



Bristol-Myers Squibb Company

MATERIAL SAFETY DATA SHEET

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

BRISTOL-MYERS SQUIBB COMPANY
Worldwide Medicines Group
P.O. BOX 191
NEW BRUNSWICK, NJ 08903
732-227-7367

DATE: June 9, 2004

Product Identification Ifex for Injection.

Chemical Name: 3-(2-Chloroethyl)-2-(2-chloroethylamino)tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide.

Synonym: Ifosfamide for Injection; (Synonyms for active pharmaceutical ingredient - MJ9325. Ifos; Ifosfamid; Ifosfamide; Iphosphamide; Isoendoxan; Isofosfamide; Isophosphamide; MJF 9325)

How Supplied: Lyophilized powder in vials.

Product Use: Ifex contains ifosfamide and is used to treat certain neoplastic diseases.

Chemical Family: Oxazaphosphorine.

Molecular Formula: C₇H₁₅Cl₂N₂O₂P.

CAS NUMBER: 3778-73-2.

EMERGENCY CONTACTS:

Transportation: CHEMTREC (800)424-9300. For all international transportation emergencies call CHEMTREC at 703-527-3887, collect call accepted.

EMERGENCY OVERVIEW: This white crystalline powder is a cytotoxic agent used in the treatment of certain neoplastic diseases. Mutagen. Carcinogen in animal studies. May cause harm to the fetus. Following treatment with therapeutic doses, target organs may include: blood, kidneys, urinary bladder, central nervous system, and the male reproductive system. Toxic after oral ingestion. It may cause allergic skin reactions.

2. COMPOSITION/ INFORMATION ON INGREDIENTS

COMPONENTS	HAZARDOUS (Y/N)	CONCENTRATION (wt %)	CAS NUMBER	EXPOSURE GUIDELINE
Ifosfamide	Y	100	3778-73-2	0.1 mcg/m ³ BMS-DCT (1)

(1) BMS-DCT = Bristol-Myers Squibb Dust Control Target (TWA 8-hour).

3. HEALTH HAZARDS IDENTIFICATION

EFFECTS OF OVEREXPOSURE

Routes of Entry:

1. Inhalation: If material becomes airborne during manipulation there is potential for inhalation.

2. Skin contact: There is a potential for skin contact during routine handling of the vials or if the vials break or spill.

3. Ingestion: Ingestion of large quantities of this material in an occupational setting would not be expected to occur. Ingestion of trace



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HEALTH HAZARDS IDENTIFICATION (CONTINUED)

amounts of the material might occur if material contacts the hands and hands are not washed prior to eating drinking or smoking. Ifosfamide appears to be absorbed from the gastrointestinal tract, although the extent of absorption is unknown.

Acute

Ingestion: Ifex contains ifosfamide, a drug which was toxic in experimental animals when administered by the oral route. Ingestion may cause nausea, vomiting, anorexia or diarrhea. A large acute dose may cause: delayed bone marrow suppression; hemorrhagic cystitis (bleeding and inflammation of the urinary tract); reversible neurologic effects (e.g. somnolence, confusion, hallucinations, and in some instances, coma) and delayed temporary sterility.

Inhalation: There is no information concerning the potential for this material to produce symptoms after inhalation. However, ifosfamide is a highly potent drug which is believed to be absorbed through the lungs. If there is sufficient inhalation of this material, the following symptoms may be possible: delayed bone marrow suppression; hemorrhagic cystitis (bleeding and inflammation of the urinary tract); reversible neurologic effects (e.g. somnolence, confusion, hallucinations, and in some instances, coma); and delayed temporary sterility.

Skin Contact:

a. **Toxic:** There is no information concerning the potential of this material to produce symptoms after skin contact. However, ifosfamide is a highly potent drug which may be absorbed through the skin. If there is sufficient skin contact with this material, the following symptoms may be possible: delayed bone marrow suppression; hemorrhagic cystitis (bleeding and inflammation of the urinary tract); reversible neurologic effects (e.g. somnolence, confusion, hallucinations, and in some instances, coma); and delayed temporary sterility.

b. **Irritation:** Ifosfamide is a possible irritant, and may cause skin irritation after dermal exposure of 2 grams or more.

c. **Sensitization:** Possible allergic rashes upon contact.

