1999 |

Review of Two Amendments

I. Objective

The firm has replied to the reviewer's comment made in the review of the May 10, 1999 submission (bioequivalence study on Etoposide Soft Gelatin Capsule, 50 mg and dissolution data).

II. Comment:

The firm was asked to submit data to support the long-term stability of etoposide in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (approximately one year). The firm was also asked to submit the dates of study sample analysis.

The firm submitted the results of the long-term stability experiments for etoposide. The results indicated no signs of deterioration of etoposide in spiked plasma during storage period of 163 days at -25°C.

In the original submission, the integrity of the test results was not affected when the samples were stored for a duration of 177 days at -25°C (Table I).

Additionally, the firm re-analyzed the plasma samples of two subjects from the study to assess the long-term stability of etoposide in human plasma, since the latest long-term stability test did not cover one year storage of the quality control samples at -25°C.

These two subjects (subjects #16 and #25) were re-analyzed on November 2, 1999 against freshly prepared standard curves. The study samples were received on April 15, 1998 and on May 27, 1998 for subject #16 and on September 16, 1998 for subject #25. These samples have been kept at -25°C since. Subject #16 was re-analyzed after 459 days and subject #25 after 410 days. The results indicated that the concentration found in more than 90% of the samples were

within 15% of the original results reported. Therefore, actual samples have been demonstrated to be stable for at least one year after the first analysis and etoposide is stable in human plasma for more than 1 year when stored at -25°C.

The majority of the study samples from the subjects included in the statistical analysis were analyzed within an approximately period of six months following the dosing date (Table II). The long-term stability testing and the integrity testing submitted by the firm support this time period.

Reply to the Comment:

The firm's response to the comment is acceptable.

Recommendations:

1. The bioequivalence study under fasting conditions conducted by Genpharm Inc., on its Etoposide Soft Gelatin Capsules, 50 mg, lot #CS-17, comparing it to Vepesid$^{R}$ Capsules, 50 mg, manufactured by Bristol-Myers Squibb, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Genpharm's Etoposide Soft Gelatin Capsule, 50 mg, is bioequivalent to the reference product, Vepesid$^{R}$ Capsule, 50 mg, manufactured by Bristol-Myers Squibb.

2.. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of acetate buffer pH 4.5 at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

Table I 277



## APPENDIX A10

### Integrity Test

A test was performed at the end of the study to verify the integrity of the study samples. This test consisted in analyzing the original quality controls spiked on May 27, 1998 against the calibration curve spiked on September 2, 1998. This test was performed on November 20, 1998.

| Conc. Spiked (ng/mL) | Quality Controls Spiked on May 27, 1998 | | Quality Controls Spiked on September 2, 1998 | |
|---|---|---|---|---|
| | Conc. Found (ng/mL) | % Rel. Error | Conc. Found (ng/mL) | % Rel. Error |
| 50.0 | 48.5 | -3.0 | 48.8 | -2.4 |
| | 49.0 | -2.0 | 50.2 | 0.4 |
| | 45.4 | -9.2 | 48.0 | -4.0 |
| 1500.0 | 1308.6 | -12.8 | 1306.6 | -12.9 |
| | 1304.4 | -13.0 | 1329.7 | -11.4 |
| | 1309.7 | -12.7 | 1323.4 | -11.8 |
| 3500.0 | 3105.9 | -11.3 | 3487.6 | -0.4 |
| | 3180.5 | -9.1 | 3490.8 | -0.3 |
| | 3112.1 | -11.1 | 3463.8 | -1.0 |

Acceptable % relative errors (within ± 15 %) indicate that the integrity of study samples should not be affected when they are stored for a duration of 177 days at - 25°C ± 10°C in polypropylene tubes. This test was only used as an indication and an additional long term stability will be performed (stability available is 100 days at - 25°C).

Reference: CES32

Table II

Project no./Code: GP616/CES

**Dates of Study Samples Analysis for Etoposide in Human Plasma**

For first analysis, all subject's samples were analyzed in one HPLC run of 10 hours average duration.

| Subject No. | Period No | Type of Analysis | Sampling times (Hours) | First Analysis Date | Last Analysis Date |
|---|---|---|---|---|---|
| | 1 | First Analysis | All | June 1, 1998 | --- |
| | 2 | First Analysis | All | June 1, 1998 | --- |
| | 1 | Repeats | 1.667,4 | --- | August 14, 1998 |
| | 2 | Repeats | 0.334, 0.5 | --- | August 14, 1998 |
| | 2 | Repeat | 12 | --- | September 3, 1998 |
| | 1 | First Analysis | All | June 2, 1998 | June 2, 1998 |
| | 2 | First Analysis | All | June 2, 1998 | June 2, 1998 |
| | 1 | First Analysis | All | June 2, 1998 | --- |
| | 2 | First Analysis | All | June 2, 1998 | --- |
| | 1 | Repeat | 4 | --- | August 14, 1998 |
| | 2 | Repeat | 6 | --- | August 14, 1998 |
| | 1 | First Analysis | All | June 3, 1998 | June 3, 1998 |
| | 2 | First Analysis | All | June 3, 1998 | June 3, 1998 |
| | 1 | First Analysis | All | June 3, 1998 | --- |
| | 2 | First Analysis | All | June 3, 1998 | --- |
| | 1 | Repeat | 48 | --- | September 3, 1998 |
| | 2 | Repeat | 48 | --- | September 3, 1998 |
| | 1 | First Analysis | All | June 8, 1998 | --- |
| | 2 | First Analysis | All | June 8, 1998 | --- |
| | 1 | Repeats | 0.167,10 | --- | August 14, 1998 |
| | 2 | Repeats | 0,0.167,0.25,1,1.334,1.667,2,3 | --- | August 14, 1998 |
| | 2 | Repeats | 0.334,0.5,0.75,2.5,4 | --- | August 18, 1998 |
| | 1 | First Analysis | All | June 8, 1998 | --- |
| | 2 | First Analysis | All | June 8, 1998 | --- |
| | 1 | Repeats | 0.5,0.75,36 | --- | August 14, 1998 |
| | 1 | Repeat | 1.667 | --- | August 18, 1998 |
| | 2 | Repeat | 1.667 | --- | August 14, 1998 |
| | 1 | First Analysis | All | June 9, 1998 | --- |
| | 2 | First Analysis | All | June 9, 1998 | --- |
| | 2 | Repeat | 48 | --- | September 3, 1998 |
| | 1 | First Analysis | All | June 9, 1998 | --- |
| | 2 | First Analysis | All | June 9, 1998 | --- |
| | 1 | Repeats | 0.167,0.25,24,36,48 | --- | August 14, 1998 |
| | 2 | Repeats | 0,0.25,0.334,24,36,48 | --- | August 14, 1998 |
| | 1 | First Analysis | All | June 10, 1998 | --- |
| | 2 | First Analysis | All | June 10, 1998 | --- |
| | 1 | Repeats | All | --- | November 13, 1998 |
| | 2 | Repeats | All | --- | November 13, 1998 |
| | 1 | First Analysis | All | June 10, 1998 | --- |
| | 2 | First Analysis | All | June 10, 1998 | --- |
| | 1 | Repeats | All | --- | November 18, 1998 |
| | 2 | Repeats | All | --- | November 18, 1998 |
| | 1 | First Analysis | All | June 11, 1998 | --- |
| | 2 | First Analysis | All | June 11, 1998 | --- |
| | 1 | Repeat | 0.75 | --- | August 18, 1998 |
| | 1 | Repeat | 48 | --- | November 13, 1998 |
| | 2 | Repeat | 1 | --- | August 18, 1998 |
| | 2 | Repeat | 48 | --- | September 3, 1998 |

