CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-078

Generic Name: Ifosfamide for Injection USP

Sponsor: American Pharmaceutical Partners, Inc.

Approval Date: May 28, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 76-078

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CENTER FOR DRUG
EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-078

APPROVAL LETTER

ANDA 76-078

MAY 28 2002

American Pharmaceutical Partners, Inc.
Attention: Kathleen Dungan
2045 North Cornell Avenue
Melrose Park, IL 60160

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ifosfamide for Injection USP, packaged in 1 g and 3 g single-dose vials.

Reference is also made to your amendments dated April 20, September 20, and October 23, 2001; and March 25, 2002. Reference is also made to your patent amendments dated August 3, November 2, and December 13, 2001.

The reference listed drug product (RLD), Ifex® for Injection of Bristol Myers Squibb Company Pharmaceutical Research Institute, upon which you have based your application is currently subject to a period of patent protection which expires on March 3, 2008, (U. S. Patent No. 4,882,452, (the '452 patent). Your application contains a Paragraph IV Certification to the '452 patent under Section 505(j)(2)(A)(vii)(IV) of the Act. This certification states that your manufacture, use, or sale of this drug product will not infringe upon the '432 patent. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the '452 paten before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that American Pharmaceutical Partners, Inc. (APP) has complied with the requirements of Section 505(j)(2)(B) of the Act, and that no action for patent infringement was brought against APP within the statutory forty-five day period.

We also note that the RLD is currently in the Discontinued Product List of the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book". Under 21 CFR 314.161(a)(1), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. Reference is made to the Federal Register Notice (Volume 67, No. 93) issued Tuesday, May 14, 2002, entitled "Determination That Ifex (Ifosfamide for Injection), 1-Gram and 3-Gram Vials, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness. This determination allows the agency to approve an ANDA for this drug product.

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 Ifosfamide for Injection, 1 g/vial and 3 g/vial, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ifex® for Injection of Bristol Meyers Squibb Company Pharmaceutical Research Institute).

Furthermore, we note that APP was the first applicant to submit a substantially complete ANDA with a Paragraph IV Certification to the RLD. Therefore, with this approval APP is eligible for 180-days of market exclusivity for this drug product as provided for under the Drug rice Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments in Section 505(j)(5)(B)(iv) of the Act. Such exclusivity will begin to run from the date APP begins commercial marketing of the drug product.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

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,

/S/

Gary Buehler 5/28/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

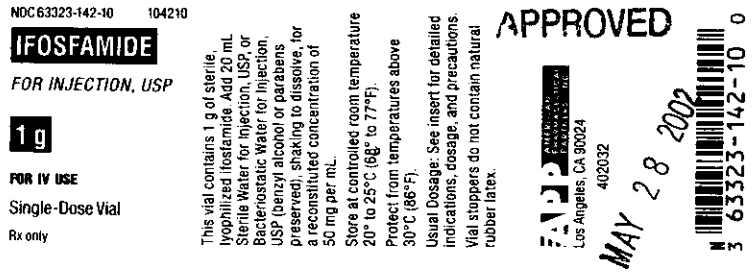
76-078

Final Printed Labeling

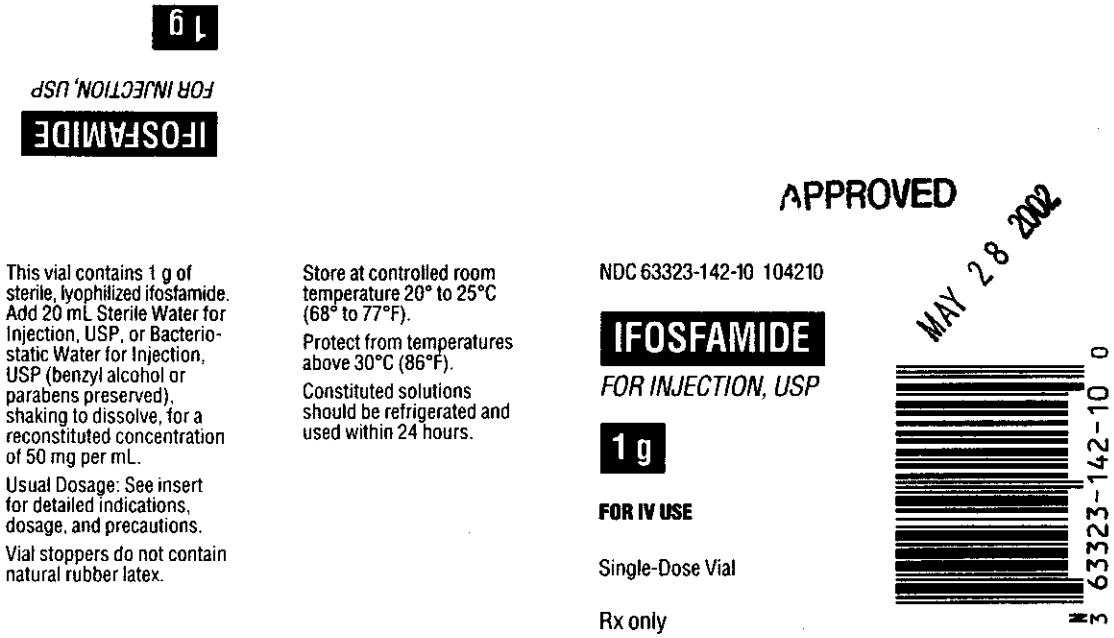
ANDA 76-078
Ifosfamide for Injection, USP

Amendment – Response to
8/2/01 Deficiency Letter

Vial Label
(Product Code 104300 – 3 g/vial)



Vial Label
(Product Code 104210 – 1 g/vial)



Carton
(Product Code 104210 – 1 g/vial)

Extra

ANDA 76-078
Ifosfamide for Injection, USP

Amendment – Response to
8/2/01 & 8/21/01 Deficiency Letters

Product Code 104300
3 g Carton

3 63323-143-00 8

NDC 63323-143-00 104300

IFOSFAMIDE

FOR INJECTION, USP

3 g

MAY 28 2002
APPROVED

FOR IV USE

Single-Dose Vial

Rx only

AMERICAN PHARMACEUTICAL PARTNERS, INC.

AMERICAN PHARMACEUTICAL PARTNERS, INC.

Store at controlled room temperature 20° to 25°C (68° to 77°F).

Protect from temperatures above 30°C (86°F).

Constituted solutions should be refrigerated and used within 24 hours.

This vial contains 3 g of sterile, lyophilized ifosfamide. Add 60 mL Sterile Water for Injection, USP, or Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved), shaking to dissolve, for a reconstituted concentration of 50 mg per mL.

Usual Dosage: See insert for detailed indications, dosage, and precautions.

Vial stoppers do not contain natural rubber latex.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

3 g

IFOSFAMIDE

FOR INJECTION, USP

62751

for 5 consecutive days. Treatment is repeated every 3 weeks or after recovery from hematologic toxicity (Platelets ≥100,000/μL, WBC ≥4,000/μL). In order to prevent bladder toxicity, Ifosfamide for Injection should be given with extensive hydration consisting of at least 2 liters of oral or intravenous fluid per day. A protector, such as mesna, should also be used to prevent hemorrhagic cystitis. Ifosfamide for Injection should be administered as a slow intravenous infusion lasting a minimum of 30 minutes. Although Ifosfamide for Injection has been administered to a small number of patients with compromised hepatic and/or renal function, studies to establish optimal dose schedules of Ifosfamide for Injection in such patients have not been conducted.

Preparation for Intravenous Administration/ Stability

Injections are prepared for parenteral use by adding *Sterile Water for Injection, USP*, or *Bacteriostatic Water for Injection, USP* (benzyl alcohol or parabens preserved), to the vial and shaking to dissolve. Use the quantity of diluent shown below to constitute the product:

Dosage Strength	Quantity of Diluent	Final Concentration
1 gram	20 mL	50 mg/mL
3 grams	60 mL	50 mg/mL

Solutions of ifosfamide may be diluted further to achieve concentrations of 0.6 to 20 mg/mL in the following fluids:

5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP
Sterile Water for Injection, USP

Because essentially identical stability results were obtained for Sterile Water admixtures as for the other admixtures (5% Dextrose Injection, 0.9% Sodium Chloride Injection, and Lactated Ringer's Injection), the use of large volume parenteral glass bottles, Viaflex bags or PAB™ bags that contain intermediate concentrations or mixtures of excipients (e.g., 2.5% Dextrose Injection, 0.45% Sodium Chloride Injection, or 5% Dextrose and 0.9% Sodium Chloride Injection) is also acceptable.

