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March 9, 2001

VIA HAND DELIVERY
Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Comments of Bristol-Myers Squibb Company
Petition Docket Number 01P-0061/CP 1 (Ifosfamide for Injection, USP)

On behalf of Bristol-Myers Squibb Company ("BMS"), the undersigned submits these comments pursuant to 21 C.F.R. § 10.30(d), in response to the Citizen Petition filed by Tom Stothoff of American Pharmaceutical Partners, Inc. ("APP"), and received by the Food and Drug Administration ("FDA") on February 2, 2001. The Citizen Petition seeks permission from FDA to file an abbreviated new drug application ("ANDA") for Ifosfamide for Injection, USP, and a determination of whether the listed drug, IFEX® (ifosfamide for injection) was withdrawn by BMS for safety or effectiveness reasons. BMS requests that the Commissioner of Food and Drugs find that BMS's cancer drug IFEX, appearing on the Discontinued Drug Product List in FDA's publication Approved Drug Products With Therapeutic Equivalence Evaluations (the "Orange Book"), has not been withdrawn and is not separately marketed by BMS for reasons of safety or effectiveness.

I. BACKGROUND

IFEX, used in combination with certain other approved antineoplastic agents, is indicated for third line chemotherapy of germ cell testicular cancer. In the IFEX developmental clinical studies, it was observed that urotoxic side effects, especially hemorrhagic cystitis, were frequently associated with the administration of IFEX. For this reason, FDA appeared reluctant to approve IFEX without the assurance that MESNEX® (mesna) Injection, a drug indicated for

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reducing the incidence of ifosfamide-induced hemorrhagic cystitis, would also be available through an approved NDA. Thus, the IFEX NDA and the MESNEX NDA were both approved on December 30, 1988 with the indication section of the IFEX package insert stating that IFEX "should ordinarily be used in combination with a prophylactic agent for hemorrhagic cystitis, such as mesna." As a result and to help ensure against the dangerous urotoxicity risk, BMS has always sold IFEX only in combination packages with MESNEX, as stated in the package insert:

> **HOW SUPPLIED**
> IFEX® (ifosfamide for injection) is only available in combination packages with the uroprotective agent MESNEX® (mesna) injection.
> IFEX (ifosfamide for injection)/MESNEX® (mesna) Injection.

Following the 1988 approvals, there were two combination kits of IFEX and MESNEX. The first contained 1-gram single dose vials of IFEX and 200mg single dose ampules of MESNEX. The 1gm/vial IFEX was designated NDA No. 19763 001. The second contained 3-gram single dose vials of IFEX and 400-mg single dose ampules of MESNEX. The 3gm/vial IFEX was designated NDA No. 19763 002. Unlike IFEX, which was only sold in the combination kit, MESNEX was also sold alone, as its uroprotective properties are also useful with other chemotherapeutic agents. In October 1992, BMS added a MESNEX 1-gram vial to the IFEX/MESNEX Kits.

In 1998, the FDA, on its own initiative, ended the separate listing treatment for IFEX and MESNEX in the Orange Book. Whereas previously IFEX and MESNEX had been separately listed, the FDA replaced the IFEX-only listings (001 and 002) under the IFEX NDA with two new product numbers -- 003 and 004 -- for two new product names: the "IFEX/MESNEX Kit 1gm/vial; 100mg/ml", and the "IFEX/MESNEX Kit, 3mg/vial; 100mg/ml". Presumably because BMS has always marketed IFEX in a combination pack with MESNEX, the FDA moved the separate IFEX listing to the Discontinued Drug Product List in the Orange Book. BMS did not, however, withdraw or cease marketing IFEX in any form. Therefore, BMS never withdrew or ceased to market IFEX in any form, rather the FDA modified the Orange Book listing to conform with the manner in which IFEX has always been marketed, as the IFEX/MESNEX Kit.