Project no./Code: GP616/CES

**Dates of Study Samples Analysis for Etoposide in Human Plasma**

| Subject No | Period No | Type of Analysis | Sampling times (Hours) | First Analysis Date | Last Analysis Date |
|---|---|---|---|---|---|
| | 1 | First Analysis | All | June 11, 1998 | June 11, 1998 |
| | 2 | First Analysis | All | June 11, 1998 | June 11, 1998 |
| | 1,2 | First Analysis | The results were unacceptable according to SOP. | | |
| | 1 | Second Analysis | All | June 20, 1998 | --- |
| | 2 | Second Analysis | All | June 20, 1998 | --- |
| | 1 | Repeats | 1,1.334,1.667,2 | --- | August 18, 1998 |
| | 2 | Repeats | 0.75,1,1.334 | --- | August 18, 1998 |
| | 1,2 | First Analysis | The results were unacceptable according to SOP. | | |
| | 1 | Second Analysis | All | July 30, 1998 | --- |
| | 2 | Second Analysis | All | July 30, 1998 | --- |
| | 1 | Repeat | 48 | --- | September 3, 1998 |
| | 2 | Repeat | 0.75 | --- | August 18, 1998 |
| | 2 | Repeat | 48 | --- | September 3, 1998 |
| | 1,2 | First Analysis | The results were unacceptable according to SOP. | | |
| | 1 | Second Analysis | All | July 31, 1998 | --- |
| | 2 | Second Analysis | All | July 31, 1998 | --- |
| | 2 | Repeat | 48 | --- | August 14, 1998 |
| | 1,2 | First Analysis | The results were unacceptable according to SOP. | | |
| | 1 | Second Analysis | All | July 31, 1998 | July 31, 1998 |
| | 2 | Second Analysis | All | July 31, 1998 | July 31, 1998 |
| | 1 | First Analysis | All | June 19, 1998 | --- |
| | 2 | First Analysis | All | June 19, 1998 | --- |
| | 1 | Repeat | 0 | --- | August 14, 1998 |
| | 2 | Repeats | 0,0.167 | --- | August 14, 1998 |
| | 1 | First Analysis | All | June 20, 1998 | June 20, 1998 |
| | 2 | First Analysis | All | June 20, 1998 | June 20, 1998 |
| | 1 | First Analysis | All | September 17, 1998 | --- |
| | 2 | First Analysis | All | September 17, 1998 | --- |
| | 1 | Repeat | 0.5 | --- | September 23, 1998 |
| | 1 | First Analysis | All | September 17, 1998 | --- |
| | 2 | First Analysis | All | September 17, 1998 | --- |
| | 1 | Repeat | 36 | --- | September 23, 1998 |
| | 1 | First Analysis | All | September 17, 1998 | --- |
| | 2 | First Analysis | All | September 17, 1998 | --- |
| | 2 | Repeat | 48 | --- | September 30, 1998 |
| | 1 | First Analysis | All | September 18, 1998 | --- |
| | 2 | First Analysis | All | September 18, 1998 | --- |
| | 1 | Repeat | 0,25 | --- | September 23, 1998 |
| | 2 | Repeats | 1,334,10,24,36 | --- | September 23, 1998 |
| | 1 | First Analysis | All | September 18, 1998 | --- |
| | 2 | First Analysis | All | September 18, 1998 | --- |
| | 1 | Repeat | 48 | --- | September 23, 1998 |
| | 2 | Repeat | 48 | --- | September 23, 1998 |
| | 1 | First Analysis | All | September 18, 1998 | --- |
| | 2 | First Analysis | All | September 18, 1998 | --- |
| | 1 | Repeats | 0,334,48 | --- | September 23, 1998 |
| | 1 | *Stability Repeat* | *All* | *November 2, 1999* | *November 2, 1999* |
| | 2 | *Stability Repeat"* | *All* | *November 2, 1999* | *November 2, 1999* |
| | 1 | *Stability Repeat"* | *All* | *November 2, 1999* | *November 2, 1999* |
| | 2 | *Stability Repeat"* | *All* | *November 2, 1999* | *November 2, 1999* |

Note:

The first analysis date - day on which the subject samples f run was started.

The last analysis date - day on which the repeat analysis of a subject's particular samples were run.

Further explanation on dates when subject's samples were analyzed

Recruiting of volunteers with remission from various cancers took longer than expected. The difficulty in recruiting subjects had extended the study dosing from October 1997 for subject no. 1 to March 1998 for subject no. 20.

For the subject nos. 1 to 20 (except No 18) for periods 1 and 2, the first and second aliquots were received on April 15, 1998 and May 27, 1998, respectively. For the subject nos. 21, 22, 24, 25, 26, and 27 for periods 1 and 2, the first and second aliquots were received on September 10, 1998 and September 16, 1998, respectively.

The existing stability data on etoposide in plasma only extended to 100 days, and as a consequence, it was decided to analyze the samples of subject nos. 1 to 20 (except no. 18). The blinding was maintained, and no interim statistical analysis was conducted. The last six subjects were later recruited and dosed, and their samples were analyzed (still blinded) in the last two weeks of September 1998 (17-30).

Samples of subject no. 16 and 25 were re-analyzed on November 2, 1999, and the results demonstrated the stability of etoposide in plasma stored at -25°C for at least 405 days.

GENPHARM

NDA ORIG AMENDMENT AB

December 16, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

***TELEPHONE***
***BIOEQUIVALENCE***
***AMENDMENT***

**RE: ANDA No. 75-635**
**ETOPOSIDE CAPSULES, USP**
**50 mg**

Dear Sir/Madam:

This ***BIOEQUIVALENCE TELEPHONE AMENDMENT*** to our ANDA # 75-635 is in response to the telephone request on Dec 6/99 by Patricia Wade, FDA Project Manager to Frank R. Sisto, Mylan Pharmaceuticals Inc.

For the reviewers' convenience, we have formatted our amendment such that each comment made by the FDA has been restated, followed by our response to the comments.

We have enclosed one (1) archival and one (1) pharmacokinetic review copy of the application in accordance with 21 CFR § 314.96.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm directly at 1-800-661-7134 or you may contact our US agent, Dr. John O'Donnell at (304) 599-2595.

Thank you for your prompt handling of this submission.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 21 1999
OGD

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

Dec 16/99
(date)

Etoposide Soft Gelatin Capsules
50 mg
ANDA #75-635
Reviewer: Moheb H. Makary
W 75635SD.599

Genpharm Inc.
Etobicoke, Canada
Submission Date:
May 10, 1999

Review of a Bioequivalence Study and Dissolution Data

I. Objective:

Genpharm, Inc., has submitted an *in vivo* bioequivalence study (single-dose fasting) comparing its test product Etoposide Soft Gelatin Capsules, 50 mg, to the reference listed product, Bristol-Myers Squibb's Vepesid$^R$ Capsules, 50 mg. The firm also submitted comparative *in vitro* dissolution data.

II. Background:

Etoposide, also known as VP-16, is a semi-synthetic derivative of podophyllotoxin used in the treatment of certain neoplasms. Etoposide occurs as a white to yellow-brown crystalline powder and is sparingly soluble in water (0.03 mg/mL) and slightly soluble in alcohol (0.76 mg/mL).

It can be administered intravenously or orally and the doses are generally calculated by body surface area. Etoposide is indicated in the combination treatment of refractory testicular tumors and small cell lung cancer (SCLC). It is also used for treating some Kaposi sarcomas in AIDS patients and some mammary tumors. This drug is cell cycle dependent and acts apparently in the $G_2$ phase. It inhibits cells to undergo prophase at low concentrations and induces lysis of cells entering mitosis at high concentrations. These two responses seem to be dose dependent.

The pharmacokinetics of intravenous etoposide are best described by a biphasic disposition with a terminal half-life ranging between 4-11 hours. The total body clearance of etoposide is independent of the dose in the 100-600 mg/m$^2$ range, suggesting linear kinetics in that range. This is further supported by the dose proportional increases of AUC and Cmax. This linearity is shared by oral etoposide up to at least 250 mg/m$^2$. The absolute bioavailability of the soft gel capsules is approximately

50%, resulting in oral doses being twice the intravenous doses.