Constituted or constituted and further diluted solutions of Ifosfamide for Injection should be refrigerated and used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED:

Ifosfamide for Injection, USP, lyophilized is available as:

Product No.	NDC No.	
104210	63323-142-10	Ifosfamide for Injection, USP, 1 gram single-dose vial, packaged individually.
104300	63323-143-00	Ifosfamide for Injection, USP, 3 gram single-dose vial, packaged individually.

Vial stoppers do not contain natural rubber latex.

Store at controlled room temperature 20° to 25°C (68° to 77°F).

Protect from temperatures above 30°C (86°F).

Procedures for proper handling and disposal of anticancer drugs should be considered. Skin reactions associated with accidental exposure to Ifosfamide for Injection may occur. The use of gloves is recommended. If Ifosfamide for Injection solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES:

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985; 253 (11):1590-1592.
3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc. D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia:

AMERICAN PHARMACEUTICAL PARTNERS, INC.

APPROVED

45929/Issued: August 2001

IFOSFAMIDE
FOR INJECTION, USP

Rx only

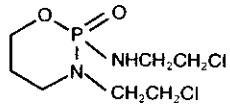
MAY 28 2002

WARNING

Ifosfamide for Injection, USP should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Urotoxic side effects, especially hemorrhagic cystitis, as well as CNS toxicities such as confusion and coma have been associated with the use of ifosfamide. When they occur, they may require cessation of ifosfamide therapy. Severe myelosuppression has been reported (see **"ADVERSE REACTIONS"**).

DESCRIPTION:

Ifosfamide for Injection, USP single-dose vials for constitution and administration by intravenous infusion each contain 1 gram or 3 grams of sterile, lyophilized ifosfamide. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Ifosfamide is 3-(2-chloroethyl)-2-[(2-chloroethyl)amino] tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide. Its structural formula is:



$C_7H_{15}Cl_2N_2O_2P$ **M.W. 261.1**

Ifosfamide is a white crystalline powder that is soluble in water.

CLINICAL PHARMACOLOGY:

Ifosfamide has been shown to require metabolic activation by microsomal liver enzymes to produce biologically active metabolites. Activation occurs by hydroxylation at the ring carbon atom 4 to form the unstable intermediate 4-hydroxyifosfamide. This metabolite rapidly degrades to the stable urinary metabolite 4-ketoifosfamide. Opening of the ring results in formation of the stable urinary metabolite, 4-carboxyifosfamide. These urinary metabolites have not been found to be cytotoxic. N, N-*bis* (2-chloroethyl)-phosphoric acid diamide (ifosphoramide) and acrolein are also found. Enzymatic oxidation of the chloroethyl side chains and subsequent dealkylation produces the major urinary metabolites, dechloroethyl ifosfamide and dechloroethyl cyclophosphamide. The alkylated metabolites of ifosfamide have been shown to interact with DNA.

In vitro incubation of DNA with activated ifosfamide has produced phosphotriesters. The treatment of intact cell nuclei may also result in the formation of DNA-DNA cross-links. DNA repair most likely occurs in G-1 and G-2 stage cells.

Pharmacokinetics

Ifosfamide exhibits dose-dependent pharmacokinetics in humans. At single doses of 3.8 to 5 g/m², the plasma concentrations decay biphasically and the mean terminal elimination half-life is about 15 hours. At doses of 1.6 to 2.4 g/m²/day, the plasma decay is monoexponential and the terminal elimination half-life is about 7 hours. Ifosfamide is extensively metabolized in humans and the metabolic pathways appear to be saturated at high doses.

After administration of doses of 5 g/m² of ^{14}C-labeled ifosfamide, from 70% to 86% of the dosed radioactivity was recovered in the urine, with about 61% of the dose excreted as parent compound. At doses of 1.6 to 2.4 g/m² only 12% to 18% of the dose was excreted in the urine as unchanged drug within 72 hours.

Two different dechloroethylated derivatives of ifosfamide, 4-carboxyifosfamide, thiodiacetic acid and cysteine conjugates of chloroacetic acid have been identified as the major urinary metabolites of ifosfamide in humans and only small amounts of 4-hydroxyifosfamide and acrolein are present. Small quantities

3 grams	60 mL	50 mg/mL

Solutions of ifosfamide may be diluted further to achieve concentrations of 0.6 to 20 mg/mL in the following fluids:

5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP
Sterile Water for Injection, USP

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4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.
5. Jones, RB, *et al*: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center, CA-A Cancer Journal for Clinicians 1983; (Sept./Oct.) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990;47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK-PRACTICE GUIDELINES). Am J Health-Syst Pharm 1996; 53:1669-1685.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

45929
Issued: August 2001

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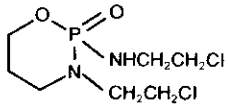

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In vitro incubation of DNA with activated ifosfamide has produced phosphotriesters. The treatment of intact cell nuclei may also result in the formation of DNA-DNA cross-links. DNA repair most likely occurs in G-1 and G-2 stage cells.

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After administration of doses of 5 g/m² of ^{14}C-labeled ifosfamide, from 70% to 86% of the dosed radioactivity was recovered in the urine, with about 61% of the dose excreted as parent compound. At doses of 1.6 to 2.4 g/m² only 12% to 18% of the dose was excreted in the urine as unchanged drug within 72 hours.

Two different dechloroethylated derivatives of ifosfamide, 4-carboxyifosfamide, thiodiacetic acid and cysteine conjugates of chloroacetic acid have been identified as the major urinary metabolites of ifosfamide in humans and only small amounts of 4-hydroxyifosfamide and acrolein are present. Small quantities (nmole/mL) of ifosfamide mustard and 4-hydroxyifosfamide are detectable in human plasma. Metabolism of ifosfamide is required for the generation of the biologically active species and while metabolism is extensive, it is also quite variable among patients.

In a study at Indiana University, 50 fully evaluable patients with germ cell testicular cancer were treated with Ifosfamide for Injection in combination with cisplatin and either vinblastine or etoposide after failing (47 of 50 patients) at least two prior chemotherapy regimens consisting of cisplatin/vinblastine/bleomycin, (PVB), cisplatin/vinblastine/actinomycin D/bleomycin/cyclophosphamide, (VAB6), or the combination of cisplatin and etoposide. Patients were selected for remaining cisplatin sensitivity because they had previously responded to a cisplatin containing regimen and had not progressed while on the cisplatin containing regimen or within 3 weeks of stopping it. Patients served as their own control based on the premise that long term complete responses could not be achieved by retreatment with a regimen to which they had previously responded and subsequently relapsed.

Ten of 50 fully evaluable patients were still alive 2 to 5 years after treatment. Four of the 10 long term survivors were rendered free of cancer by surgical resection after treatment with the

ifosfamide regimen; median survival for the entire group of 50 fully evaluable patients was 53 weeks.

INDICATIONS AND USAGE:
Ifosfamide for Injection, used in co[illegible]n with certain other approved antineoplastic agents, is indicated for third line chemotherapy of germ cell testicular cancer. It should ordinarily be used in combination with a prophylactic agent for hemorrhagic cystitis, such as mesna.

CONTRAINDICATIONS:
Continued use of Ifosfamide for Injection is contraindicated in patients with severely depressed bone marrow function (see **WARNINGS** and **PRECAUTIONS** sections). Ifosfamide for Injection is also contraindicated in patients who have demonstrated a previous hypersensitivity to it.

WARNINGS:
Urinary System
Urotoxic side effects, especially hemorrhagic cystitis, have been frequently associated with the use of ifosfamide. It is recommended that a urinalysis should be obtained prior to each dose of ifosfamide. If microscopic hematuria (greater than 10 RBCs per high power field), is present, then subsequent administration should be withheld until complete resolution.