II. FDA Determination of Reasons for Withdrawal

An ANDA must rely on a reference listed drug. 21 U.S.C. § 355(j)(2). If a listed drug has ceased to be offered for sale by its manufacturer, a person wishing to submit an ANDA for the drug must petition FDA for a determination of whether the drug was withdrawn for reasons of safety or effectiveness[1] and must include all evidence available to the petitioner concerning the reasons for withdrawal. 21 C.F.R. § 314.122(a); 21 C.F.R. § 314.161(b). An Agency determination that the drug was withdrawn from sale (or never marketed at all) for

[1] FDA has determined that, for purposes of § 314.161, never marketing an approved drug product is equivalent to withdrawing the drug product from sale. See, e.g., 65 Fed. Reg. 38561 (June 21, 2000).

reasons bearing on safety or effectiveness precludes submission of an ANDA for that drug product. 21 C.F.R. § 314.122(c).

In determining whether a drug was withdrawn from sale for reasons of safety or effectiveness, the Agency considers the evidence in the petition[2] and any other evidence before the Agency. 21 C.F.R. § 314.122(b). The preamble to FDA's proposed ANDA regulations provides the only specific guidance for the Agency's inquiry, and states that the Agency's determination is an

> attempt[] to focus on the intent of the manufacturer. . . .The legislative history of this provision makes clear, however, Congress' intent that the agency examine whether the manufacturer had safety or effectiveness concerns about the withdrawn drug independent of the reasons given by the manufacturer for the withdrawal. . . .The agency's inquiry, therefore, will focus on whether there were sufficient concerns about safety and effectiveness to make a withdrawal from sale likely and reasonable. . . .The agency will also consider other factors in determining whether a market withdrawal was for safety and effectiveness reasons, such as increases in the number of adverse drug reactions reported on the drug and published or unpublished studies of the drug questioning its safety or effectiveness.

54 Fed. Reg. 26872, 28907 (July 10, 1989).[3]

III. FDA's Review of the APP Citizen Petition

A. BMS Has Never Withdrawn or Ceased to Market IFEX.

The Citizen Petition filed by APP seeks permission from FDA to file an ANDA for ifosfamide for injection, USP, and a determination of whether the listed drug, IFEX® (ifosfamide for injection) was withdrawn by BMS for safety or effectiveness reasons. BMS, however, has never withdrawn or ceased to market IFEX in any form. As the regulatory history of IFEX and MESNEX makes clear, BMS has always marketed IFEX with MESNEX in the combination package since the time of their approval. Presumably the FDA moved the IFEX-only listings to the Discontinued Drug Product List to conform the listing of IFEX with the manner in which it has always been marketed. Therefore, the drug product has always been the IFEX/MESNEX kit, and there is no withdrawn or non-marketed product. Accordingly, the FDA should deny APP's Citizen Petition on the grounds that there is no withdrawn or non-marketed drug.

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[2] APP has not provided any evidence whatsoever in its petition.

[3] In a recent Draft Guidance, FDA has reaffirmed that the criteria in the proposed rule are still to be applied to an agency determination of reason for product withdrawal. See Guidance for Industry, Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications, at 6 (Draft, October 2000).

B. BMS Has Never Marketed IFEX as a Single Product For Safety Reasons.

Even if the FDA determines that there has been a withdrawn or non-marketed drug, there are at least three reasons why FDA must conclude that BMS does not market IFEX without MESNEX because of safety concerns.

First, as the IFEX labeling makes clear, to be safe, IFEX should be administered in conjunction with a uroprotective agent, such as MESNEX. This, in fact, is the reason that the IFEX labeling states that "IFEX® (ifosfamide for injection) is only available in combination packages with the uroprotective agent MESNEX® (mesna) injection." The transcript of the Oncologic Drugs Advisory Committee ("ODAC") that recommended the approval of IFEX is replete with concerns about the necessity of using mesna with ifosfamide. See, e.g., Remarks of Gerald Sokol, M.D., FDA Oncologic Drugs Advisory Committee Transcript at 67-68, April 19, 1988 (". . . not to use mesna in [third line testicular cancer patients] is certainly jeopardizing these patients very significantly . . .") Similarly, the ODAC raised legitimate concerns about the availability of mesna for use with ifosfamide once both drugs gain full approval:

> DR. MOERTEL: . . . This is not the only disease that ifosfamide and mesna is rumbling around for. Is there a question then about whether or not the supply would be ready to meet the demand that might occur in not only the indication but in these other diseases where this drug will be used once it gets out on the market?
>
> DR. TEMPLE: Obviously I can't give you a fully definitive answer on that. We can certainly explore it but I would expect the labeling would have a fairly strong statement that says **you shouldn't be using this unless you can get mesna.**

Exchange between Charles G. Moertel, M.D. and Robert Temple, M.D., Tr. at 139-40 (emphasis added).

