DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Karen Horgan-Peltier, BSN, ET
Director, Promotional Compliance
Bristol-Myers Squibb
PO Box 4500
Princeton, NJ 08543-4500

RE: NDA # 19-763
Ifex® (ifosfamide) Injection
MACMIS ID# 9593

Dear Ms. Horgan-Peltier:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional materials disseminated by Bristol-Myers Squibb (BMS) for Ifex (ifosfamide) Injection that are false, misleading, or otherwise in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, the following promotional materials promote unapproved uses and/or broaden the approved indication of Ifex:

- Journal Advertisement (ID# H5-K003R1)
- Website www.bms.com
- Website www.ifex.com

Promotion of Unapproved Uses

Ifex is indicated for third line chemotherapy of germ cell testicular cancer in combination with certain other approved antineoplastic agents. The product specific BMS website www.ifex.com contains the webpage (http://www.bms.com/donc/hprofx/data/fx1122.html) entitled "Continuous vs. Divided vs. Single Dose (1122)" that provides information for unapproved uses of Ifex. For example, the following statements are made:

> *"...in humans, under the protection of mesna, the continuous infusion of ifosfamide over five days leads to an increase of a) the maximum tolerated dose (MTD) compared with single daily short-term infusion and b) responses in **some solid tumors, ie, soft tissue sarcomas**."*

> *"Antman, cited a series of patients, with **advanced sarcoma**, treated with 8 to 10 gm/m² of ifosfamide by bolus or continuous infusion. The response rate for the 64 patients receiving bolus administration was 23% compared with 12% for the 60 patients receiving a continuous infusion schedule (p=.09). The authors found a statistically significant difference in response rates for **soft tissue sarcomas** between*

bolus infusion vs. continuous infusion with the higher response rate through the bolus arm."

"Anderson, treated a series of 47 ***poor risk small-cell lung cancer patients*** *with a regimen of bolus ifosfamide at 1.5 g/m² with equidose mesna as a 30 minute infusion followed by 100 mg of oral etoposide daily for eight days. The overall response rate was 60% (75% for limited stage and 48% for extensive stage of the disease), and the overall median survival was seven months. Therapy was well tolerated."*

Furthermore, the product specific BMS website www.ifex.com also contains an informational database which leads to a webpage (http://www.bms.com/cgi-bin/bmscom/litdb/onclgy /search.cgi) entitled "Search." This webpage includes a list of unapproved uses for Ifex. Specifically, Ifex can be matched to one or all of **seventy-two** "Tumor or Disease Term[s]," via pull down menus. From here electronic information about unapproved uses are presented. For example, selecting Ifex and the Tumor or Disease Term "Small Intestine Carcinoma" results in the retrieval of two informational pieces about this unapproved use. Thus, BMS is promoting Ifex for unapproved uses.

Unsubstantiated Claims

The claims "The patient undergoing outpatient treatment may experience daily activities nearer to a normal routine. There may be less disruption of lifestyle when the patient returns to a home environment" are made in the journal advertisement. These claims are misleading because they suggest that Ifex therapy minimizes disruption of a patient's daily activities or lifestyle during third line treatment of germ cell testicular cancer using Ifex in combination with certain other approved antineoplastic agents. These claims are not supported by substantial evidence because none of the seven articles and abstracts submitted by BMS to support these claims discuss the use of Ifex and its affect on daily activities. Thus, these articles and abstracts are inadequate to substantiate the claims made by BMS.

In addition, these claims combined with the pictorial representations of a very healthy-looking patient are misleading. The patient is not representative of a patient population that has already undergone first and second line chemotherapy and is now receiving third line chemotherapy containing a drug with a boxed warning of severe CNS toxicity, including coma, a well as significant side effects such as moderate to severe myelosuppression (50%), alopecia (83%), nausea-vomiting (58%), and hematuria (46%).

Failure to Comply with CFR 314.81(b)(3)(i)

Since the web-based promotional materials discussed here were not submitted on Form FDA 2253 at the time of initial dissemination, BMS has violated the post-marketing reporting requirements of the Act.

Requested Actions

BMS should immediately cease distribution of this and other similar promotional materials for Ifex® that contain the same or similar claims or presentations. BMS should submit a written response to DDMAC on or before March 27, 2001, describing its intent and plans to comply

with the above. In its letter to DDMAC, BMS should include the date on which this and other similarly violative materials were discontinued.

BMS should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID # 9593 in addition to the NDA number. DDMAC reminds BMS that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

/s/

Joseph Grillo
3/13/01 04:05:50 PM

1-800-426-7644

Ifex®
Continuous vs. Divided vs. Single Dose

Your request concerns Ifex® (sterile ifosfamide) when administered as a continuous infusion vs. daily divided doses vs. a single daily dose.

Klein[1] reported experimental and clinical studies showing that: 1) animals, under protection of mesna, can tolerate significantly increased doses of ifosfamide; 2) fractionated administration of ifosfamide is less toxic than single push-injection of the same total daily dose and therapeutically more effective, and 3) in humans, under the protection of mesna, the continuous infusion of ifosfamide over five days leads to an increase of a) the maximum tolerated dose (MTD) compared with single daily short-term infusion and b) responses in some solid tumors, ie, soft tissue sarcomas.

Brade[2] noted that by giving the uroprotector mesna concomitantly and following the application of ifosfamide, the former dose-limiting urotoxicity can be controlled with single ifosfamide doses escalated up to 5 gm/m² given by IV infusion over 30 minutes or up to 8 gm/m² given as a 24 hour continuous infusion.