The metabolic fate of etoposide has not been completely determined. Etoposide appears to be metabolized principally at the D ring to produce hydroxy acid; this metabolite appears to be pharmacologically inactive.

The disposition of etoposide is both by renal and non-renal routes, the latter being under the form of metabolites. There is no evidence of a first-pass effect for oral etoposide but there is a large intra- and inter-subject variability in the AUC and Cmax values, both after oral and IV administration.

Etoposide is commercially available as an injectable solution (100 mg/5 mL) and soft gelatin capsules for oral administration (50 mg/capsule) from Bristol-Myers Squibb.

III. Study# GEN-501 For Single-Dose Fasting Bioequivalence Of Genpharm's Etoposide Soft Gelatin Capsules, 50 mg

Clinical site: ClinSites/LeeCoast Research
Ft Myers, FL

Analytical site:

Study dates:

Group I (subjects 1-6)
Period I 10/20/1997
Period II 10/27/1997

Group II (subjects 7-11)
Period I 12/7/1997
Period II 12/14/1997

Group III (subjects 12-16)
Period I 1/18/1998
Period II 1/25/1998

Group IV (subjects 17-20)*
Period I 3/15/1998
Period II 3/22/1998

Group V (subjects 21-24)*
Period I 8/18/1998
Period II 8/25/1998

Group VI (subjects 25-27)
Period I 8/24/1998
Period II 8/31/1998

* Subjects 18 and 23 were not enrolled in the study.

Sample analysis: The analysis was performed over the period of June 1, 1998 to November 18, 1998.

Study design: This was an open label, single-dose, randomized, two-treatment, two-period, two-sequence crossover study using fasted men and women.

Subjects: The subjects recruited were former cancer patients who had been previously treated with an alkylating agent and were in remission at the time of dosing. Due to the difficulty in recruiting this type of subject, dosing took place in six separate clinical groups. Twenty-five subjects completed both phases of drug administration. Although there was difficulty in subject recruitment, the study was terminated strictly as a result of the expiration of the reference product (August 1998).

Selection criteria: Selection criteria listed in Vol. 1.2, page 0497.

Dose and treatment: All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:

Test Product: a) 1x50 mg Etoposide Capsule (Genpharm), lot #CS-17, batch size Capsules (actual yield capsules), Exp. 10/98, potency 98.4%, content uniformity 98.4%.

Reference Product: b) 1x50 mg Vepesid$^{R}$ Capsule (Bristol-Myers Squibb), lot #WG017, Exp. 8/1998, potency 98.0%.

| | |
|---|---|
| Washout period: | One week |
| Food and fluid intake: | Subjects fasted overnight for at least 10 hours before dosing and for 4 hours thereafter. Water was not permitted for one hour before until one hour after dosing, but was allowed at all other times. Standard meals were provided at approximately 4 and 9 hours after drug administration, and at appropriate times thereafter. |

Assay Methodology

An method for determination of etoposide in human plasma was performed.

| | |
|---|---|
| Sensitivity: | The limit of quantitation (LOQ) was 20 ng/mL for etoposide. |
| Linearity: | Linear responses were between 20 to 5000 ng/mL for etoposide. |
| Assay specificity: | Assay of blank samples revealed no interference with the analyte or the internal standard. |
| Recovery: | Overall recovery was 100.3% for etoposide. |
| Precision: | Interday variability was assessed with replicate control samples analyzed on separate days. The between-day coefficients of variation ranged from 8.6% to 11.9% for etoposide. Intraday precision was calculated using six spiked samples at each of three concentration levels (50.0, 1500.0, and 3500.0 ng/mL) for etoposide. The coefficients of variation ranged from 1.7% to 2.8% for etoposide. |
| Stability: | Freeze/Thaw: Etoposide was spiked into plasma at concentration levels of 50.0, 1500.0 and 3500.0 ng/mL. Frozen plasma samples were found to be stable for |

etoposide through four freeze-thaw cycles.

Long Term Frozen Stability:

Stability was assessed by the analysis of spiked plasma samples with etoposide at 50.0 ng/mL, 1500.0 ng/mL and 3500.0 ng/mL. These samples were prepared and frozen at -20°C and -80°C. The samples were thawed and assayed. Assay results demonstrated the stability of etoposide in frozen plasma for 100 days when stored at -20°C and -80°C. The analytical validation stated that long-term (one year) stability will be completed sometime in 1999.

Blood samples: Blood samples were collected at: 0 (prior to dosing), 0.167, 0.25, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing. Plasma was extracted and stored frozen pending assay.

Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for etoposide. An analysis of variance (ANOVA) was applied to log-transformed and non-transformed bioequivalence parameters to determine any statistically significant ($p<0.05$) differences between the drug formulations. The 90% confidence intervals were calculated for each bioequivalence parameter.

IV. In Vivo Results:

Twenty-five (25) male and female subjects were entered and completed the study. All adverse events were mild or moderate. No serious adverse events occurred during the study (Vol 1.2, page 0489).

The firm reported that immediately prior to period II dosing of group 1 (subjects 1-6 on 10/27/1997), it was noted by ClinSites/LeeCoast staff that the high/low thermometer inside the refrigerator storing the test and

reference samples of etoposide had registered a low temperature of -7 degree Celsius. A satisfactory temperature had been noted 24 hours earlier. The test and reference drugs therefore had been exposed to temperature storage conditions below that recommended by the innovator company (2 to 8 $^{o}$C or 36-46 $^{o}$F, PDR 1999) for up to 24 hours. The precise exposure time is unknown. Dosing of period II for group 1 was carried out, as at the time, the temperature drop could not be confirmed. As the *in vivo* effect of the freezing temperatures on the two formulations cannot be predicated, the data from the six subjects have been excluded from the final statistical analysis. As the a six subjects had completed both periods of dosing, their plasma samples were analyzed and for completeness and informational purpose only, the data from these subjects have been included in Appendix S-1).

The plasma concentrations and pharmacokinetic parameters for are summarized in Table I.

Table I

Mean Etoposide Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x50 mg Etoposide Capsule Under Fasting Conditions
(N=19)

| Time hr | Genpharm Test Product Lot # CS-17 ng/mL (CV%) | Bristol-Myers Squibb Reference Product Lot # WG017 ng/mL (CV%) |
|---|---|---|
| 0 | 0.00 | 0.00 |
| 0.167 | 0.00 | 4.30 (318) |
| 0.25 | 37.92 (241) | 267.03 (256) |
| 0.33 | 371.93 (177) | 501.56 (164) |
| 0.5 | 1543.17 ( 89) | 1782.50 ( 81) |
| 0.75 | 2703.61 ( 58) | 2926.46 ( 41) |
| 1 | 2889.45 ( 46) | 3068.64 ( 37) |
| 1.33 | 2747.09 ( 42) | 2958.36 ( 35) |
| 1.67 | 2456.42 ( 37) | 2707.25 ( 41) |
| 2 | 2368.79 ( 34) | 2491.84 ( 36) |
| 2.5 | 2089.64 ( 31) | 2278.85 ( 34) |
| 3 | 1918.14 ( 27) | 2041.11 ( 33) |
| 4 | 1561.08 ( 27) | 1664.47 ( 28) |
| 6 | 1138.02 ( 26) | 1220.65 ( 25) |

| | | |
|---|---|---|
| 8 | 844.04 ( 26) | 874.04 ( 26) |
| 10 | 604.32 ( 29) | 635.56 ( 32) |
| 12 | 451.96 ( 31) | 481.31 ( 38) |
| 16 | 281.23 ( 45) | 294.38 ( 39) |
| 24 | 143.39 ( 48) | 140.81 ( 48) |
| 36 | 62.43 ( 64) | 57.09 ( 59) |
| 48 | 27.06 ( 97) | 26.11 (102) |