For these reasons, FDA made the approval of IFEX dependent upon the inclusion of the labeling statement that IFEX "should ordinarily be used in combination with a prophylactic agent for hemorrhagic cystitis, such as mesna."[4] Furthermore, the FDA appeared reluctant to approve the IFEX NDA alone without the assurance that MESNEX would also be available. BMS co-packaged IFEX with MESNEX to provide greater assurance that physicians would co-administer mesna with ifosfamide than would be achieved if ifosfamide were sold alone. The sale of an ifosfamide-only product could increase the likelihood that mesna might not be available at the time ifosfamide is administered, which could result in ifosfamide being inappropriately

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[4] The December 30, 1988 approval letter for IFEX (attached at Exhibit A) states that:

> ...the product is safe and effective for use as recommended in the enclosed marked up draft labeling. Accordingly, the application, with the requested labeling revisions, is approved effective on the date of this letter. These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, may render the product misbranded and an unapproved new drug.

Thus, FDA required BMS to include the reference to mesna in the IFEX labeling as a condition of final approval.

administered. As a result, there could be a greater potential for urotoxic side effects in patients treated inappropriately without mesna.

Second, in addition to the safety information in the IFEX labeling relating to the combination use of IFEX and MESNEX, medical literature supports the proposition that IFEX should only be used in combination with MESNEX. In fact, many published articles support the necessity of administering MESNEX when IFEX is used. An abbreviated bibliography of some of these articles is attached as Exhibit B. Because a consensus exists among FDA, BMS, and the scientific community that administration of IFEX should *always* include MESNEX, the sale of IFEX without MESNEX increases the likelihood of IFEX being administered inappropriately, and therefore should be considered unsafe.

Third, the manner in which IFEX is co-administered with MESNEX must be considered. Due to a delayed onset of possible severe urotoxic reactions, it is essential that MESNEX be available to patients receiving IFEX not only at initial administration, but also for a dose at four and eight hours post IFEX administration as indicated in the package insert for IFEX. Medical literature also supports the use of MESNEX for a period of up to 24 hours after IFEX is administered. Therefore, an adequate supply of MESNEX must accompany each and every vial of IFEX to ensure safe administration.

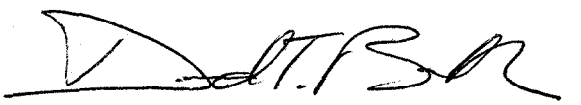
BMS has never sought to market IFEX alone because of these safety concerns. Indeed, FDA, the ODAC and the medical community at large share these safety concerns, making it unlikely that BMS could receive approval from FDA to market IFEX alone, even if it were to seek such a result. Therefore, the issue before the FDA should not be whether the IFEX listing was withdrawn, but whether it is appropriate for an ifosfamide product to be marketed without mesna. If even one patient does not receive mesna as needed at the time ifosfamide is administered because it is not available, a grave injustice will have occurred. BMS has always marketed IFEX in a combination package with MESNEX because it believes sale of an ifosfamide-only product would not address the safety concerns raised by the FDA and the ODAC and would, therefore, be unsafe. FDA should therefore deny APP's Citizen Petition.

IV. Conclusion

There is no doubt that administration of IFEX without MESNEX is unsafe. This safety concern has persisted since the original FDA review of IFEX and continues to exist today. Based upon this concern for potential severe urotoxic reactions, BMS has chosen to market IFEX only in the IFEX/MESNEX Kit. This decision has been supported by the FDA and is reflected in the FDA-requested changes to the IFEX labeling and the FDA decision to end the separate listing treatment of IFEX and MESNEX in the Orange Book. BMS has never withdrawn or ceased to market IFEX in any form and believes that the FDA moved the IFEX-only listings to the Discontinued Drug Product List to reflect the manner in which IFEX has always been marketed, as the IFEX/MESNEX Kit. BMS also believes that based upon information available in 1988, as well as information made available since that time, FDA must determine that safety concerns led

to the BMS decision to refrain from marketing IFEX without MESNEX. Therefore, the FDA should deny APP's Citizen Petition because no form of IFEX has ever been withdrawn or non-marketed and because the sale of an ifosfamide-only product would be unsafe.