Further administration of ifosfamide should be given with vigorous oral or parenteral hydration.

Hematopoietic System
When ifosfamide is given in combination with other chemotherapeutic agents, severe myelosuppression is frequently observed. Close hematologic monitoring is recommended. White blood cell (WBC) count, platelet count and hemoglobin should be obtained prior to each administration and at appropriate intervals. Unless clinically essential, ifosfamide should not be given to patients with a WBC count below 2000/μL and/or a platelet count below 50,000/μL.

Central Nervous System
Neurologic manifestations consisting of somnolence, confusion, hallucinations and in some instances, coma, have been reported following ifosfamide therapy. The occurrence of these symptoms requires discontinuing ifosfamide therapy. The symptoms have usually been reversible and supportive therapy should be maintained until their complete resolution.

Pregnancy
Animal studies indicate that the drug is capable of causing gene mutations and chromosomal damage *in vivo*. Embryotoxic and teratogenic effects have been observed in mice, rats and rabbits at doses 0.05 to 0.075 times the human dose. Ifosfamide can cause fetal damage when administered to a pregnant woman. If ifosfamide is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS:
General
Ifosfamide should be given cautiously to patients with impaired renal function as well as to those with compromised bone marrow reserve, as indicated by: leukopenia, granulocytopenia, extensive bone marrow metastases, prior radiation therapy, or prior therapy with other cytotoxic agents.

Laboratory Tests
During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. Urine should also be examined regularly for red cells which may precede hemorrhagic cystitis.

Drug Interactions
The physician should be alert for possible combined drug actions, desirable or undesirable, involving ifosfamide even though ifosfamide has been used successfully concurrently with other drugs, including other cytotoxic drugs.

Wound Healing
Ifosfamide may interfere with normal wound healing.

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

Nursing Mothers
Ifosfamide is excreted in breast milk. Because of the potential for serious adverse events and the tumorigenicity shown for ifosfamide in animal studies, 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.

Carcinogenesis, Mutagenesis, Impairment

ADVERSE REACTIONS:
In patients receiving ifosfamide as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity. Dose fractionation, vigorous hydration, and a protector such as mesna can significantly reduce the incidence of hematuria, especially gross hematuria, associated with hemorrhagic cystitis. At a dose of 1.2 g/m² daily for 5 consecutive days, leukopenia, when it occurs, is usually mild to moderate. Other significant side effects include alopecia, nausea, vomiting, and central nervous system toxicities.

Adverse Reaction	*Incidence (%)
Alopecia	83
Nausea-Vomiting	58
Hematuria	46
Gross Hematuria	12
CNS Toxicity	12
Infection	8
Renal Impairment	6
Liver Dysfunction	3
Phlebitis	2
Fever	1
Allergic Reaction	<1
Anorexia	<1
Cardiotoxicity	<1
Coagulopathy	<1
Constipation	<1
Dermatitis	<1
Diarrhea	<1
Fatigue	<1
Hypertension	<1
Hypotension	<1
Malaise	<1
Polyneuropathy	<1
Pulmonary Symptoms	<1
Salivation	<1
Stomatitis	<1

*Based upon 2,070 patients from the published literature in 30 single agent studies.

Hematologic Toxicity
Myelosuppression was dose related and dose limiting. It consisted mainly of leukopenia and, to a lesser extent, thrombocytopenia. A WBC count <3000/μL is expected in 50% of the patients treated with ifosfamide single agent at doses of 1.2 g/m² per day for 5 consecutive days. At this dose level, thrombocytopenia (platelets <100,000/μL) occurred in about 20% of the patients. At higher dosages, leukopenia was almost universal, and at total dosages of 10 to 12 g/m² /cycle, one half of the patients had a WBC count below 1000/μL and 8% of patients had platelet counts less than 50,000/μL. Myelosuppression was usually reversible and treatment can be given every 3 to 4 weeks. When ifosfamide is used in combination with other myelosuppressive agents, adjustments in dosing may be necessary. Patients who experience severe myelosuppression are potentially at increased risk for infection. Anemia has been reported as part of postmarketing surveillance.

Digestive System
Nausea and vomiting occurred in 58% of the patients who received ifosfamide. They were usually controlled by standard antiemetic therapy. Other gastrointestinal side effects include anorexia, diarrhea, and in some cases, constipation.

Urinary System
Urotoxicity consisted of hemorrhagic cystitis, dysuria, urinary frequency and other symptoms of bladder irritation. Hematuria occurred in 6% to 92% of patients treated with ifosfamide. The incidence and severity of hematuria can be significantly reduced by using vigorous hydration, a fractionated dose schedule and a protector such as mesna. At daily doses of 1.2 g/m² for 5 consecutive days without a protector, microscopic hematuria is expected in about one half of the patients and gross hematuria in about 8% of patients.

Renal toxicity occurred in 6% of the patients treated with ifosfamide as a single agent. Clinical signs, such as elevation in BUN or serum creatinine or decrease in creatinine clearance, were usually transient. They were most likely to be related to tubular damage. One episode of renal tubular acidosis which progressed into chronic renal failure was reported. Proteinuria and acidosis also occurred in rare instances. Metabolic acidosis was reported in 31% of patients in one study when ifosfamide was administered at doses of 2 to 2.5 g/m²/day for 4 days. Renal tubular acidosis, Fanconi syndrome, renal rickets, and acute renal failure have been reported. Close clinical monitoring of serum and urine chemistries including phosphorus, potassium, alkaline phosphatase and other appropriate laboratory studies is recommended. Appropriate replacement therapy should be administered as indicated.

Central Nervous System
CNS side effects were observed in 12% of

Further administration of ifosfamide should be given with vigorous oral or parenteral hydration.

Hematopoietic System
When ifosfamide is given in combination with other chemotherapeutic agents, severe myelosuppression is frequently observed. Close hematologic monitoring is recommended. White blood cell (WBC) count, platelet count and hemoglobin should be obtained prior to each administration and at appropriate intervals. Unless clinically essential, ifosfamide should not be given to patients with a WBC count below 2000/μL and/or a platelet count below 50,000/μL.

Central Nervous System
Neurologic manifestations consisting of somnolence, confusion, hallucinations and in some instances, coma, have been reported following ifosfamide therapy. The occurrence of these symptoms requires discontinuing ifosfamide therapy. The symptoms have usually been reversible and supportive therapy should be maintained until their complete resolution.

Pregnancy
Animal studies indicate that the drug is capable of causing gene mutations and chromosomal damage *in vivo*. Embryotoxic and teratogenic effects have been observed in mice, rats and rabbits at doses 0.05 to 0.075 times the human dose. Ifosfamide can cause fetal damage when administered to a pregnant woman. If ifosfamide is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS:
General
Ifosfamide should be given cautiously to patients with impaired renal function as well as to those with compromised bone marrow reserve, as indicated by: leukopenia, granulocytopenia, extensive bone marrow metastases, prior radiation therapy, or prior therapy with other cytotoxic agents.

Laboratory Tests
During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. Urine should also be examined regularly for red cells which may precede hemorrhagic cystitis.

Drug Interactions
The physician should be alert for possible combined drug actions, desirable or undesirable, involving ifosfamide even though ifosfamide has been used successfully concurrently with other drugs, including other cytotoxic drugs.

Wound Healing
Ifosfamide may interfere with normal wound healing.

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

Nursing Mothers
Ifosfamide is excreted in breast milk. Because of the potential for serious adverse events and the tumorigenicity shown for ifosfamide in animal studies, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Ifosfamide has been shown to be carcinogenic in rats, with female rats showing a significant incidence of leiomyosarcomas and mammary fibroadenomas.

The mutagenic potential of ifosfamide has been documented in bacterial systems *in vitro* and mammalian cells *in vivo*. *In vivo*, ifosfamide has induced mutagenic effects in mice and *Drosophila melanogaster* germ cells, and has induced a significant increase in dominant lethal mutations in male mice as well as recessive sex-linked lethal mutations in Drosophila.