Pharmacokinetic Parameters

| | Test | Reference | T/R | 90% CI |
|---|---|---|---|---|
| AUC(0-t) (ng.hr/mL) | 19911.1(25) | 21027.1(26) | 0.95 | 86.2-100.0 |
| AUCinf (ng.hr/mL) | 20675.7(27) | 22282.1(27) | 0.93 | 83.7-101.5 |
| Cmax (ng/mL) | 3200.1(37) | 3492.3(34) | 0.92 | 81.8-100.7 |
| Tmax (hr) | 1.1 | 1.0 | | |
| Kel(1/hr) | 0.075 | 0.078 | | |
| t1/2 (hr) | 10.45 | 9.92 | | |

| | Mean SD | Mean SD | RMSE |
|---|---|---|---|
| LnAUC (0-t) | 9.86( 0.29) | 9.91 ( 0.30) | 0.12 |
| LnAUCinf | 9.90( 0.30) | 10.00 ( 0.32) | 0.14 |
| LnCmax | 8.00( 0.40) | 8.09 ( 0.42) | 0.17 |

1. For Genpharm's Etoposide, the mean AUC(0-t), AUCinf and Cmax values were 5.3%, 7.2% and 8.4% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

2. The etoposide plasma levels peaked at one hour for both the test and the reference products following the administration of etoposide dosing under fasting conditions.

3. Additional analysis of variance was performed by the reviewer, after employing the following model

Y = GRP SEQ SUBJ(SEQ*GRP) PER(GRP) TRT GRP*TRT;
Since the group*treatment effect was not significant, it was dropped from the subsequent ANOVA model used for data analysis.

The 90% confidence intervals for log-transformed AUC(0-t), AUCinf and Cmax calculated using the above model remained within the acceptable range of 80-125%.

4. The labeling for Vepeside$^{R}$ (etoposide) Capsules states that the capsules are to be stored under refrigeration 2°-8°C (36-46°F) with the directions of "Do Not Freeze". Although the study drug (both test and reference) was found to be stored at -7 °C (below the temperature range of 2°-8°C at which the study drug was supposed to be stored) prior to period II dosing of group 1, subjects 1-6, the dosing proceeded. Since the effect of the freezing temperature on the two formulations cannot be predicted, excluding the six subjects from the statistical analysis of the study is justified.

V. Formulation:

The formulation for Etoposide Soft Gelatin Capsules, 50 mg, is shown in Table II.

VI. In Vitro Dissolution Testing: (USP Methods)

Method #1 (Seventh Supplement, USP-NF)

| | |
|---|---|
| Method: | USP 23 apparatus I at 50 rpm |
| Medium: | Mixture of 20 mL of acetic acid, 200 mL of absolute alcohol, and 500 mL of water; 500 mL |
| Number of Capsules | 12 |
| Test product: | Genpharm's Etoposide capsules 50 mg, lot #CS-17 |
| Reference product: | Bristol-Myers Squibb's Vepesid$^{R}$ Capsules, 50 mg, lot #WG017 |
| Spectification: | NLT 45 minutes |

Method #2 (Ninth Supplement, USP-NF)

| | |
|---|---|
| Method: | USP 23 apparatus II at 50 rpm |
| Medium: | 900 mL of acetate buffer pH 4.5 |
| Number of Capsules | 12 |
| Test product: | Genpharm's Etoposide capsules 50 mg, lot #CS-17 |
| Reference product: | Bristol-Myers Squibb's Vepesid$^{R}$ Capsules, 50 mg, lot #WG017 |
| Spectification: | NLT in 30 minutes |

Dissolution testing results are shown in Table III.

VII. Comments:

1. The firm's *in vivo* bioequivalence study conducted on its Etoposide Soft Gelatin Capsules, 50 mg, under fasting conditions is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions for etoposide.

2. Ten subjects used concomitant medications on 29 occasions during the 10 hours preceding and following study drug administration. In most cases, these medications were given at the same time prior to or after dosing for the test product as for the reference product. Some of the concomitant medications are known to have no effect on the pharmacokinetic parameters of the study drug. Since subjects receiving concomitant medications were dosed with both test and reference products, the concomitant medications used in the study should have no impact on the study.

3. The *in vitro* dissolution testing for the test product Etoposide Soft Gelatin Capsules, 50 mg, is acceptable.

4. On February 9, 1995, OGD granted a waiver to the firm on the minimum batch size requirement of capsules. For this drug product, a small *in vivo* bioequivalence batch size of capsules is acceptable.

VIII. Deficiency Comment:

The firm should submit data to support the long-term stability of Etoposide in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (approximately one year).

XI. Recommendations:

1. The bioequivalence study under fasting conditions conducted by Genpharm Inc., on its Etoposide Soft Gelatin Capsules, 50 mg, lot #CS-17, comparing it to Vepesid$^{R}$ Capsules, 50 mg, manufactured by Bristol-Myers Squibb, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment.

2. The dissolution testing conducted by the firm on its Etoposide Capsules, 50 mg, lot #CS-17, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of acetate buffer pH 4.5 at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the deficiency comment and recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 7/22/99
FT INITIALLED BDAVIT Barbara M Davit Date: 7/23/99

Concur: Dale P. Conner Date: 9/20/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/6-28-99, 7-23-99, 75635SD 599

PROTOCOL GEN-501

LEAST-SQUARES MEAN ETOPOSIDE PLASMA CONCENTRATIONS (N=19)

