APPLICATION NUMBER:

75-635

APPROVAL LETTER
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,

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

9/19/01
APPLICATION NUMBER:
75-635

APPROVED DRAFT LABELING
ETOPOSIDE CAPSULES USP, 50 MG

WARNINGS

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

DESCRIPTION

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin and in the treatment of certain neoplastic diseases. It is 4'-Demethylepipodophyllotoxin 9-[2-(6-methyl-2-pyridyl)ethyl] -O-glucuronoside. It is very soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.56 and a molecular formula of C28H35NO13.

Etoposide may be administered either intravenously or orally. Etoposide is available as 50 mg dark pink oblong capsules. Each capsule contains 50 mg of etoposide in a vehicle consisting of cetyl alcohol, methyl paraben, propylene glycol, and distilled water. The soft gelatin capsules contain androstrolin, gelatin and glycerin with the following dye system: iron oxide and titanium dioxide; the capsules are printed with edible ink containing hydroxypropyl methylcellulose, propylene glycol and synthetic black oxide.

The structural formula is:

\[
\text{Chemical Structure Image}
\]

CLINICAL PHARMACOLOGY

Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the G2 portion of the cell cycle in mammalian cells. Two different dose-dependent responses are seen. At high concentrations (10 mg/mL or more), loss of G1 cell population is observed. At low concentrations (0.3 to 10 mg/mL), cells are arrested at the S phase. It does not interfere with microtubular assembly. The edematous macrovascular effect of etoposide appears to be a result of inhibition of DNA strand breaks by an interaction with DNA topoisomerase II or the formation of free radicals.

MECHANISMS

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

2. Mean volumes of distribution at steady state fail in the range of 18 to 29 liters or 7 to 11 L/m². Etoposide enters the CSF poorly. Although it is detectable in CSF and intracranial tumors, the concentrations are lower than in extracerebral tumors and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and similar in primary tumors and normal tissues of the myometrium. In vitro, etoposide is a potent inhibitor of human plasma proteinases. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. In a study by the effect of other therapeutic agents on the intravascular binding of carbon-14 labeled etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and spinipaxl protein-bound etoposide at concentrations achieved in vivo.

3. Etoposide binding ratios correlate directly with serum albumin in patients with cancer and in normal volunteers. The unbound fraction of etoposide significantly correlates with bilirubin level in cancer patients. Data have suggested a significant inverse correlation between serum albumin concentration and free fraction of etoposide (see PRECAUTIONS).

After intravenous administration of 2 mg/kg etoposide (70-290 mg/m²), mean recoveries of deactivation in the urine range from 32 to 37%, and fecal recoveries range from 0 to 16% of dose. Less than 50% of an intravenous dose is excreted in the urine as etoposide with meal recoveries of 8 to 35% within 24 hours.

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

Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the normal clearance of etoposide. The major urinary metabolite of etoposide in adults O-demethylation of the dimethoxyphenyl ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

After either intravenous infusion of 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 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 oral 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
- Other epithelial cancers

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 with differential, and urinalysis. In children, an evaluation for central nervous system dysfunction should be performed daily during therapy. 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, exophthalmos, 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 a few 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 judgment of the physician. Reinstatement of etoposide therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alibertie attention to possible recurrence of toxicity.

Patients with low serum albumin may be at an increased risk for etoposide associated
they should be performed prior to each cycle of therapy and at appropriate intervals during and after therapy. At least one determination should be done prior to each dose of toposide.

renal impairment

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

<table>
<thead>
<tr>
<th>Measured Creatinine Clearance</th>
<th>100% of dose</th>
<th>75% of dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 mL/min</td>
<td>50 mL/min</td>
<td>12.5 mL/min</td>
</tr>
</tbody>
</table>

Subsequent etoposide dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearances <15 mL/min and further dose reduction should be considered in these patients.

carcinogenesis (see WARNINGS), Mutagenesis, Impairment of Fertility

Etoposide has been shown to be mutagenic in Ames assay.

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

Reversible testicular atrophy was present in rats treated with etoposide intravenously for 30 days at 0.5 mg/kg/day (about 1.66% of the human dose on a mg/m² basis).

pregnancy

'pregnancy CATEGORY D' (see WARNINGS).

nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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.

DIVERSE REACTIONS

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

Leukemoid Reaction

Leukopenia 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 administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Fever and infection have also been reported in patients with etoposide. Death associated with myelosuppression has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported (see WARNINGS).