In pregnant mice, resorptions increased and anomalies were present at day 19 after 30 mg/m² dose of ifosfamide was administered on day 11 of gestation. Embryolethal effects were observed in rats following the administration of 54 mg/m² doses of ifosfamide from the 6th through the 15th day of gestation and embryotoxic effects were apparent after dams received 18 mg/m² doses over the same dosing period. Ifosfamide is embryotoxic to rabbits receiving 88 mg/m²/day doses from the 6th through the 18th day after mating. The number of anomalies was also significantly increased over the control group.

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

Constipation	<1
Dermatitis	<1
Diarrhea	<1
Fatigue	<1
Hypertension	<1
Hypotension	<1
Malaise	<1
Polyneuropathy	<1
Pulmonary Symptoms	<1
Salivation	<1
Stomatitis	<1

*Based upon 2,070 patients from the published literature in 30 single agent studies.

Hematologic Toxicity
Myelosuppression was dose related and dose limiting. It consisted mainly of leukopenia and, to a lesser extent, thrombocytopenia. A WBC count <3000/μL is expected in 50% of the patients treated with ifosfamide single agent at doses of 1.2 g/m² per day for 5 consecutive days. At this dose level, thrombocytopenia (platelets <100,000/μL) occurred in about 20% of the patients. At higher dosages, leukopenia was almost universal, and at total dosages of 10 to 12 g/m²/cycle, one half of the patients had a WBC count below 1000/μL and 8% of patients had platelet counts less than 50,000/μL. Myelosuppression was usually reversible and treatment can be given every 3 to 4 weeks. When ifosfamide is used in combination with other myelosuppressive agents, adjustments in dosing may be necessary. Patients who experience severe myelosuppression are potentially at increased risk for infection. Anemia has been reported as part of postmarketing surveillance.

Digestive System
Nausea and vomiting occurred in 58% of the patients who received ifosfamide. They were usually controlled by standard antiemetic therapy. Other gastrointestinal side effects include anorexia, diarrhea, and in some cases, constipation.

Urinary System
Urotoxicity consisted of hemorrhagic cystitis, dysuria, urinary frequency and other symptoms of bladder irritation. Hematuria occurred in 6% to 92% of patients treated with ifosfamide. The incidence and severity of hematuria can be significantly reduced by using vigorous hydration, a fractionated dose schedule and a protector such as mesna. At daily doses of 1.2 g/m² for 5 consecutive days without a protector, microscopic hematuria is expected in about one half of the patients and gross hematuria in about 8% of patients.

Renal toxicity occurred in 6% of the patients treated with ifosfamide as a single agent. Clinical signs, such as elevation in BUN or serum creatinine or decrease in creatinine clearance, were usually transient. They were most likely to be related to tubular damage. One episode of renal tubular acidosis which progressed into chronic renal failure was reported. Proteinuria and acidosis also occurred in rare instances. Metabolic acidosis was reported in 31% of patients in one study when ifosfamide was administered at doses of 2 to 2.5 g/m²/day for 4 days. Renal tubular acidosis, Fanconi syndrome, renal rickets, and acute renal failure have been reported. Close clinical monitoring of serum and urine chemistries including phosphorus, potassium, alkaline phosphatase and other appropriate laboratory studies is recommended. Appropriate replacement therapy should be administered as indicated.

Central Nervous System
CNS side effects were observed in 12% of patients treated with ifosfamide. Those most commonly seen were somnolence, confusion, depressive psychosis, and hallucinations. Other less frequent symptoms include dizziness, disorientation, and cranial nerve dysfunction. Seizures and coma with death were occasionally reported. The incidence of CNS toxicity may be higher in patients with altered renal function.

Other
Alopecia occurred in approximately 83% of the patients treated with ifosfamide as a single agent. In combination, this incidence may be as high as 100%, depending on the other agents included in the chemotherapy regimen. Increases in liver enzymes and/or bilirubin were noted in 3% of the patients. Other less frequent side effects included phlebitis, pulmonary symptoms, fever of unknown origin, allergic reactions, stomatitis, cardiotoxicity, and polyneuropathy.

OVERDOSAGE:
No specific antidote for ifosfamide is known. Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur.

DOSAGE AND ADMINISTRATION:
Ifosfamide for Injection should be administered intravenously at a dose of 1.2 g/m² per day

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-078

CHEMISTRY REVIEW(S)

1. **CHEMISTRY REVIEW NO.** 1

2. **ANDA #** 76-078

3. **NAME AND ADDRESS OF APPLICANT**

American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park, IL 60160

4. **LEGAL BASIS FOR SUBMISSION**

NDA 19-763 Ifex® (Bristol Myers Squibb)

The drug product is currently discontinued, and a Citizen's Petition is pending if it was withdrawn for safety or efficacy.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Ifosfamide

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

N/A

9. **AMENDMENTS AND OTHER DATES:**

December 22, 2000	Original Submission
April 20, 2001	Amendment (revisions to Sterility Assurance)

10. **PHARMACOLOGICAL CATEGORY**

Antineoplastic

11. **Rx or OTC**

Rx

12. **RELATED IND/NDA/DMF(s)**

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM**

Injection

14. **POTENCY**

1 gm/vial
3 gm/vial

15. **CHEMICAL NAME AND STRUCTURE**

See USP 24, page 861.

16. **RECORDS AND REPORTS**

N/A

17. **COMMENTS**

18. **CONCLUSIONS AND RECOMMENDATIONS**

This ANDA is not approvable. Inform the applicant of deficiencies listed in item 38 of the review.

19. **REVIEWER:** **DATE COMPLETED:**

Shirley S. Brown July 17, 2001

APPEARS THIS WAY
ON ORIGINAL

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Chemistry Closed

1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 76-078

3. **NAME AND ADDRESS OF APPLICANT**

American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park, IL 60160

4. **LEGAL BASIS FOR SUBMISSION**

NDA 19-763 Ifex® (Bristol Myers Squibb)

The drug product is currently discontinued, and a Citizen's Petition to determine if it was withdrawn for safety or efficacy is pending.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Ifosfamide

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

N/A

9. **AMENDMENTS AND OTHER DATES:**

December 22, 2000	Original Submission
April 20, 2001	Amendment (revisions to Sterility Assurance)
August 3, 2001	Amendment (re. Patent Certification)
*September 20, 2001	Amendment (responding to deficiencies)
*October 23, 2001	Telephone Amendment

*subject of this review.

10. **PHARMACOLOGICAL CATEGORY**

Antineoplastic

11. **Rx or OTC**

Rx

12. **RELATED IND/NDA/DMF(s)**

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM

Injection

14. POTENCY

1 gm/vial
3 gm/vial

15. CHEMICAL NAME AND STRUCTURE

See USP 24, page 861.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

A. The applicant was asked to note and acknowledge the following comments in their response:

(1) **The microbiologist's review of the submission for sterility assurance is pending.**

Response: This amendment contains a response to Microbiology deficiencies per the August 21, 2001 letter.

(2) **A review of your bioequivalence information is pending.**

Response: Acknowledged.

(3) **A satisfactory compliance evaluation of facilities referenced in the ANDA is required for approval. We have requested an evaluation from the Office of Compliance.**

Response: Acknowledged.

(4) **Your response must also address the labeling deficiencies.**

Response: Deficiencies are addressed. A copy of the August 3, 2001 amendment revising the patent certification from a Paragraph II certification to a Paragraph IV certification is provided (Attachment 10).

(5

a literature reference in the Merck Index, 12th Edition.

B. Review of request for waiver of *in-vivo* bioequivalence studies is pending.

C. A satisfactory compliance evaluation of facilities referenced in the ANDA is pending.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Chemistry is closed. Bioequivalence status, EER and Citizens Petition are pending.

19. **REVIEWER:**

/S/

Shirley S. Brown

DATE COMPLETED:

10/25/01

October 16, 2001
October 24, 2001 (revised per 10/23/01 Telephone Amendment)

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ON ORIGINAL

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ANDA # 76-078/ADDENDUM TO CHEMISTRY REVIEW #2

AMENDMENTS AND OTHER DATES: (since completion of CR #2):
November 2 and December 13, 2001 Amendments (Patent Issues)
March 25, 2002 Amendment (alternate testing facility)

BIOEQUIVALENCY STATUS

The Division of Bioequivalence agrees that the information submitted by American Pharmaceutical Partners, Inc. demonstrates that its Ifosfamide for Injection, USP, 1 g/vial and 3 g/vial falls under 21 CFR 320.22 (d)(2) of the Bioavailability/Bioequivalence regulations. The waivers of in vivo bioequivalence study requirements for Ifosfamide for Injection, USP, 1 g/vial and 3 g/vial are granted. Review signed by the Director, Division of Bioequivalence on May 14, 2002.