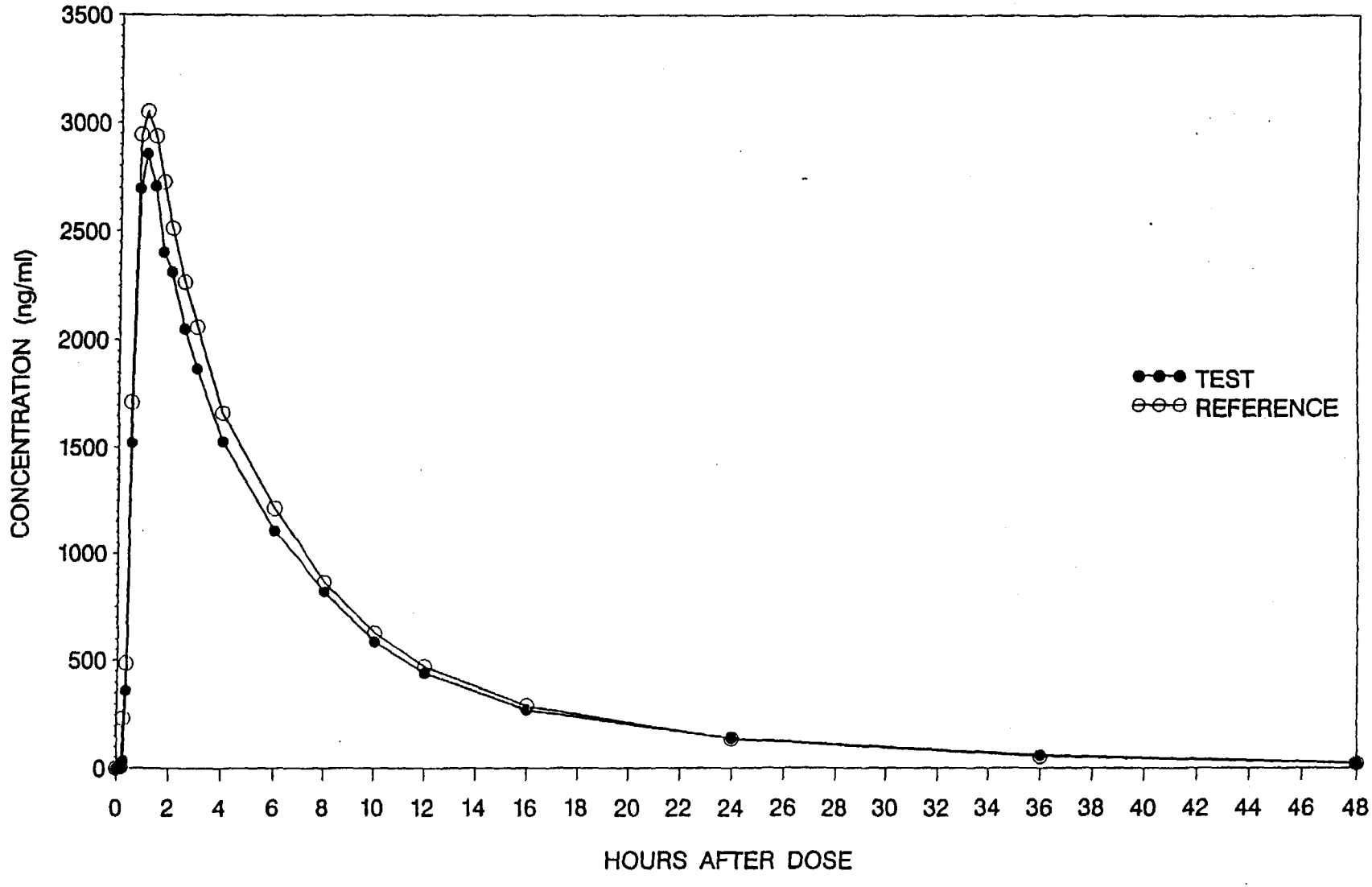

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Etoposide Capsules
Dose Strength: 50 mg
ANDA No.: 75-635
Firm: Genpharm Inc.
Submission Date: May 10, 1999
File Name: 40237SDW.N98

I. Conditions for Dissolution Testing: Seventh Supplement, USP-NF

USP 23 Basket: X Paddle: RPM: 50
No. Units Tested: 12
Medium: 20 mL acetic acid, 200 mL absolute alcohol and 500 mL Water; 500 mL
Specifications: NLT in 45 minutes
Reference Drug: Vepeside
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Lot #CS-17 Strength(mg) 50 | | | Reference Product Lot #WG017 Strength(mg) 50 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 15 | 9.97 | | 3.1 | 9.26 | | 5.1 |
| 30 | 60.17 | | 15.9 | 68.09 | | 21.7 |
| 45 | 101.56 | | 1.7 | 102.56 | | 0.58 |
| 60 | 101.2 | | 1.0 | 101.82 | | 0.54 |

II. Conditions for Dissolution Testing: Ninth Supplement, USP-NF

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL acetate buffer pH 4.5
Specifications: NLT n 30 minutes
Reference Drug: Vepeside
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Lot #CS-17 Strength(mg) 50 | | | Reference Product Lot #WG017 Strength(mg) 50 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 10 | 11.73 | | 10.8 | 10.43 | | 7.2 |
| 20 | 90.13 | | 13.1 | 97.07 | | 10.1 |
| 30 | 99.24 | | 0.77 | 100.38 | | 1.31 |
| 40 | 98.76 | | 0.82 | 100.45 | | 1.1 |

| | |
|---|---|
| Date | 6/28/99 |
| USER | MHM |
| n = | 4 |
| F2 = | 69.13 |
| ANDA # | 75-635 |
| Drug | Etoposide |

| 7th Test | USP Ref | (R-T)2 |
|---|---|---|
| 9.97 | 9.26 | 0.50 |
| 60.17 | 68.09 | 62.73 |
| 101.6 | 102.6 | 1.00 |
| 101.2 | 101.8 | 0.44 |

| | |
|---|---|
| Date | 6/28/99 |
| USER | MHM |
| n = | 4 |
| F2 = | 70.96 |
| ANDA # | 75-635 |
| Drug | Etoposide |

| 9th Test | USP Ref | (R-T)2 |
|---|---|---|
| 11.73 | 10.43 | 1.69 |
| 90.13 | 97.07 | 48.16 |
| 99.24 | 100.4 | 1.30 |
| 98.76 | 100.5 | 2.86 |

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 75-635

# ADMINISTRATIVE DOCUMENTS

# APPROVAL SUMMARY PACKAGE

**ANDA NUMBER:** 75-635

**FIRM:** Genpharm Inc.

**DOSAGE FORM:** Capsules

**STRENGTH:** 50 mg

**DRUG:** Etoposide Capsules USP, 50 mg

**cGMP STATEMENT/EER UPDATED STATUS:** Acceptable 07/09/01.

**BIO STUDY:** Acceptable, 12/23/99.

**METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):**
N/A, USP DS/DP

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

Yes.
The proposed commercial packaging configuration is Blister 10's.

**LABELING:**
Labeling, Acceptable, 12/23/99

**STERILIZATION VALIDATION (IF APPLICABLE):** N/A

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

| Lot# | Lot CS-17 (bio/stability) |
|---|---|
| Batch size | |

NDS Source: DMF Holder:
DMF #:

| Last DMF updates | Most Recent Review | Status |
|---|---|---|
| 04/27/01 | 05/08/01 | Adequate |

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

| Lot# | Lot CS-17 (bio/stability) |
|---|---|
| Batch size | |

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

| | |
|---|---|
| Executed Batch size | |
| **Production Batch size** | |
| Comments | Within 10X |

Bing Cai 9/5/01
Review Chemist

Mike Smela
Team Leader

M Smela 9/5/01

Division of Chemistry I
OGD/CDER
08/29/01

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75635/000** Priority: Org Code: **600**
Stamp: **14-MAY-1999** Regulatory Due: Action Goal: District Goal: **14-APR-2000**
Applicant: **GENPHARM**
**C/O PAR PHARMACEUTICAL INC**
**1 RAM RIDGE RD**
**SPRING VALLEY, NY 10977**
Brand Name:
Established Name: **ETOPOSIDE**
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **50MG**

FDA Contacts:

| | | | |
|---|---|---|---|
| **M. DILLAHUNT** | **(HFD-613)** | **301-827-5848** | **, Project Manager** |
| **B. CAI** | **(HFD-620)** | **301-827-5848** | **, Review Chemist** |
| **M. SMELA JR** | **(HFD-625)** | **301-827-5848** | **, Team Leader** |

Overall Recommendation:

**ACCEPTABLE on 12-DEC-2000 by M. GARCIA (HFD-322) 301-594-0095**

Establishment:
**GENPHARM PHARMACEUTICALS IN**
**37, 85 ADVANCE,212-214 NORSEMAN**
**ETOBICOKE, , CA**
DMF No:
AADA No:

Profile: **CSG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE PACKAGER**

---

Establishment:
MF No:
AADA No:

Profile: **CTL**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-AUG-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**
Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

---

Establishment:
DMF No:
AADA No:

Profile: CSG
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-DEC-2000**
Decision: **ACCEPTABLE**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason:

Establishment: DMF No:
ER AADA No:

Profile: CTL OAI Status: NONE Responsibilities: DRUG SUBSTANCE OTHER TESTER
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-AUG-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: DMF No: 9966
AADA No:

) 77

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE MANUFACTURER
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-JUN-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**APPROVAL SUMMARY**
**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

---

**ANDA Number: 75-635** **Date of Submission: December 6, 1999**
**Applicant's Name: GenPharm**
**Established Name: Etoposide Capsules USP, 50 mg**

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Unit Dose Blister Label: Satisfactory as of December 6, 1999 submission.
Unit Dose Carton Label: (20's – 2 x 10 blister cards)) Satisfactory as of December 6, 1999 submission.
Professional Package Insert Labeling: Satisfactory as of December 6, 1999 submission.