Gastrointestinal Toxicity

Nausea and vomiting are the major gastrointestinal toxicities. The severity of this nausea and vomiting is generally mild to moderate with treatment discontinuance required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Nausea and vomiting are more frequent after oral administration than after intravenous infusion.

Hypotension

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

Other Toxicities

The following adverse reactions have been infrequently reported: abdominal pain, aftersense, constipation, dysphagia, asthenia, fatigue, malaise, somnolence, transient cortical blindness, optic neuritis, interstitial pneumonitis/pulmonary fibrosis, fever, sepsis (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 tables that follow 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.

<table>
<thead>
<tr>
<th>AVERSE DRUG EFFECT</th>
<th>PERCENT REPORTED INCIDENCE</th>
<th>RANGE OF INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia (less than 1,000 WBC/mm³)</td>
<td>3-17</td>
<td></td>
</tr>
<tr>
<td>Leukopenia (less than 4,000 WBC/mm³)</td>
<td>60-91</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (less than 50,000 platelets/mm³)</td>
<td>1-20</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (less than 100,000 platelets/mm³)</td>
<td>22-41</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>0-33</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>31-43</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0-2</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>10-13</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1-3</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1-6</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>8-66</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1-2</td>
<td></td>
</tr>
</tbody>
</table>

OVERDOSE

No proven antidotes have been established for etoposide overdose.

DOSAGE AND ADMINISTRATION

Etoposide Capsules

In small cell lung cancer, the recommended dose of Etoposide Capsules is twice the IV dose rounded to the nearest 50 mg (i.e., Two times 35 mg/m²/day for 4 days to 50 mg/m²/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. There is no general agreement on the guidelines 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:


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.


Manufactured by:

R.P. Scherer Canada Inc.
Windsor, Ontario
Canada N8Y 4S2
ETOPOSIDE
Capsules USP
50 mg
Rx only

20 Capsules Unit Dose

NDC 55567-050-02

GENPHARM

Approved SEP 19 2001

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

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
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(5aH)-one-, 9-
[[(4,6-O-ethylidene-β-L-glucopyranosyl)oxy]-5,8,8a,9-
tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-
[5α,5αβ,8αα,9β(R*)]]-

![Chemical Structure Diagram]

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:**

Bing Cai, Ph.D.  **DATE COMPLETED:**  **DATE REVISED:**

03/30/01
Contain Trade Secret, Commercial/Confidential Information and are not releasable.

John 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 filing: 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. **DOSSAGE 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(5aH)-one—, 9-
   [{4,6-O-ethylidene-β-D-glucopyranosyl]oxy}-5,8,8a,9-
   tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-
   [5a,5αβ,8α,9β(R*)]]—.

![Chemical Structure]

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

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 Pfeifer
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 Acknowledgement (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. C29H32O13. 588.56. 33419-42-0
Furo[3',4':6,7]naphtho[2,3-d]-1,3dioxol-6(5aH)-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*)].

![Chemical Structure](image)

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
Page(s) __________

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Information and are not releasable.

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 request 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
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_{33}O_{13}. 588.56. 33419-42-0
   Furo[3',4':6,7]naphtho[2,3-d]-1,3dioxol-6(5aH)-one-, 9-
   [(4,6-O-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-
   tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-
   [5α,5αβ,8αα,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:**  
    Bing Cai, Ph.D.  
    **DATE COMPLETED:**  
    07/31/00  
    **DATE REVISED:**
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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\textsubscript{29}H\textsubscript{32}O\textsubscript{13}. 588.56. 33419-42-0
    Furo[3',4':6,7]naptho[2,3-d]-1,3dioxol-6(5aH)-one-, 9-
    [(4,6-O-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-
    tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-
    [5a,5αβ,8αα,9β(R*)]]-

[Chemical structure image]

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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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 Pfieyer
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. **DOSSAGE FORM:** Capsules

14. **POTENCY:** 50 mg

15. **CHEMICAL NAME AND STRUCTURE:**
Etoposide. C29H32O13. 588.56. 33419-42-0
Furo[3',4':6,7]naphtho[2,3-d]-1,3dioxol-6(5aH)-one-, 9-
[(4,6-O-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-
tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5P-
[5α,5αβ,8αα,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:**

Bing Cai, Ph.D.

**DATE COMPLETED:**

08/29/01
Contain Trade Secret,
Commercial/Confidential
Information and are not releasable.
APPLICATION NUMBER:
75-635

CORRESPONDENCE
APPLICATION NUMBER:
75-635

BIOEQUIVALENCE
Etoposide Soft Gelatin Capsules
50 mg
ANDA #75-635
Reviewer: Moheb H. Makary
W 75635SD.N99

Genpharm Inc.
Etobicoke, Canada
Submission Date:
November 22, 1999
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® 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® 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, Ph.D.
Division of Bioequivalence
Review Branch III
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.