Satisfactory

ESTABLISHMENT INSPECTION

Per the March 25, 2002 Amendment: The following facility is proposed as an alternate facility to perform chemistry analytical testing on the drug substance and the drug product:

American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park, Illinois

cGMP Certification statement for this facility is provided.

Note: This facility was listed as a sterility testing facility per the initial submission, and was included on the 27-DEC-2000 EER. The Overall Recommendation per the EER Summary Report is Acceptable. The alternate facility is acceptable.

EER - Acceptable on Nov. 20, 2001 by Garcia.

Satisfactory

DMF CHECKLIST FOR ANDA # 76-078, ADDENDUM TO REVIEW #2

Remains current as per Review #2. No new amendments submitted to DMF

CONCLUSION AND RECOMMENDATION

The application is approvable.

REVIEWER:

/S/

Shirley S. Brown

DATE COMPLETED:

May 24, 2002

May 15, 2002

May 22, 2002 (revised)

cc:

ANDA 76-078
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/SBrown /S/ 5/24/02

HFD-625/MSmela /S/ 5/24/02

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F/T by: md/5/22/02

APPROVABLE

MINOR AMENDMENT

ANDA 76-078

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

AUG - 2 2001

TO: APPLICANT: American Pharmaceutical Partners, Inc. TEL: (708) 547-2384

ATTN: Tom Stothoff FAX: (708) 343-4269

FROM: Michelle Dillahunt PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ifosfamide for Injection USP, 1gm/vial and 3 gm/vial.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

EMC Comments attached

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-078

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #1
August 3, 2001

A. 1. **ANDA 76-078**

APPLICANT: American Pharmaceutical Partners, Inc.

2. PRODUCT NAME: Ifosfamide for Injection, USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1g in 30mL vial and 3g in 100mL vial; Lyophilized powder; I/V

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antineoplastic

B. 1. DATE OF INITIAL SUBMISSION: December 22, 2000
Subject of this Review (Recd. December 27, 2000)

2. DATE OF AMENDMENT: April 20, 2001
Subject of this Review (Recd. April 23, 2001)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: July 27, 2001

C. REMARKS: The subject drug product is manufactured by American Pharmaceutical Partners, Inc. at its Melrose Park, IL manufacturing facility. The subject drug is [redacted] in 30 and 100-mL glass vials in the [redacted]

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant" found at the end of this review. The above deficiencies represent a **Minor** amendment.

/S/ 8/20/01
Nrapendra Nath, Ph. D.

/S/ 8/20/01

cc: Original **ANDA**
Duplicate ANDA
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Drafted by N. Nath, HFD 600; V:\microrev\76-078.doc
Initialed by A. High

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OFFICE OF GENERIC DRUGS, HFD-620

Microbiology Review #2

October 1, 2001

A. 1. **ANDA** 76-078

APPLICANT: American Pharmaceutical Partners, Inc.

2. PRODUCT NAME: Ifosfamide for Injection, USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1g in 30mL vial and 3g in 100mL vial; Lyophilized powder; I/V

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antineoplastic

B. 1. DATE OF INITIAL SUBMISSION: December 22, 2000 (Recd. December 27, 2000)

2. DATE OF AMENDMENT: September 20, 2001 **Subject of this Review (Recd. September 21, 2001)**

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: September 28, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated August 21, 2001.

D. CONCLUSIONS: The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

/S/

Nrapendra Nath, Ph. D. 10/2/01

/S/

10/3/01

CC: Original **ANDA**
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Drafted by N. Nath, HFD 600; V:\microrev\76-078a1.doc
Initialed by A. High

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-078

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-078
SPONSOR : American Pharmaceutical Partners, Inc.
DRUG AND DOSAGE FORM : Ifosfamide for Injection, USP
STRENGTH(S) : 1 g/vial in a 30 mL vial and 3 g/vial in a 100 mL vial
TYPES OF STUDIES : N/A
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A
DISSOLUTION : N/A.
WAIVER : Acceptable

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III
INITIAL : /S/ _____ DATE : 3/19/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III
INITIAL : __ /S/ _____ DATE : 3/19/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : _ /S/ _____ DATE : 5/14/02

BIOEQUIVALENCY COMMENTS

ANDA: 76-078

APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Ifosfamide for Injection, USP,
1 g/vial in 30 mL vial & 3 g/vial in 100 mL vial

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

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,

/S/

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-078
SPONSOR : American Pharmaceutical Partners, Inc.
DRUG AND DOSAGE FORM : Ifosfamide for Injection, USP
STRENGTH(S) : 1 g/vial in a 30 mL vial and 3 g/vial in a 100 mL vial
TYPES OF STUDIES : N/A
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A
DISSOLUTION : N/A.
WAIVER : Acceptable

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III
INITIAL : /S/ _____ DATE : 3/19/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III
INITIAL : ___ /S/ _____ DATE : 3/19/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : ___ /S/ _____ DATE : 5/14/02

Ifosfamide for Injection
1 g/vial in 30 mL vial
3 g/vial in 100 mL vial
ANDA # **76-078**
Reviewer: Z.Z. Wahba
File #76078w.d00

American Pharmaceutical Partners
Melrose Park, IL
Submission Dates:
December 22, 2000

Review of Waiver Requests

Background

1. The firm has requested a waiver from *in vivo* bioavailability requirements for its Ifosfamide for Injection, 1 g/vial in 30 mL vial, and 3 g/vial in 100 mL vial.

2. The RLD Bristol Myers Squibb's IFEX® for injection, 1 gm/vial and 3 gm/vial is on the discontinued drug product list in the 2001 Orange Book. Currently, IFEX® for Injection is marketed only co-packaged with mesna under the name IFEX/MESNEX. The innovator claims marketing of stand-alone Ifosfamide for Injection without co-packaging with mesna would be unsafe because co-administration with mesna is necessary to avoid urotoxic side effects and co-packaging provides greater assurance that physicians will administer mesna with Ifosfamide for Injection.

3. On 01/31/2001, the firm submitted a Citizen Petition (CP) for Ifosfamide for Injection, USP. The CP is seeking determination whether IFEX® was withdrawn from the market by Bristol-Myers Squibb for safety or effectiveness reasons.

4. On 06/28/2000, the Office of Generic Drugs (OGD) submitted a memorandum to the Division of Oncology Drug Product, seeking a determination whether the single ingredient non-co-packaged drug product approved under NDA #19-763, IFEX® (Ifosfamide), can be marketed as a stand-alone product (see Attachment #1).

5. On 07/11/2000, Dr. John R. Johnson, Acting Deputy Director Division of Oncology Drug Products provided the following reply: The FDA has no requirement that co-administered products must be co-packaged even if the co-administration is necessary for safety reasons. Ifsofamide for Injection could be approved without co-packaging with mesna without compromising patient safety (see Attachment #2).

Formulations (NOT TO BE RELEASED UNDER FOI)

Comparative formulation of the test and the reference products are as follows:

Ingredient	Test Product[1]		Reference Product[2]	
	1 g/vial	3 g/vial	1 g/vial	3 g/vial
Ifosfamide, USP	1.00 g	3.00 g	1.00	3.00

1 [redacted]

2 The RLD is Bristol Myers Squibb's IFEX® for injection, 1 gm/vial and 3 gm/vial.

COMMENTS

1. The compositions of the test products are qualitatively and quantitatively same as that of the reference products.

2. The waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR320.22 (b)(1).

3. In accordance with 21 CFR 314.161(a)(1)&(c), the Agency may make a determination whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons prior to approving an abbreviated new drug application that refers to the listed drug. The Agency shall publish its determination in the Federal Register.