Eye Contact: The material should be handled as a potential eye irritant. It may cause conjunctivitis.

Other: Ifosfamide is intended for intravenous injection under the supervision of physicians experienced in cancer chemotherapy. Acute adverse effects associated with systemic exposure to ifosfamide may include: delayed bone marrow suppression; hemorrhagic cystitis (bleeding and inflammation of the urinary tract); and reversible neurologic effects (e.g. somnolence, confusion, hallucinations, in some instances, coma); and delayed temporary sterility.

Chronic: Ifosfamide is generally intended for intravenous injection under the supervision of physicians experienced in cancer chemotherapy. Adverse effects associated with chronic systemic exposure to ifosfamide may include: bone marrow suppression; hemorrhagic cystitis (bleeding and inflammation of the urinary tract); reversible neurologic effects (e.g. somnolence, confusion, hallucinations, and in some instances, coma); skin pigmentation changes and hair loss. Other less frequent adverse effects included: pulmonary symptoms; fever; allergic reactions; cardiotoxicity; and, polyneuropathy.



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HEALTH HAZARDS IDENTIFICATION (CONTINUED)

Exposure Guideline Summary: Ifosfamide is a cytotoxic drug used alone or in combination with other chemotherapeutic drugs to treat various types of cancer. A dust control target of 0.1 mcg/m³ in air (8-hour time-weighted average concentration) has been established for workplace exposure to ifosfamide. Adherence to this target level should protect most employees who handle this drug from experiencing adverse effects from this substance, however, exposure to this substance should be maintained as low as reasonably possible.

Carcinogen Lists IARC: Group 3. NTP: No. OSHA: No.

Ifosfamide has been classified in Group 3 by IARC (not classifiable as to its potential to cause carcinogenicity in humans). See also section 11.

Target Organs: Target organs identified in humans after treatment with therapeutic doses of this material by the parenteral route include: blood, genital-urinary tract (urinary bladder and kidneys), central nervous system, and male reproductive system. Other organ systems which undergo rapid cellular division may also be targets after systemic exposure.

Medical Conditions Aggravated by Exposure: Therapeutic doses of this material may aggravate blood disorders. Persons with impaired renal function may also be at increased risk following therapeutic exposure.

Medical Surveillance Recommendation: A pre-placement physical examination and history for employees with potential exposure to ifosfamide is recommended. A complete blood count with differential, blood test for renal and liver function, and a urine analysis may be taken to provide a baseline. Based on opportunity for exposure and duration of exposure a periodic follow-up examination may be considered. This exam is overseen by a physician thoroughly knowledgeable about both the toxicity of ifosfamide and the extent of work place exposure. It is recommended that the content be similar to the pre-placement exam. Employees, who are pregnant, are breast-feeding, or who are concerned with other reproductive issues should be encouraged to consult with the occupational health physician monitoring worker's health.

FOR MORE INFORMATION REFER TO SECTION 11: TOXICOLOGICAL INFORMATION

4. FIRST AID MEASURES

Ingestion: Obtain medical attention. Do not induce vomiting. Never give anything by mouth to an unconscious person.

Inhalation: Move to fresh air. Oxygen or artificial respiration if needed. Obtain medical attention.

Skin Contact: Wash off immediately with plenty of water for at least 15 minutes. Take off contaminated clothing and shoes immediately. Obtain medical attention. Wash contaminated clothing before reuse.

Eye Contact: Hold eyelids apart and flush eyes with plenty of water for at least 15 minutes. Get medical attention immediately.

Note to physicians: Ifosfamide is a mutagen and a cytotoxic drug. When administered parenterally, it is a toxic drug with a low therapeutic index.



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5. FIRE FIGHTING MEASURES

Flash point: Not applicable.