<table>
<thead>
<tr>
<th>Conc. Spiked (ng/mL)</th>
<th>Quality Controls Spiked on May 27, 1998</th>
<th>Quality Controls Spiked on September 2, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conc. Found (ng/mL)</td>
<td>% Rel. Error</td>
</tr>
<tr>
<td>50.0</td>
<td>48.5</td>
<td>-3.0</td>
</tr>
<tr>
<td></td>
<td>49.0</td>
<td>-2.0</td>
</tr>
<tr>
<td></td>
<td>45.4</td>
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</tr>
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<td>-9.1</td>
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<tr>
<td></td>
<td>3112.1</td>
<td>-11.1</td>
</tr>
</tbody>
</table>

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

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.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Period No.</th>
<th>Type of Analysis</th>
<th>Sampling times (Hours)</th>
<th>First Analysis Date</th>
<th>Last Analysis Date</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>First Analysis</td>
<td>All</td>
<td>June 1, 1998</td>
<td>---</td>
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</tr>
<tr>
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<td>All</td>
<td>June 1, 1998</td>
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</tr>
<tr>
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<td>First Analysis</td>
<td>1.667, 4</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
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<td>0.334, 0.5</td>
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<td>---</td>
</tr>
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</tr>
<tr>
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<td>June 2, 1998</td>
<td>---</td>
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</tr>
<tr>
<td>2</td>
<td>First Analysis</td>
<td>All</td>
<td>June 2, 1998</td>
<td>---</td>
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<tr>
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<td>June 2, 1998</td>
<td>---</td>
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</tr>
<tr>
<td>2</td>
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<td>June 2, 1998</td>
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</tr>
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<tr>
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<td>---</td>
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</tr>
<tr>
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<td>Repeat</td>
<td>48</td>
<td>---</td>
<td>---</td>
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<td>June 8, 1998</td>
<td>---</td>
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</tr>
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<td>June 8, 1998</td>
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<tr>
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<td>---</td>
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<tr>
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<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
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<td>All</td>
<td>June 9, 1998</td>
<td>---</td>
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<td>---</td>
</tr>
<tr>
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<tr>
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<td>45</td>
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</tr>
<tr>
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<td>Repeat</td>
<td>48</td>
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<td>Repeat</td>
<td>48</td>
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</tr>
</tbody>
</table>
## Dates of Study Samples Analysis for Etoposide in Human Plasma

<table>
<thead>
<tr>
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<th>Period No.</th>
<th>Type of Analysis</th>
<th>Sampling Times (Hours)</th>
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<th>Last Analysis Date</th>
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<tr>
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<td>July 30, 1998</td>
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<td>Second Analysis</td>
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<td>July 31, 1998</td>
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<td>48</td>
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<td>September 17, 1998</td>
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<td>1.34, 10.24, 36</td>
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<td></td>
<td>2</td>
<td>First Analysis</td>
<td>All</td>
<td>September 18, 1998</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Repeat</td>
<td>48</td>
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<td>---</td>
</tr>
<tr>
<td></td>
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<td>Repeat</td>
<td>48</td>
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<td>1.2</td>
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<td>All</td>
<td>November 2, 1999</td>
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<td>September 23, 1998</td>
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<td>Stability Repeat</td>
<td>All</td>
<td>November 2, 1999</td>
<td>September 23, 1998</td>
</tr>
</tbody>
</table>

**Note:**

The first analysis date - day on which the subject samples 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.
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

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.

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

(date)
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® 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 G2 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/m² 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/m². 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).


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® 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 °C or 36-46 °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 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)

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

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

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

\[ Y = GRP \times SEQ \times SUBJ(SEQ*GRP) \times PER(GRP) \times TRT \times GRP*TRT; \]

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® (etoposide) Capsules states that the capsules are to be stored under refrigeration 2°C-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°C-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)

<table>
<thead>
<tr>
<th>Method #1 (Seventh Supplement, USP-NF)</th>
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<tbody>
<tr>
<td>Method: USP 23 apparatus I at 50 rpm</td>
</tr>
<tr>
<td>Medium: Mixture of 20 mL of acetic acid, 200 mL of absolute alcohol, and 500 mL of water; 500 mL</td>
</tr>
<tr>
<td>Number of Capsules: 12</td>
</tr>
<tr>
<td>Test product: Genpharm's Etoposide capsules 50 mg, lot #CS-17</td>
</tr>
<tr>
<td>Reference product: Bristol-Myers Squibb's Vepesid® Capsules, 50 mg, lot #WG017</td>
</tr>
<tr>
<td>Specification: NLT 45 minutes</td>
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</table>