RECOMMENDATION

1. The Division of Bioequivalence agrees that the information submitted by American Pharmaceutical Partners, Inc. demonstrates that its Ifosfamide for Injection, USP, 1 g/vial in 30 mL vial and 3 g/vial in 100 mL vial falls under 21 CFR Section 320.22 (b)(1) of Bioavailability/ Bioequivalence Regulations. The waivers of in vivo bioequivalence study requirements for Ifosfamide for Injection, USP, 1 g/vial in a 30 mL vial and 3 g/vial in a

100 mL vial are granted. From the bioequivalence point of view, the Division of Bioequivalence deems American Pharmaceutical Partners' Ifosfamide for Injection, USP, 1 g/vial and 3 g/vial to be bioequivalent to Bristol Myers Squibb's IFEX® for injection, 1 gm/vial and 3 gm/vial.

2. Note: The approval of this product is pending the approval of the Citizen Petition (CP) for Ifosfamide for Injection.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III /S/ 3/16/01

RD INITIALLED BDAVIT /S/ Date: 3/19/01
FT INITIALLED BDAVIT

Concur: _____ Date: 3/26/2001
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS

ANDA: 76-078

APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Ifosfamide for Injection, USP,
1 g/vial in 30 mL vial & 3 g/vial in 100 mL vial

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

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,

/S/

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

CC: ANDA: 76-078
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba /S/ 3/19/01
HFD-658/ B. Davit /S/ 3/19/01
HFD-650/ D. Conne /S/ 3/26/2001

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BIOEQUIVALENCY - ACCEPTABLE submission date: 12/22/2000

ok 1. **WAIVER (WAI)** Strengths: 1 g/vial in a 30 mL vial
Outcome: AC

ok 2. **WAIVER (WAI)** Strengths: 3 g/vial in a 100 mL vial
Outcome: AC

OUTCOME DECISIONS: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-078

ADMINISTRATIVE DOCUMENTS

ANDA NUMBER 76-078

FIRM: American Pharmaceutical Partners, Inc.

DOSAGE FORM: Injection

STRENGTH: 1 gm/ vial, 3 g/vial

DRUG: Ifosfamide

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 20-NOV-2001

BIO STUDY:

The Division of Bioequivalence agrees that the information submitted by American Pharmaceutical Partners, Inc demonstrates that its Ifosfamide for Injection, USP, 1 g/vial and 3 g/vial falls under 21 CFR 320.22 (d)(2) of the Bioavailability/Bioequivalence regulations. The waivers of in vivo bioequivalence study requirements for Ifosfamide for Injection, USP, 1 g/vial and 3 g/vial are granted.

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

N/A

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

30 ml Vial: [redacted]

100 ml Vial: [redacted]

Closure: [redacted]

Seal: [redacted]

LABELING

Satisfactory per the September 24, 2001 Approval Summary.

STERILIZATION VALIDATION (IF APPLICABLE):

Recommended for approval on the basis of sterility assurance per October 1, 2001 review.

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

[redacted] - 1 g/vial
[redacted] - 3 g/vial

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

Same batches.

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

[redacted] - 1 g/vial
[redacted] - 3 g/vial

Same Process

Review Chemist: Shirley S. Brown /S/ 5/24/02
Team Leader: Mike Smela /S/ - 5/24/02
Date: May 15, 2002

V:\FIRMSAM\APP\LTRS&REV\check76.078

F/T by:md/5/22/02

Attachment #1 OGD 00-235

cc: GB CP
RH DH

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 28, 2000 /S/

FROM: Gary Buehler, Acting Director
Office of Generic Drugs 6/28/00

SUBJECT: Marketing Determination for Non-Co-Packaged Drug Product (Ifex, NDA 19-763)

TO: Richard Pazdur, M.D., Director
Division of Oncologic Drug Products

THROUGH: Robert Temple, M.D., Director
Office of Drug Evaluation I /S/ 7/5/00

The Office of the Chief Counsel has requested that OGD obtain formal determination from the Division of Oncologic Drug Products as to whether ifosfamide for injection can be approved as a stand-alone drug product. Therefore, OGD is seeking a determination whether the single ingredient non-co-packaged drug product approved under NDA 19-763, Ifex (Ifosfamide), can be marketed.

In accordance with 21 CFR 314.161(a)(1) & (c), the Agency may make a determination whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons prior to approving an abbreviated new drug application that refers to the listed drug. The Agency shall publish its determination in the Federal Register.

Bristol-Myers Squibb (BMS) is claiming that an ANDA for an ifosfamide-only product should not be approved because it would be unsafe. This contention is based on Ifex labeling directing administration only in conjunction with a uroprotective agent such as Mesnex (mesna) in order to avoid urotoxic side effects. BMS also states in their correspondence that the combination packaging containing the uroprotective agent Mesnex provides greater assurance that physicians will co-administer mesna injection with ifosfamide for injection. Therefore, ifosfamide-only generic products would be unsafe.

Before an ANDA can be approved for an ifosfamide for injection drug product, the Agency must make a determination whether it is safe to approve an ifosfamide for injection drug product that is not co-packaged with mesna injection. The determination will then be forwarded to the Regulatory Policy Staff for publication in the Federal Register.

We look forward to your response and would appreciate an answer as soon as possible since a formal response to BMS is dependent upon your determination.

If you have any questions or require further information regarding this issue, you may contact Don Hare, Special Assistant to the Director, Office of Generic Drugs at 301-827-5845.

Q:\firms-am\bristol\memos\00-06-28

Attachment #2

MEMORANDUM

DATE July 11, 2000

FROM John R. Johnson, M.D., Acting Deputy Director Division of Oncologic Drug Products /S/ 7-11-00

SUBJECT Marketing Determination for Non-Co-Packaged Drug Product (Ifex for Injection, NDA 19763)

TO Gary Buehler, Acting Director Office of Generic Drugs

THROUGH Robert Temple, M.D., Director Office of Drug Evaluation I

Dr. Pazdur has asked me to respond to your Memorandum to Dr. Pazdur, dated June 28, 2000, because Dr. Pazdur is recused from participating in matters involving Bristol-Myers Squibb. Your Memorandum asks for a formal determination as to whether Ifosfamide for Injection as approved under NDA 19763 can be approved as a stand-alone product without co-packaging with mesna. Ifex for Injection is marketed only co-packaged with mesna and the labeling states that "A protector, such as mesna, should also be used to prevent hemorrhagic cystitis". You indicate that Bristol-Myers Squibb claims marketing of stand-alone Ifosfamide for Injection without co-packaging with mesna would be unsafe because co-administration with mesna is necessary to avoid urotoxic side effects and co-packaging provides greater assurance that physicians will administer mesna with Ifosfamide for Injection.

Many oncologic products are routinely co-administered with other products. In the vast majority of cases these products are not co-packaged. For example the labeling of Bristol-Myers Squibb's Taxol requires several premedications for safe administration, but none of the premedications is co-packaged with Taxol. The FDA has no requirement that co-administered products must be co-packaged even if the co-administration is necessary for safety reasons. Imposition of such a requirement would be a major change with far reaching effects and should not be undertaken without strong evidence of the benefit to patients. Unless data is provided to the contrary, it is my opinion that

Ifosfamide for Injection could be approved without co-packaging with mesna without compromising patient safety. The benefit to cancer patients of increased competition in the marketplace outweighs any unproven theory that co-packaging provides greater safety.

Note that mesna is available as a single entity.
RT 10/12/00

APPEARS THIS WAY
ON ORIGINAL

Wahba, Zakaria Z

om:	West, Robert L
nt:	Tuesday, May 14, 2002 7:34 AM
o:	Wahba, Zakaria Z
Cc:	Sanchez, Aida L; Dillahunt, Michelle; Smela Jr, Michael; Brown, Shirley S; Ames, Timothy W
Subject:	FW: FR Publications of Interest for 5/14/02

Zack:

Today's publication of the F.R. Notice for Ifosfamide as a single entity drug product should permit you to conclude your bio review for ANDA 76-078.