Revisions needed post-approval:
**BASIS OF APPROVAL:**
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: VePesid Capsules
NDA Number: 19-557/S-023 – 19557
NDA Drug Name: Etoposide capsules
NDA Firm: Bristol-Myers Squibb
Date of Approval of NDA Insert and supplement #: April 2, 1999
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

## REVIEW OF PROFESSIONAL LABELING CHECK LIST

| Established Name | Yes | No | N.A. |
|---|---|---|---|
| Different name than on acceptance to file letter? | | X | |
| Is this product a USP item? If so, USP supplement in which verification was assured. USP 23 | X | | |
| Is this name different than that used in the Orange Book? | | X | |
| If not USP, has the product name been proposed in the PF? | | | X |
| **Error Prevention Analysis** | | | |
| Has the firm proposed a proprietary name? If yes, complete this subsection. | | X | |
| Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? | | | X |
| Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? | | | X |
| **Packaging** | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | | X |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | X | |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | X | |

| | | | |
|---|---|---|---|
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | X | | |
| Are there any other safety concerns? | | X | |
| **Labeling** | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
| Has applicant failed to clearly differentiate multiple product strengths? | | X | |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| **Labeling(continued)** | Yes | No | N.A. |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | X | |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | X | |
| **Scoring:** Describe scoring configuration of RLD and applicant (page #) in the FTR | | | |
| Is the scoring configuration different than the RLD? | | X | |
| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | X | |
| **Inactive Ingredients:** (FTR: List page # in application where inactives are listed) | | | |
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | X | | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray? | | X | |
| Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION? | | X | |
| Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) | | X | |
| **USP Issues:** (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | | X | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| **Bioequivalence Issues:** (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| **Patent/Exclusivity Issues?:** FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | X | |

**FOR THE RECORD:**

1. The reference listed drug for this product is VePesid(Bristol-Myers Squibb; NDA#19-557/S-023;

approved April 2, 1999).

2. The applicant certifies there are no patents/exclusivities in effect for this product. See Vol. 1.1, page 24 and 26.
3. The product will be manufactured by
. See Vol. 1.4, page 1687.
4. Other outside firms are utilized for testing only. See Vol. 1.4, page 1725.

5. Container/Closure
Unit Dose:
Film and Foil Backing. See Vol. 1.4, page 1861.

6. Finished Product - 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. See Vol. 1.1, page 44

7. Product Line - Etoposide Capsules are available in dark pink oblong capsules with "E50" printed in black ink packaged in blisters of 10 in cartons of 20. See Vol. 1.1, page 55.
8. Components/Composition
Innovator: Each liquid filled, soft gelatin capsule contains:
Active: Etoposide 50 mg in a vehicle consisting of citric acid, glycerin, purified water and polyethylene glycol
Inactive: gelatin
Gycerin
Soribtol
Purified water
ethyl and propyl)
Iron oxide
Titanioum dioxide

Applicant:
Active: Etoposide 50 mg in a vehicle consisting of citric acid, glycerin, purified water, and polyethylene glycol
Inactive: gelatin
Glycerin
Anidrisorb (
Iron oxide
Titanium dioxide

See Vol. 1.1, page 1525.

9. Storage/Dispensing
NDA: Capsules are to be stored under refrigeration 2°-8°C(36°-46°F). DO NOT FREEZE. Dispense in child-resistant containers.
ANDA: Capsules are to be stored under refrigeration 2°-8°C(36°-46°F). DO NOT FREEZE. Dispense in child-resistant containers.
USP: Preserve in tight containers in a cold place. Do not freeze.
See Vol. 1.1, page 55 and USP 23, page 649.

---

**Date of Review: December 17, 1999**
**Date of Submission: December 6, 1999**

**Reviewer:** [signature] **Date:** 12/23/99

**Team Leader:** [signature] **Date:** 12/23/1999

cc:

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

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**ANDA Number: 75-635 Date of Submission: May 10, 1999**

**Applicant's Name: GenPharm**

**Established Name: Etoposide Capsules USP, 50 mg**

Labeling Deficiencies:

1. UNIT DOSE CONTAINER

   a. Satisfactory in draft.

2. UNIT DOSE CARTON (20'S- 2 X 10 blister card)

   a. Include the storage recommendation on the principle display panel as does the reference listed drug.

3. INSERT

   a. DESCRIPTION

      i. Revise the molecular weight to read "588.56" rather than "588.58".

   b. INDICATIONS AND USAGE

      i. Delete the first indication "Refractory Testicular Tumors" as it only applies to the injectable dosage form.

      ii. Revise the second indication to read as follows:

      **Small Cell Lung Cancer** - Etoposide capsules in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.

c. WARNINGS

i. Delete the second paragraph of this section.

ii. Pregnancy-

A. Increase the font of "1/2" to be equal to "1/7th" in sentence one of paragraph two of this subsection.

d. PRECAUTIONS

i. Include the following to appear as the last subsection under PRECAUTIONS:

**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.

e. ADVERSE REACTIONS

i. Gastrointestinal Toxicity -

A. Include the following to appear as sentence four of this subsection:

Mild to severe mucositis/esophagitis may occur.

ii. Other Toxicities -

A. Revise the first paragraph of this subsection to read as follows:

…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.

f. DOSAGE AND ADMINISTRATION

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

...nearest 50 mg (i.e., Two times 35 mg/$m^2$/day for 4 days to 50 mg/$m^2$/day for 5 days).

ii. Revise the first sentence of paragraph two of this section to read as follows:

The dosage should be modified to take...

iii. Administration Precautions

Delete this subsection as it only applies to the injectable dosage form.

iv. Include the following to appear just prior to the **Procedures for proper handling and disposal** subsection under DOSAGE AND ADMINISTRATION

**Stability**
Etoposide capsules must be stored under refrigeration 2°-8°C(36°-46°F). The capsules are stable for 24 months under such refrigeration conditions.

g. REFERENCES

i. Delete references 1 through 3, then renumber the remaining references 1 through 7.

Please revise your unit-dose container labels, unit-dose carton and insert labeling, as instructed above, and submit 12 copies of final printed unit-dose container labels, along with 12 copies of final printed unit-dose carton and insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes:
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

GENPHARM

N/AM

ORIG AMENDMENT

*FAX AMENDMENT*

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**Re: ANDA No. 75-635**
**Fax Amendment**
**Etoposide USP**
**50 mg Capsules**

Dear Sir/Madam:

Please find enclosed Genpharm's response to the deficiency letter received August 20, 2001 and the revised environmental assessment hard copy.

We have enclosed: one (1) archival copy, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

Please note that the deficiency list and this response contains information that Genpharm Inc. and The Mattson Jack Group consider to be confidential commercial information. As such, we request that we review redacted information prior to its release under The Freedom of Information Act, (As Amended) 1986, (5USC§552) AND 21CFR20.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

Yours sincerely,

for Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.

Date

AUG 27 2001

DGD

EVALUATION AND RESEARCH

GENPHARM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

***MINOR AMENDMENT***

**Re: ANDA No. 75-635**
**Minor Amendment**
**Etoposide**
**50 mg Capsules**

ORIG AMENDMENT

Dear Sir/Madam:

Please find enclosed Genpharm's response to the minor amendment letter received May 31, 2001 from OGD. Genpharm Inc. has filed an ANDA (75-635) pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for generic Etoposide Capsules USP, 50 mg. An Environmental Assessment has been submitted pursuant to 21 CFR part 25.

We have enclosed: one (1) archival copy, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

Yours sincerely,

for Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.

July 30, 2001
Date

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GENPHARM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

***MINOR AMENDMENT***

N|AM

**Re: ANDA No. 75-635**
**Minor Amendment**
**Etoposide USP**
**50 mg Capsules**

Dear Sir/Madam:

Please find enclosed Genpharm's response to the deficiency letter received August 6, 2001 and the revised environmental assessment hard copy.