Respectfully submitted,



BRISTOL-MYERS SQUIBB COMPANY
David T. Bonk
Vice President & Associate General Counsel
Intellectual Property

Exhibit A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-763

DEC 30 1988

Bristol-Myers Company
5 Research Parkway
P.O. Box 5100
Wallingford, Connecticut 06492-7660

1-6-89 Copied For:

Attached Memo
NDA 19-763 Correspondence Binder
FDA Correspondence Binder
FDA Approval Letters Binder

Attention: Cheryl L. Anderson
Manager
Drug Regulatory Affairs

Dear Ms. Anderson:

Please refer to your December 9, 1987 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Ifex (sterile ifosfamide).

We acknowledge receipt of your amendments dated July 7, August 3, November 10, 15, 22 and December 1 and 16, 1988.

We also acknowledge the December 28, 1988 amendment submitted by your supplier for the bulk drug substance which provides a commitment to improve the water supply system by June 1, 1989 for the manufacture of ifosfamide in Bielefeld.

Reference also is made to the December 29, 1988 telephone conversation between Dr. George Gill of your company and Ms. Sandy Barnes of this administration in which he agreed that Bristol-Myers would test each can of the bulk ifosfamide powder individually for sterility and apyrogenicity and would perform a feasibility study on developing a lyophilized dosage form of ifosfamide.

We have completed the review of this application, including the draft labeling submitted on December 16, 1988, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked up draft labeling. Accordingly, the application, with the requested labeling revisions, is approved effective on the date of this letter.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the final printed labeling when it is available. Please individually mount seven ofthe copies on heavy weight paper or similar material. For administrative purposes this

submission should be designated "FPL for approved NDA 19-763". Approval of this FPL by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

While all other aspects of this application have been found to be approvable the required validation of the analytical methods has not been completed. In such a case, the policy of the Center for Drug Evaluation and Research is to proceed with approval. We expect your cooperation to help resolve expeditiously any problems that may occur with respect to validations.

We are unaware of any studies that describe the pharmacokinetics of Ifex for the dosing regimen that is proposed in the package insert and when given in conjunction with the other drugs with which it will be prescribed. Pharmacokinetic data in compromised hepatic and/or renal function patients would be of interest since the drug undergoes metabolic activation by microsomal liver enzymes and its metabolites are excreted predominantly via the kidney. If such studies are conducted, ifosfamide and its active metabolites in the plasma and urine should be quantitated rather than using a non-specific assay. We would like to meet with you to discuss additional pharmacokinetic studies to improve the information in the labeling.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Oncology and Radiopharmaceutical Drug Products and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFD-240
Room 10B-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit one market package of the drug when it is available. We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Cathie Schumaker
Project Manager
Oncology Drug Products
(301) 443-5197

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

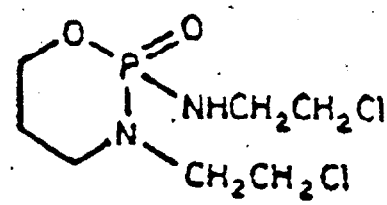
IFEX® (sterile ifosfamide)

WARNING

Ifex 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 Ifex. When they occur, they may require cessation of Ifex therapy. Severe myelosuppression has been reported. (See "Adverse Reactions" section.)

DESCRIPTION

IFEX (sterile ifosfamide) single-dose vials for constitution and administration by intravenous infusion each contain 1 gram or 3 grams of sterile 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. The molecular formula is $C_7H_{15}Cl_2N_2O_2P$ and its molecular weight is 261.1. Its structural formula is:



Ifosfamide is a white crystalline powder that is soluble in

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 crosslinks. 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 - 5.0 gm/m^2, the plasma concentrations decay biphasically and the mean terminal elimination half-life is about 15 hours. At doses of 1.6 - 2.4 gm/m^2/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 gm/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 gm/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~~ Ifx (2) 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 three 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.