<table>
<thead>
<tr>
<th>Method #2 (Ninth Supplement, USP-NF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method: USP 23 apparatus II at 50 rpm</td>
</tr>
<tr>
<td>Medium: 900 mL of acetate buffer pH 4.5</td>
</tr>
<tr>
<td>Number of Capsules: 12</td>
</tr>
<tr>
<td>Test product: Genpharm's Etoposide capsules 50 mg, lot #CS-17</td>
</tr>
<tr>
<td>Reference product: Bristol-Myers Squibb's Vepesid® Capsules, 50 mg, lot #WG017</td>
</tr>
<tr>
<td>Specification: NLT in 30 minutes</td>
</tr>
</tbody>
</table>
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® 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
FT INITIALLED BDAVIT Date: 7/23/99

Concur: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/6-28-99. 7-23-99. 7523580 500
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

<table>
<thead>
<tr>
<th>USP 23 Basket: X</th>
<th>Paddle:</th>
<th>RPM: 50</th>
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</thead>
<tbody>
<tr>
<td>No. Units Tested: 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium: 20 mL acetic acid, 200 mL absolute alcohol and 500 mL Water: 500 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specifications: NLT in 45 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference Drug: Vepeside</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay Methodology:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

II. Results of In Vitro Dissolution Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Minutes)</th>
<th>Test Product Lot #CS-17 Strength (mg) 50</th>
<th>Reference Product Lot #WG017 Strength (mg) 50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean %</td>
<td>Range</td>
</tr>
<tr>
<td>15</td>
<td>9.97</td>
<td>3.1</td>
</tr>
<tr>
<td>30</td>
<td>60.17</td>
<td>15.9</td>
</tr>
<tr>
<td>45</td>
<td>101.56</td>
<td>1.7</td>
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<tr>
<td>60</td>
<td>101.2</td>
<td>1.0</td>
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II. Conditions for Dissolution Testing: Ninth Supplement, USP-NF

<table>
<thead>
<tr>
<th>USP 23 Basket:</th>
<th>Paddle: X</th>
<th>RPM: 50</th>
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<tbody>
<tr>
<td>No. Units Tested: 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium: 900 mL acetate buffer pH 4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specifications: NLT in 30 minutes</td>
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<td></td>
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<tr>
<td>Reference Drug: Vepeside</td>
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<td></td>
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<tr>
<td>Assay Methodology:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

II. Results of In Vitro Dissolution Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Minutes)</th>
<th>Test Product Lot #CS-17 Strength (mg) 50</th>
<th>Reference Product Lot #WG017 Strength (mg) 50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean %</td>
<td>Range</td>
</tr>
<tr>
<td>10</td>
<td>11.73</td>
<td>10.8</td>
</tr>
<tr>
<td>20</td>
<td>90.13</td>
<td>13.1</td>
</tr>
<tr>
<td>30</td>
<td>99.24</td>
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<td>40</td>
<td>98.76</td>
<td>0.82</td>
</tr>
<tr>
<td>Date</td>
<td>6/28/99</td>
<td>USER</td>
</tr>
<tr>
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**ANDA #** 75-635  
**Drug** Etoposide

<table>
<thead>
<tr>
<th>Date</th>
<th>6/28/99</th>
<th>USER</th>
<th>MHM</th>
<th>n = 4</th>
<th>9th USP</th>
<th>Test</th>
<th>Ref</th>
<th>(R-T)2</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td>F2 = 70.96</td>
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</table>

**ANDA #** 75-635  
**Drug** Etoposide
ANDA NUMBER: 75-635

FIRM: Genpharm Inc.

DOSSAGE FORM: Capsules

STRENGTH: 50 mg

DRUG: Etoposide Capsules USP, 50 mg

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


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.?):

<table>
<thead>
<tr>
<th>Lot#</th>
<th>Lot CS-17 (bio/stability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch size</td>
<td></td>
</tr>
</tbody>
</table>

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?)