We have enclosed: one (1) archival copy, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

Please note that the deficiency list and this response contains information that Genpharm Inc. and The Mattson Jack Group consider to be confidential commercial information. As such, we request that we review redacted information prior to its release under The Freedom of Information Act, (As Amended) 1986, (5USC§552) AND 21CFR20.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

Yours sincerely,

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 17 2001
OGD

Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.

August 14, 2001
Date

GENPHARM

Inadequate response to 5/31/01 deficiency. Convert to correspondence.
M Shugle 7/5/01

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*MINOR AMENDMENT*

**Re: ANDA No. 75-635**
**Minor Amendment**
**Etoposide**
**50 mg Capsules**

NEW CORRESP

NC

Dear Sir/Madam:

Please find enclosed Genpharm's response to the minor amendment letter received May 31, 2001 from OGD. In addition, Genpharm is submitting information to provide for an alternate stand-alone packaging site, PCI Contract Services. A cGMP certification is presented to support the addition of PCI Contract Services. PCI Contract Services will package Genpharm's Etoposide Capsules, 50 mg in the container/closure systems as outlined in ANDA #75-635.

In a letter to industry dated February 18, 1997 from the Department of Health and Human Services, a commitment to place the first production batch of the product on long-term stability studies is required when adding a new stand-alone packaging site. Since this product is not yet marketed, the first three production batches of the product packaged at PCI will be placed on long-term stability. Please find enclosed Genpharm's stability commitment as outlined in ANDA No. 75-635 for Etoposide Capsules, 50 mg.

We have enclosed: one (1) archival copy, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

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.....2

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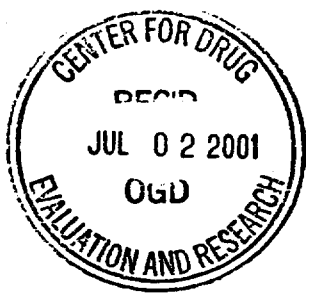
GENPHARM

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

Yours sincerely,

Dr. Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.

June 28 2001
Date

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MAY 31 2001

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiency presented below represents a MINOR deficiency.

As your drug substance is manufactured from wild plants, your ANDA must contain an Environmental Assessment. Your agent was notified of this by telephone on April 20, 2001. Please refer to the "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications" on the CDER Homepage and/or contact Ms. Nancy Sager of OPS should you desire additional information. A categorical exclusion is not appropriate as the use of wild plants is considered an Extraordinary Circumstance.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

GENPHARM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*TELEPHONE AMENDMENT*

ORIG AMENDMENT
N/AM

**Re: ANDA No. 75-635**
**Telephone Amendment**
**Etoposide**
**50 mg Capsules**

Dear Sir/Madam:

Please find enclosed Genpharm's response to the telephone amendment received at King and Spalding, our U.S. agent, on May 2, 2001 from OGD.

We have enclosed: one (1) archival copy, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

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Yours sincerely,

May 8, 2001

Dr. Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.
Date

GENPHARM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*MINOR AMENDMENT*

ORIG AMENDMENT
N/A

**Re: ANDA No. 75-635**
**Amendment**
**Etoposide**
**50 mg Capsules**

Dear Sir/Madam:

Please find enclosed Genpharm's response to the deficiency letters dated December 5, 2000 and April 6, 2001 from FDA.

Please note the comment in the deficiency letter dated December 5, 2000 concerning the DMF deficiencies directly corresponds to Comment 1 in the deficiency letter dated April 6, 2001. As a result, both comments have been addressed in response 1, which is supported by a response letter from , dated April 27, 2001.

We have enclosed: one (1) archival copy, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

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APR 30 2001
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Yours sincerely,

Dr. Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.

April 27, 2001
Date

5/1/01

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38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiency presented below represent a MINOR deficiency.

1. The for the drug substance, Etoposide USP is still inadequate. Please confirm a response from the DMF holder.

2. You have revised your specifications for drug substance and drug product to include a limit of for Any Individual Known Impurity. Please clarify your stability specification regarding the impurity limits.

3. Please provide a statement to clarify that your source for gelatin is Bovine Spongiform Encephalopathy (BSE) free. Please refer to the CDER Guidances webside for the Agency Guidance titled "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE)" for completed description.

Sincerely yours,

M Smela for 4/6/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

APR -6 2001

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiency presented below represent a MINOR deficiency.

1. The for the drug substance, Etoposide USP is still inadequate. Please confirm a response from the DMF holder.

2. You have revised your specifications for drug substance and drug product to include a limit of for Any Individual Known Impurity. Please clarify your stability specification regarding the impurity limits.

3. Please provide a statement to clarify that your source for gelatin is Bovine Spongiform Encephalopathy (BSE) free. Please refer to the CDER Guidances webside for the Agency Guidance titled "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE)" for completed description.

Sincerely yours,

M Ismela for

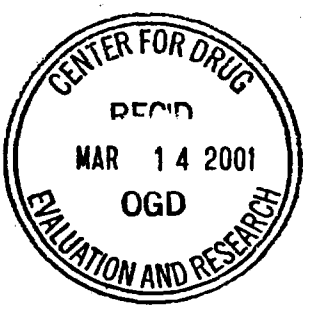
Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

GENPHARM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*AMENDMENT*

ORIG AMENDMENT
N/Am




**Re: ANDA No. 75-635**
**Amendment**
**Etoposide**
**50 mg Capsules**

Dear Sir/Madam:

This amendment to our pending ANDA No.75-635 for Etoposide 50 mg Capsules, is being submitted to propose revisions of the Etoposide drug substance and finished product specifications to be in accordance with the impurity limits as reported by , the drug substance manufacturer.

In response to a minor amendment letter dated June 22, 2000 from FDA, the finished product specifications were revised to include a limit of for Largest Single Unknown Impurity. This limit of is based on the maximum daily dose as stated in the draft Guidance for Industry "ANDAs: Impurities in Drug Products" dated December 1998.

Revising the finished product specification to include a limit of for Largest Single Unknown Impurity resulted in subsequent batches of drug substance meeting the submitted drug substance impurity specifications but failing the finished product impurity specifications (refer to page 36 to 39 of the method validation protocol report) . For example, Compound ' impurity s currently treated as an unknown although , the drug substance manufacturer has identified and characterized ( As a result, Genpharm Inc. is proposing to revise the Etoposide drug substance and finished product specifications to be in accordance with the impurity limits as reported by the drug substance manufacturer.

We have enclosed one (1) archival copy, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

3-19-01

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

GENPHARM

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

Yours sincerely,

for

Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

March 12, 2001
Date

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

DEC 5 2000

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiency presented below represent a MINOR deficiency.

The for the drug substance, Etoposide USP remains deficient and the DMF holder has been informed. Please confirm a response.

Sincerely yours,

S/ Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiency presented below represent a MINOR deficiency.

The for the drug substance, Etoposide USP remains deficient and the DMF holder has been informed. Please confirm a response.

Sincerely yours,

12/11/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

AUG 28 2000

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The for the drug substance, Etoposide USP remains deficient and the DMF holder has been informed. Please confirm a response.

2. Please revise your dissolution method to comply with the current USP 24 method (Supplement 2).

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A satisfactory compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

/s/ Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The for the drug substance, Etoposide USP remains deficient and the DMF holder has been informed. Please confirm a response.

2. Please revise your dissolution method to comply with the current USP 24 method (Supplement 2).

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A satisfactory compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

8/31/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-635 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Etoposide Soft Gelatin Capsules, 50 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23 (Ninth Supplement).

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BMD 12/17/99

RD INITIALLED BDAVIT

FT INITIALLED BDAVIT Barbara M Davit Date: 12/20/99

Concur: [signature] Date: 12/23/99

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/12-16-99, 12-20-99, 75635SD.N99

JUN 22 2000

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The : the drug substance, Etopside USP is found deficient and the DMF holder has been informed. Please confirm a response.