Thanks,

Bob

-----Original Message-----

From:	Schwemer, Tawni M
Sent:	Tuesday, May 14, 2002 7:08 AM
To:	CDER-HFD-5&7; CDER-ACPMS; CDER-INFODIS
Cc:	Herbert, Devota D; Yetter, Robert; Dupont, Jarilyn; Dupont, Jarilyn; McGinnis, Tom
Subject:	FR Publications of Interest for 5/14/02

Good morning,

Exports; Notification and Recordkeeping Requirements; Stay

export.pdf

2. Determination That IFEX (Ifosfamide for Injection), 1-Gram and 3- Gram Vials, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

ifex.pdf

Tawni

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

ANDA Number: **76-078** Date of Submission: Dec. 22, 2000
Applicant's Name: APP
Established Name: **Ifosfamide for Injection USP, 1 g and 3 g**
Labeling Deficiencies:

---

1. GENERAL COMMENT: Please update your patent certification.
2. CONTAINER (1 g and 3 g single dose vials) – Satisfactory in draft.
3. CARTON – 1's (1g and 3 g) – satisfactory in draft.
4. INSERT
   a. We encourage your to use Ifosfamide rather than [redacted] in the following sections: WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and the OVERDOSAGE sections
   b. CONTRAINDICATIONS – add "sections" to ...(see WARNINGS and PRECAUTIONS sections).
   c. PRECAUTIONS, Pregnancy – revise the subsection heading to read as follows: Pregnancy; Tetratogenic Effects; Pregnancy Category D
   d. ADVERSE REACTIONS,
      i. Hematologic Toxicity – Add the following as the last sentence: Anemia has been reported as part of postmarketing surveillance.
      ii. Urinary System, 2nd paragraph, 7th sentence - ...rickets, and acute renal failure have been reported.
   e. HOW SUPPLIED -
      i. Add "Ifosfamide for Injection USP, lyophilized is available as:...
      ii. Delete " [redacted]
   f. REFERENCES, number 7 – "Controlling Occupational Exposure to Hazardous Drugs." The article title should as a proper noun with the first letter of each word (except for "to") capitalized.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final print.

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.

/S/

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

********** -COMM. JOURNAL- ********** DATE MAY-28-2002 ***** TIME 16:48 ********

MODE = MEMORY TRANSMISSION START=MAY-28 16:46 END=MAY-28 16:48

FILE NO.=530

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	917083434269	004/004	00:01:17

-FDA CDER OGD CHEMI -

********** - ***** - **********

ANDA 76-078

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: American Pharmaceutical Partners, Inc. TEL: 708-343-6100

ATTN: Kathleen Dungan FAX: 708-343-4269

FROM: Michelle Dillahunt PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ifosfamide for Injection, USP, packaged in 1 g and 3 g single-dose vials.

We are pleased to inform you that this application is APPROVED!

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-078

CORRESPONDENCE

AMERICAN PHARMACEUTICAL PARTNERS, INC.

March 25, 2002

ARCHIVAL

Quality already submitted in ESS/ma

N/Am

DRUG AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
HFD-600, Room 150
Rockville, MD 20855-2773

Re: ANDA #76-078
Ifosfamide for Injection, USP
1 g/vial in 30-mL vial (Code 104210)
3 g/vial in 100-mL vial (Code 104300)
Manufacturing Site: Melrose Park, IL

AMENDMENT TO A PENDING ANDA

Dear Mr. Buehler:

Reference is made to our December 22, 2000 submission of an original Abbreviated New Drug Application (ANDA) for Ifosfamide for Injection, USP, ANDA #76-078.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment to include an alternate facility to perform chemistry analytical testing on the drug substance, Ifosfamide, USP, and on the drug product, Ifosfamide for Injection, USP, in ANDA #76-078.

The alternate site is APP's analytical and product development laboratory located at 2045 North Cornell Avenue, Melrose Park, Illinois. The facility is situated on [redacted], within the Village of Melrose Park, Illinois. The facility is approximately [redacted], consisting [redacted] used for laboratories and offices and [redacted] used as a warehouse. The laboratory is designed as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

RECEIVED
MAR 27 2002
OGD / CDER

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

The laboratory contains the necessary instrumentation to perform chemistry analytical testing on the drug substance, Ifosfamide, USP, and on the drug product, Ifosfamide for Injection, USP. The laboratory was used to perform stability testing of the Ifosfamide stability batches, with the exception of [redacted] testing. The Chicago District Office certified the cGMP status of the laboratory after its inspection on July 16-20, 2001. The Central File Number for the laboratory is 1421790. APP's cGMP certification for the alternate testing facility is provided with this amendment.

Furthermore, in compliance with 21 CFR 314.96(b), a true and complete copy (Field Copy) of this amendment is being provided to Arlyn Baumgarten, Acting Director, Chicago District Office, FDA.

If you have any questions or require additional information concerning this amendment, please do not hesitate to contact me at **(708) 486-2024**, or Dale Carlson, Associate Director, Regulatory Affairs, at **(708) 486-2071**.

Sincerely,

Kathleen Dungan /DC

Kathleen Dungan
Regulatory Scientist

AMERICAN PHARMACEUTICAL PARTNERS, INC.

December 13, 2001

NC

NEW CORRESP

NAT P.M.C 4/9/02

Gary Buehler, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 76-078
Ifosfamide for Injection, USP
1 g/vial in 30-mL vial (Code 104210)
3 g/vial in 100-mL vial (Code 104300)
Manufacturing Site: Melrose Park, IL

GENERAL CORRESPONDENCE

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA) for Ifosfamide for Injection, USP submitted December 22, 2000 in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). Reference is also made to our August 3, 2001 Amendment to this ANDA which changed the Patent Certification from a Paragraph III to a Paragraph IV Certification.

We have confirmed directly with Bristol-Myers Squibb Company that they did not, within the 45-day period (which expired November 29, 2001), file suit against APP to challenge the Paragraph IV Patent Certification that APP filed on August 3, 2001 to ANDA 76-078. Please see the attached communication from Bristol-Myers Squibb Company dated December 11, 2001.

If you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 486-2081** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Tom Stothoff
Sr. Regulatory Scientist

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 17 2001

/S/ 12/11/01

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

AMERICAN PHARMACEUTICAL PARTNERS, INC.

11/08/01

November 2, 2001

Gary Buehler, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

ARCHIVAL

NEW CORRESP

Re: ANDA 76-078
Ifosfamide for Injection, USP
1 g/vial in 30-mL vial (Code 104210)
3 g/vial in 100-mL vial (Code 104300)
Manufacturing Site: Melrose Park, IL

PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA) for Ifosfamide for Injection, USP submitted December 22, 2000 in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). Reference is also made to our August 3, 2001 Amendment to this ANDA which changed the patent certification from a Paragraph III to a Paragraph IV certification.

In accordance with 21 CFR 314.95(b) American Pharmaceutical Partners, Inc. (APP) is submitting this Patent Amendment to ANDA 76-078. American Pharmaceutical Partners, Inc. hereby certifies that in accordance with 21 CFR 314.95(a) notice regarding the Paragraph IV certification has been given to Asta Pharma Aktiengesellschaft, the holder of U.S. Patent #4,882,452, and to Bristol-Myers Squibb Company, the holder of the approved New Drug Application (NDA 19-763) for IFEX® (Ifosfamide for Injection, USP).

Enclosed please find copies of the return receipt postcards documenting delivery of the aforementioned Paragraph IV certification notice to patentee (received by Asta Pharma October 15, 2001) and to the NDA holder (received by Bristol-Myers Squibb October 9, 2001).

If you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 486-2081** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Tom Stothoff

Tom Stothoff
Sr. Regulatory Scientist

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

AMERICAN PHARMACEUTICAL PARTNERS, INC.

October 23, 2001

Gary Buehler, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

ARCHIVAL
NEW CORRESP
NC To FAX

Re: ANDA 76-078
Ifosfamide for Injection, USP
1 g/vial in 30-mL vial (Code 104210)
3 g/vial in 100-mL vial (Code 104300)
Manufacturing Site: Melrose Park, IL

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to our December 22, 2000 submission of an original Abbreviated New Drug Application (ANDA) for Ifosfamide for Injection, USP, ANDA # 76-078. Reference is also made to the telephone communication with Mike Smela and Shirley Brown of the FDA on October 22, 2001.