<table>
<thead>
<tr>
<th>Lot#</th>
<th>Lot CS-17 (bio/stability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch size</td>
<td></td>
</tr>
</tbody>
</table>
PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

<table>
<thead>
<tr>
<th>Executed Batch size</th>
<th>Production Batch size</th>
<th>Comments</th>
</tr>
</thead>
</table>

Within 10X

Bing Cai 5/1/01
Review Chemist

Mike Smela 9/5/01
Team Leader

Division of Chemistry I
OGD/CDER
08/29/01
### Establishment Evaluation Request

**Summary Report**

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

**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**

<table>
<thead>
<tr>
<th>Establishment:</th>
<th>GENPHARM PHARMACEUTICALS INC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AADA No.:</td>
<td>37, 85 ADVANCE, 212-214 NORSEMAN ETOBICOKE, CA</td>
</tr>
</tbody>
</table>

**Profile:** CSG  
**OAI Status:** NONE  
**Responsibilities:** FINISHED DOSAGE PACKAGER

**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 25-OCT-1999  
**Decision:** ACCEPTABLE  
**Reason:** BASED ON PROFILE

<table>
<thead>
<tr>
<th>Establishment:</th>
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<tbody>
<tr>
<td>AADA No.:</td>
<td></td>
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</tbody>
</table>

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

<table>
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<tr>
<th>Establishment:</th>
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</thead>
<tbody>
<tr>
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**Profile:** CSA  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 12-DEC-2000  
**Decision:** ACCEPTABLE

<table>
<thead>
<tr>
<th>Establishment:</th>
<th>DMF No.:</th>
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<tbody>
<tr>
<td>AADA No.:</td>
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Reason: 

Establishment: 

DMF 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: 

377

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: 19-537/5-023 – 49577
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

<table>
<thead>
<tr>
<th>Established Name</th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this product a USP item? If so, USP supplement in which verification was assured. USP 23</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this name different than that used in the Orange Book?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If not USP, has the product name been proposed in the PF?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<p>| 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 | | |</p>
<table>
<thead>
<tr>
<th><strong>Labeling</strong></th>
<th><strong>Labeling (continued)</strong></th>
<th><strong>Scoring:</strong></th>
<th><strong>Inactive Ingredients:</strong></th>
<th><strong>USP Issues:</strong></th>
<th><strong>Bioequivalence Issues:</strong></th>
<th><strong>Patent/Exclusivity Issues:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).</td>
<td>Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be red for the NDA)</td>
<td>Is the scoring configuration different than the RLD?</td>
<td>Inactive Ingredients: (FTR: List page # in application where inactives are listed)</td>
<td>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</td>
<td>Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T1/2 and date study acceptable)</td>
<td>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.</td>
</tr>
<tr>
<td>X</td>
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<td>X</td>
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</table>

**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


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
   Glycerin
   Sorbitol
   Purified water
   (ethyl and propyl)
   Iron oxide
   Titanium 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.

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

Reviewer: __________ Date: 12/23/99
Team Leader: __________ Date: 12/23/99

cc:
ANANDA 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/m²/day for 4 days to 50 mg/m²/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.

f. 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.

[Signature]

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

[Signature]

Bonnie Southen
Director, Core Technical Documentation and Submissions
GENPHARM INC.
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  
Minor Amendment  
Etoposide  
50 mg Capsules

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,

[Signature]

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

[Stamp]  
CENTER FOR DRUG
PMD
AUG 01 2001
OGD
EVALUATION AND RESEARCH
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
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,

Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.
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
Minor Amendment
Etoposide
50 mg Capsules

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.
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,

[Signature]

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

[Stamp] CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 02 2001
OUD
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,

[Signature]

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

Yours sincerely,

[Signature]
Dr. Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.
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
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 representative, Mr. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

Yours sincerely,

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

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

[Signature]
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.

1. The justification 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 0.1% 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 website 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,

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

[Signature]

March 12, 2001

Date

for

Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.
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,

[Signature]

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

Sincerely yours,

[Signature]

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

[Date: June 10]
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 application 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,

[Signature]
Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office ofGeneric 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 potential for the drug substance, Etoposide USP, to meet the criteria for dissolution 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,

[Signature]

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

[Signature]

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
RD INITIALLY BDAVIT
FT INITIALLY BDAVIT
Date: 12/20/99

Concur:
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Date: 12/23/99

Mmakary/12-16-99, 12-20-99, 75635SD.N99
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 [drug substance, Etoposide 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,

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

[Signature]
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 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,

[Signature]

Dr. 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 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,

[Signature]
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
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,

[Signature]

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

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.

[Signature]
Tirtho Uppal
Director, Regulatory Affairs

RECD
AUG 06 1999
OGD
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

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.

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.

NOV 22 1999
(Date)
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,

[Signature]

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

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.
re: Etoposide Capsules USP
50 mg
Page 2 of 2

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

[Signature]

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

[Signature]

May 10, 99 (date)