2. Please provide copies of your methods with validation reports for your in-process testing and for " Material".

3. Please include limits for other individual impurities in both the finished product release and stability specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your response to the bioequivalence deficiencies is pending review.

2. The safety concern regarding the amount of Polyethylene Glycol proposed in your product is under evaluation.

3. We have requested an establishment evaluation from the Office of Compliance and a satisfactory report is necessary for approval.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-635 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Etoposide Soft Gelatin Capsules, 50 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23 (Ninth Supplement).

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The for the drug substance, Etopside USP is found deficient and the DMF holder has been informed. Please confirm a response.

2. Please provide copies of your methods with validation reports for your in-process testing and for " Material".

3. Please include limits for other individual impurities in both the finished product release and stability specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your response to the bioequivalence deficiencies is pending review.

2. The safety concern regarding the amount of Polyethylene Glycol proposed in your product is under evaluation.

3. We have requested an establishment evaluation from the Office of Compliance and a satisfactory report is necessary for approval.

Sincerely yours,

6/11/00

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

NOV - 1 1999

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-635
APPLICANT: Genpharm Inc.
DRUG PRODUCT: Etoposide Capsules USP, 50 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. The amount of Polyethylene Glycol in your formulation appears higher than the level that has been approved for an oral dosage form. Please demonstrate that the maximum total daily amount of Polyethylene Glycol that patients may ingest from this product is safe.

2. Your drug substance supplier, has withdrawn the authorization for reference to for your company (03/23/99). Please have this problem resolved or provide an alternate source for the active drug substance and related supporting documents.

3. Please provide the details for your test method for Organic Volatile Impurities

4. Please comment on whether the drug substance is completely dissolved in your formulation. If it is not, controls for particle size and morphic form are needed.

5. Please revise your specifications for the following items to current USP requirements:
   - Glycerin USP
   - Purified Water USP

6. Please clarify your in-process specifications and test results of " Material" for the executed batch. The information provided on page 1750 of your application is not completed.

7. Please include blend uniformity analysis as an in-process control for the " Material".

8. The results from the executed batch (CS-17) indicate that several in-process tests were failed (fill moisture, hardness). Please explain.

9. Please clarify if you will monitor "Fill Weight" during the entire production. For the executed batch (CS-17), only the first production day's "Fill Weight Record" (09/03/97) was

included in your application. In addition, based on your formulation, the total mass for "  Material" is  mg. However, your specification for target "  Weight" is  mg. Please clarify.

10. Please revise your dissolution specification/test method to the current USP requirement (for both release and stability). The specification on the COA for Lot CS-17 is not updated. Please provide stability data using the revised method from your next test station.

11. Please revise your stability commitment provided on page 2304 of your submission. The storage condition is incorrect for this product.

12. There is a spelling error in your Description section of your insert: "Andrisorb" should be "Anidrisorb".

13. All manufacturing and control information for the drug product should be included in the ANDA including post approval changes. We recommend that you withdraw reference to

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The CGMP status of the firms referenced in the ANDA is currently being evaluated by our Office of Compliance. A satisfactory evaluation is required for approval.

2. Your response must also address the labeling deficiencies.

3. Please provide any available long term stability data from samples of your bio batch (CS-17).

4. Please respond to the bioequivalence deficiencies communicated to you on September 28, 1999.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-635 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Etoposide Soft Gelatin Capsules, 50 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23 (Ninth Supplement). The following deficiencies have been identified:

Please submit data to support the long-term stability of Etoposide in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (approximately one year).

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 28 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-635 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Etoposide Soft Gelatin Capsules, 50 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23 (Ninth Supplement). The following deficiencies have been identified:

Please submit data to support the long-term stability of Etoposide in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (approximately one year).

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

GENPHARM

NEW CORRESP

August 3, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**AMENDMENT**
**CORRESPONDENCE TO FILE**

**Re: Etoposide Capsules USP, 50 mg (ANDA #75-635)**

Dear Sirs;

This is to advise of that the following representative/firm has been appointed as Genpharm's US agent for the above mentioned ANDA.

John P. O'Donnell, Ph.D.
Executive Vice President
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road, P.O. Box 4310
Morgantown, West Virginia
26504-4310, U.S.A.

The telephone numbers are:

Telephone No. (304) 599-2595
Fax No. (304) 285-6409

We have enclosed one (1) archival, one (1) review and one (1) field copy of the application in accordance with 21 CFR § 314.55. We certify that the Field Copy is a true copy of the review copy of this application and has been submitted to the Office of Generic Drugs.

Should you have any questions, please do not hesitate to contact the undersigned at 1-416-207-1216.

Sincerely yours,
**Genpharm Inc.**

Tirtho Uppal
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 06 1999
OGD

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

GENPHARM

November 22, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**BIOEQUIVALENCE AMENDMENT**

ORIG AMENDMENT
N/AB

**Re: ANDA #: 75-635**
**ETOPOSIDE SOFT GELATIN CAPSULES**
**50 MG**

Please find enclosed a ***BIOEQUIVALENCE AMENDMENT*** to ANDA # 75-635 in response to the FDA's deficiency letter dated Sept 28/99 from Dr. Dale Conner pertaining to long term stability of etoposide in frozen study samples.

We have enclosed one (1) archival and one (1) pharmacokinetic review copy of the application in accordance with 21 CFR § 314.96.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm directly at 1-800-661-7134 or you may contact our US agent, Dr. John O'Donnell at (304) 599-2595.

Yours sincerely,

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

NOV 2 2 1999
(Date)

cc: Dr. John O'Donnell
Executive Vice President
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310
U.S.A.

ANDA 75-635

Par Pharmaceutical Inc.
U.S. Agent for: Genpharm Inc.
Attention: Robert A. Femia, Ph.D.
One Ram Ridge Road
Spring Valley, NY 10977

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Etoposide Capsules USP, 50 mg

DATE OF APPLICATION: May 10, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 14, 1999

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

Harvey A. Brantley for

Robert L. West, M.S., R.Ph.
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

GENPHARM

Ack for filing
S. Middleton 6/8/99
505 (j)(2)(A)

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**ORIGINAL ANDA**

**Re: Abbreviated New Drug Application**
**Etoposide Capsules USP**
**50 mg**

**May 10, 1999**

We are pleased at this time to submit an original Abbreviated New Drug Application for our product - Etoposide Capsules USP, 50 mg.

The purpose of this application is to gain FDA approval to market Etoposide Capsules USP, 50 mg, in the U.S.A. The drug product described above is the same as VEPESID®, manufactured by Bristol-Myers Squibb Oncology. We have submitted comparative information to indicate that our product is the same as the reference listed drug product. This information is presented in tabular form, comparing active ingredient, conditions of use, route of administration, dosage form, strength, bioequivalence, and labeling for the products as supplied by Genpharm Inc. and by Bristol-Myers Squibb Oncology.

Correspondence with the Office of Generic Drugs, Reference Number 94-298, is submitted following the Table of Contents regarding the approval of the *in vivo* bioequivalence batch size and the stability protocol.

We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR § 314.55. As required, three (3) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA. The number of volumes in the archival, review and field copies of the ANDA are as follows:

| | |
|---|---|
| Blue Archival Copy | 5 volumes |
| Orange Review Copy | 3 volumes |
| Red Review Copy | 3 volumes |
| Burgundy Field Copy | 3 volumes. |


GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

In addition, for the Bioequivalence Section, we have enclosed a computer diskette (2 copies) with the analytical data and bioavailability parameters in the format prescribed by the FDA. A hard copy of the diskette data is also included in section VI. The diskettes are located in the front cover of the Archival Copy of this application.

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm directly at 1-800-661-7134 or you may contact our US agent, Mr. Robert A. Femia at (914) 425-7100.

A letter of authorization, allowing Mr. Robert A. Femia to act as our U.S. agent, is included in Section XX.2.a of this application.

Yours sincerely

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

May 10/99
(date)