As requested by Mr. Smela, American Pharmaceutical Partners, Inc. (APP) is submitting this Telephone amendment to reduce the Finished Drug Product release and stability specifications for [redacted] Both the release and stability limits are being reduced from NMT [redacted] NMT [redacted] based on the currently available stability data and due to the level of variation of the instrument [redacted] Revised Finished Drug Product release and stability specifications are provided in **Attachment 1** which incorporate the proposed [redacted]

Furthermore, in compliance with 21 CFR 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

If you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 486-2081** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Tom Stothoff

Tom Stothoff
Sr. Regulatory Scientist

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 25 2001
OGD

10/29/01

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

AMERICAN PHARMACEUTICAL PARTNERS, INC.

October 23, 2001

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

ORIG AMENDMENT

FAX: 301-594-0180
7 Pages

Re: **ANDA 76-078**
Ifosfamide for Injection, USP
1 g/vial in 30-mL vial (Code 104210)
3 g/vial in 100-mL vial (Code 104300)
Manufacturing Site: Melrose Park, IL

TELEPHONE AMENDMENT

Dear Ms. Brown:

Attached please find a Telephone Amendment to the above referenced Abbreviated New Drug Application. A hard copy of this amendment is also being submitted simultaneously to the Office of Generic Drugs.

If you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at (708) 486-2081 or Dale Carlson, Associate Director, Regulatory Affairs at (708) 486-2071.

Sincerely,

Tom Stothoff
Sr. Regulatory Scientist

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
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AMERICAN PHARMACEUTICAL PARTNERS, INC.

ORIG AMENDMENT
N/AM

September 20, 2001

ARCHIVAL

Gary Buehler, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 76-078
Ifosfamide for Injection, USP
1 g/vial in 30-mL vial (Code 104210)
3 g/vial in 100-mL vial (Code 104300)
Manufacturing Site: Melrose Park, IL

MINOR Chemistry, Labeling and Microbiology Amendment

Dear Mr. Buehler:

Reference is made to our December 22, 2000 submission of an original Abbreviated New Drug Application (ANDA) for Ifosfamide for Injection, USP, ANDA # 76-078. Reference is also made to the attached August 2, 2001 MINOR Chemistry and Labeling Deficiency Letter and the August 21, 2001 Microbiology Deficiency Letter to this application.

American Pharmaceutical Partners, Inc. (APP) is submitting this MINOR amendment in response to each of the comments made in your communications dated August 2 and August 21, 2001. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response. Twelve copies of Final Printed Labeling (FPL) are included in this response.

Furthermore, in compliance with 21 CFR 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

If you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 547-2384** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 547-2373**.

Sincerely,

Tom Stothoff

Tom Stothoff
Sr. Regulatory Scientist

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

AMERICAN PHARMACEUTICAL PARTNERS, INC.

August 3, 2001

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 76-078
Ifosfamide for Injection, USP
1gm/vial
3g/vial

AMENDMENT TO THE ORIGINAL ANDA

Dear Mr. Buehler:

Reference is made to our December 22, 2000 submission of an Abbreviated New Drug Application (ANDA) for Ifosfamide for Injection, ANDA 76-078. This submission is made to change the patent certification in the original ANDA from a Paragraph III Certification to a Paragraph IV Certification with respect to U.S. Patent No. 4882452.

Included in this amendment is a Paragraph IV Patent Certification and Exclusivity Statement, which certifies that U.S. Patent No. 4882452 will not be infringed by the manufacture, use or sale of Ifosfamide for Injection, USP by APP.

In compliance with 21 CFR 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at (708) 547-3618.

Sincerely,

Mitchall G. Clark
Vice-President, Regulatory Affairs

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

AMERICAN PHARMACEUTICAL PARTNERS, INC.

Patient Certification and Exclusivity Statement

Paragraph IV Certification:

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, Patient Certification is hereby provided for our Abbreviated New Drug Application for Ifosfamide for Injection, USP ANDA 76-078.

American Pharmaceutical Partners, Inc. (APP) hereby certifies that in accordance with Section 505(j)(2)(A) (vii) (IV) of the Federal Food, Drug, and Cosmetic Act that U.S. Patent No. 4882452 held by Bristol Myers Squibb Company will not be infringed by the manufacture, use or sale of Ifosfamide for Injection, USP for which this Abbreviated New Drug Application is submitted.

In accordance with Section 505(j)(2)(B) (iii), American Pharmaceutical Partners, Inc. further states that appropriate notice regarding this "Paragraph IV" certification, as required under Section 505(j)(2)(B)(ii), will be provided to:

(I) each owner of the patient that is the subject of the certification, or the representative of such owner designated to receive such notice, and

(II) the holder (Bristol Myers Squibb) of the approved application under section (b), specifically New Drug Application 19-763, for the drug that is claimed by the patent or a use of which is claimed by the patient or the representative of such holder designated to receive such notice.

Exclusivity Statement:
American Pharmaceutical Partners, Inc. (APP) certifies that there are no exclusivity periods in effect with respect to the Ifosfamide for Injection, USP drug product which has been referenced by APP in their ANDA # 76-078 Ifosfamide for Injection, USP.

As described elsewhere in this application, marketing approval is sought for the following strengths of Ifosfamide for Injection, USP:

1g/vial in 30-mL vial
3g/vial in a 100-mL vial

American Pharmaceutical Partners, Inc.

By: _____ Date: 8/3/01

Mitchall G. Clark
Vice-President, Regulatory Affairs

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

ANDA 76-078

American Pharmaceutical Partners, Inc.
Attention: Tom Stothoff
2045 North Cornell Avenue
Melrose Park, IL 60160

FEB 2 2001

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.

Reference is also made to the telephone conversation dated January 29, 2001 and your correspondence dated January 31, 2001.

NAME OF DRUG: Ifsofamide for Injection USP, 1 gm/vial and 3 gm/vial

DATE OF APPLICATION: December 22, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 27, 2000

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

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

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

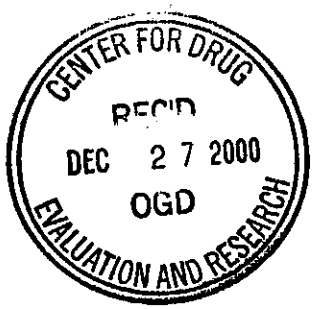
/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AMERICAN PHARMACEUTICAL PARTNERS, INC.

Ack for filing 1/31/01
/S/
Sosy Reyes
Concur.
/S/ 01-FEB-2001
/S/

December 22, 2000



Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: Ifosfamide for Injection, USP
1 g/vial in 30-mL vial (Code 104210)
3 g/vial in 100-mL vial (Code 104300)
Manufacturing Site: Melrose Park, IL
Number of Volumes: 6 Volumes

ORIGINAL ANDA

Dear Mr. Buehler:

This Abbreviated New Drug Application is submitted in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for Ifosfamide for Injection, USP. The reference listed drug is IFEX®, manufactured by Bristol Myers Squibb Company.

American Pharmaceutical Partners, Inc. will manufacture this product in manufacturing facilities located at 2020 Ruby Street, Melrose Park, IL 60160. This application contains all the information required describing the chemistry, manufacturing and control of Ifosfamide for Injection, USP. This application contains a request for the waiver of *in vivo* bioequivalence studies. **This application also contains microbiology and sterility assurance information, which is provided in Section XXII.**

The application has been formatted according to the information in the Guidance for Industry: Organization of an ANDA, dated February 1999. An Executive Summary explaining the organization of this application is included after the cover letter. The application consists of 6 volumes.

2045 NORTH CORNELL AVENUE
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American Pharmaceutical Partners Inc. is filing an archival copy (in a blue folder) of the ANDA that contains all the information required in the ANDA, and a technical review copy (in a red folder) which contains all of the information in the archival copy with the exception of the bioequivalence section (Section VI). Three copies of the analytical methods validation section are included in red folders. Four copies of the draft labeling are included in both the archival and the review copies. A separate copy of the bioequivalence section is provided in an orange folder. The bioequivalence section consists of a request for a waiver from the need to conduct a bioequivalence study.

Furthermore, in compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this Abbreviated New Drug Application is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606. We certify that the Field Copy is a true and complete copy of this Abbreviated New Drug Application.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(708) 547-2384** or Mitchall Clark, Vice President, Regulatory Affairs, at **(708) 547-3618**.

Sincerely,

Tom Stothoff

Tom Stothoff
Senior Regulatory Scientist