INDICATION AND USAGE

Ifex, ~~when~~ used in combination 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 ~~co-protective agent,~~ ~~as mesna~~ prophylactic agent for chemotherapeutic cytitis, such as mesna

CONTRAINDICATIONS

Continued use of Ifex is contraindicated in patients with severely depressed bone marrow function (See WARNINGS and PRECAUTIONS sections). Ifex 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 Ifex. It is recommended that a urinalysis should be obtained prior to each dose of Ifex. If microscopic hematuria, (greater than 10 RBC's per high power field), is present, then subsequent administration should be withheld until complete resolution.

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

Hematopoietic System

When Ifex 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, Ifex 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 Ifex therapy. The occurrence of these symptoms requires discontinuing Ifex 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 - 0.075 times the human dose. Ifosfamide can cause fetal damage when administered to a pregnant woman. If Ifex 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

Ifex 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

Pregnancy "Category D". See WARNINGS section.

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/m^2 dose of ifosfamide was administered on Day 11 of gestation. Embryolethal effects were observed in rats following the administration of 54 mg/m^2 doses of ifosfamide from the sixth through the fifteenth day of gestation and embryotoxic effects were apparent after dams received 18 mg/m^2 doses over the same dosing period. Ifosfamide

is embryotoxic to rabbits receiving 89 mg/m²/day doses from the sixth through the eighteenth day after mating. The number of anomalies was also significantly increased over the control group.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In patients receiving Ifex as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity. Dose fractionation, vigorous hydration and a uroprotector such as mesna can significantly reduce the incidence of hematuria, especially gross hematuria associated with hemorrhagic cystitis. At a dose of 1.2 gm/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 Ifex single agent at doses of 1.2 gm./m² per day for five 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 10-12 gm/m²/cycle, one-half of the patients had a WBC count below 1000/µL and 8% of patients had

platelet counts less than 50,000μL. Myelosuppression was usually reversible and treatment can be given every 3 to 4 weeks. When Ifex 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.

Digestive System

Nausea and vomiting occurred in 58% of the patients who received Ifex. 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 32% of patients treated with Ifex. The incidence and severity of hematuria can be significantly reduced by using vigorous hydration, a fractionated dose schedule and a [illegible] protector such as mesna. At daily doses of 1.2 gm/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 Ifex was administered at doses of 2.0 - 2.5 gm/m²/day for 4 days.

Central Nervous System

CNS side effects were observed in 12% of patients treated with Ifex. 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 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 Ifex 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 Ifex 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

Ifex should be administered intravenously at a dose of 1.2 gm/m² per day for five consecutive days. Treatment is repeated every three weeks or after recovery from hematologic toxicity (Platelets ≥ 100,000/μL , WBC ≥ 4,000/μL). In order to prevent bladder toxicity, Ifex should be given with extensive hydration consisting of at least two liters of oral or intravenous fluid per day. A [redacted] protector, such as mesna, should also be used to prevent hemorrhagic cystitis. Ifex should be administered as a slow intravenous infusion lasting a minimum of 30 minutes. Although Ifex has been administered to a small number of patients with compromised hepatic and/or renal function, studies to establish optimal dose schedules of Ifex 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 reconstitute the product:

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

Reconstituted solutions are chemically and physically stable for one week at 30°C or three weeks at 5°C.

Solutions of ifosfamide may be diluted further to achieve concentrations of 0.6 to 20mg/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

Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags, or PAB™ bags, are physically and chemically stable for at least one week at 30°C or six weeks at 5°C.

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.

The microbiological qualities of the constituted products or prepared admixtures should be considered, particularly where unpreserved vehicles are used.

Dilutions of Ifex not prepared by constitution with Bacteriostatic Water for Injection, USP; (benzyl alcohol or parabens preserved), should be reconstituted and used ~~promptly (preferably~~ within 6 hours~~)~~.

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

HOW SUPPLIED

Ifex (sterile ifosfamide)

NDC 0015-0556-41 - 1 gram Single Dose Vial, carton of 5

NDC 0015-0557-41 - 3 gram Single Dose Vial, carton of 1

The dry powder may be stored at room temperature. Storage above 104°F (40°C) should be avoided.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Skin reactions associated with accidental exposure to Ifex may occur. The use of gloves is recommended. If Ifex 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. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Exhibit B

EXHIBIT B

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