Cerny[3] characterized his findings that dose fractionation of ifosfamide increases the therapeutic index; continuous administration over three to five days carries the lowest risk of encephalopathy and is superior to the daily fractionated dose schedule. The authors further state there is no evidence that high serum ifosfamide levels are required for treating most malignancies (though for soft-tissue sarcoma additional studies are needed). With the introduction of portable infusion pumps, ambulatory chemotherapy may become an attractive option.

Antman[4], cited a series of patients, with advanced sarcoma, treated with 8 to 10 gm/m² of ifosfamide by bolus or continuous infusion. The response rate for the 64 patients receiving bolus administration was 23% compared with 12% for the 60 patients receiving a continuous infusion schedule ($p=.09$). The authors found a statistically significant difference in response rates for soft tissue sarcomas between bolus infusion vs. continuous infusion with the higher response rate through the bolus arm. Concern was expressed since patients receiving continuous infusion ifosfamide appeared to have as good or better prognostic characteristics when entered into the study compared to patients entered on the bolus protocol. There were no differences in response for bony sarcomas. The authors further state that the incidence of neurotoxicity and other toxic effects was, in fact, lower for the continuous infusion schedule allowing a high dose of ifosfamide to be delivered.

Anderson[5], treated a series of 47 poor risk small-cell lung cancer patients with a regimen of bolus ifosfamide at 1.5 g/m² with equidose mesna as a 30 minute infusion followed by 100 mg of oral etoposide daily for eight days. The overall response rate was 60% (75% for limited stage and 48% for extensive stage of the disease), and the overall median survival was seven months. Therapy was well tolerated.

In summary, the optimal schedule and dosing of ifosfamide requires further study before definitive recommendations can be made. Continuous infusion appears to afford maximal dose administration with reduced toxicity compared to fractionated or single day bolus administration. Outside of the intriguing data by Antman, there is no evidence to support the superiority of bolus vs. fractionated vs. continuous infusion of ifosfamide in other tumor types.

Current Labeling

Ifex (sterile ifosfamide), 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 prophylactic agent for hemorrhagic cystitis, such as mesna.

This letter may contain information not found in the package insert. For full prescribing information and a complete list of Adverse Events, please consult the official package circular.

We hope you find this information helpful. If you need further assistance, please contact our Medical Department at 1-800-426-7644.

Thank you for your interest in the Bristol-Myers Squibb Oncology/Immunology Division.

References

1. Klein H O, et al. Therapeutic effects of single-push or fractionated injections or continuous infusion of oxazaphosphorines (cyclophosphamide, ifosfamide, and Asta Z 7557). *Cancer*. 1984;54:1193-1203.

2. Brade W P, et al. Ifosfamide - dosing and scheduling. *Contr Oncol*. 1987;26:22-52. (Karger, Basel).

3. Cerny T, et al. Ifosfamide by continuous infusion to prevent encephalopathy. *Lancet*. 1990;335;175.

4. Antman K H, et al. Ifosfamide and mesna: Response and toxicity at standard - and high-dose schedules. *Semin Oncol*. 1990 Apr.;17(2)(4):68-73.

5. Anderson H, et al. Therapy for poor - risk patients with small-cell lung cancer using bolus ifosfamide and oral etoposide. *Cancer Chemother Pharmacol*. 1990;26:71-74.

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Search

Select your search parameters:

Agent
Ifosfamide

Administration
Any

Tumor or Disease Term
Small Intestine Carcinoma

Side Effects
Any

Display 50 **entries per page.**

Submit Query

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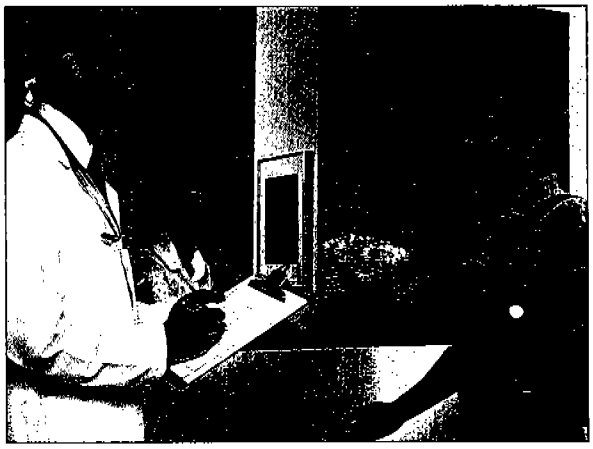
[illegible] Dec 6 09:07:35 2000

The Convenient Ifex® (ifosfamide for injection) Route...



Office/Outpatient Chemotherapy

- The patient undergoing outpatient treatment may experience daily activities nearer to a normal routine. There may be less disruption of lifestyle when the patient returns to a home environment.

- Outpatient treatment avoids the need for hospital admissions for the sole purpose of chemotherapy administration.

Ifex, in combination with other approved agents, is indicated for refractory testicular cancer. Dose-limiting toxicities are urotoxicity and myelosuppression, primarily leukopenia. Use of the uroprotector mesna reduces the possibility of hematuria, especially gross hematuria. At standard dosages of Ifex, leukopenia is usually mild to moderate.

IFEX®

(ifosfamide for injection)

BRISTOL-MYERS SQUIBB ONCOLOGY

Bristol-Myers Squibb Company
Princeton, NJ 08543
U.S.A.

Please see adjacent page for brief summary of full prescribing information.
You can reach Bristol-Myers Squibb Oncology Medical Services at 1-800-426-7644.
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