Autoignition Temperature: Not available.

Flammability Limits

LEL: Not available.

UEL: Not available.

Combustibility of Dusts: Fine powders are considered to be combustible. Provide appropriate bonding and grounding protection to control static charges. Powder handling equipment such as dust collectors, dryers, and mills may require additional protective measures (i.e. explosion venting).

Extinguishing Media: In case of fire use water, carbon dioxide, foam or dry chemical.

Firefighting Instructions: Firefighters should wear self-contained breathing apparatus, flame and chemical resistant clothing, boots and gloves. Evacuate personnel to upwind direction, remove unneeded material and cool container(s) with water from a maximum distance.

Hazardous Combustion Products: May include CO, CO₂, C₁₂, HCl, NO_x, PO_x, and possibly some carcinogenic compounds.

Unusual Hazards: Contains a cytotoxic anticancer drug. Avoid ingestion, inhalation, and skin contact. Decontaminate protective equipment with detergent and water after use.

6. ACCIDENTAL RELEASE MEASURES

Spill/Clean-up: Isolate area to restrict unnecessary persons. Put on suitable protective clothing and equipment. At minimum, wear double gloves (see section 8 for suitable materials), impervious disposable coveralls with closed front, long sleeves and elastic cuffs, and shoe covers or boots to protect from dusts, splashes, or sprays, chemical safety goggles, and a respirator with Class 100 or high efficiency particulate air filter. Select respirator depending on the nature and quantity of spilled material. Collect spilled material (lyophile) with paper toweling and moisten prior to pick up to minimize dust generation. For cleaning spills of reconstituted liquid material use adsorbent material to soak up spill. Clean area using several washes with detergent and water. Treat product and contaminated materials as hazardous waste and place in a suitable container for disposal. Incineration is recommended (Section 13). A trained chemist may refer to: Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Antineoplastic Agents, IARC Scientific Publications No. 73, page 65-71, 1985, for techniques suitable for both destruction and decontamination of the material.

SEE SECTION 8 FOR APPROPRIATE PROTECTIVE CLOTHING/EQUIPMENT TO BE WORN DURING SPILL CLEAN-UP.

7. HANDLING AND STORAGE

Handling Precautions: Avoid ingestion, inhalation, skin and eye contact. Use gloves and protective clothing as recommended in section 8. Use care to avoid



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HANDLING AND STORAGE (CONTINUED)

vial breakage and/or spillage. See relevant guidance for handling of cytotoxic materials. Minimize dust generation.

Container Requirements: Comply with federal and international regulations. Packaging Group III. See also 49 CFR 173.4.

Storage Conditions: Stable at or below room temperature.

8. EXPOSURE CONTROLS AND PERSONAL PROTECTION

Ventilation Requirements: Local mechanical exhaust ventilation is recommended to minimize employee exposure. Control exposure by enclosure of processes whenever possible. A ventilated cabinet, for example a biological safety cabinet (BSC), should be used for preparation of this drug, or as determined appropriate by an industrial hygienist.

Respiratory Protection: When engineering controls are not sufficient to control exposure, or if BSC is not available, wear an approved* dust respirator with Class 100 or high efficiency particulate air (HEPA) filter, or powered air-purifying respirator; self-contained breathing apparatus should be available for emergency use. Select respirator type depending on quantity handled, task and other existing controls.

Eye Protection: Wear chemical safety goggles (ANSI Z87.1).

Protective Gloves: Protective Gloves: Wear gloves at all times when handling vials, including when unpacking, inspecting, or transporting within a facility. Disposable chemotherapy gloves made from nitrile, neoprene, polyurethane and natural latex have been shown to have low permeability to this material. Use of double gloves are recommended when manipulating material, such as during dose preparation and administration. Gloves should be changed regularly and removed immediately after overt contamination. Check gloves frequently to ensure that there are no "pinholes" or rips and that the compound is not penetrating through. Use care when removing and disposing of gloves in order to minimize exposure. Persons who are allergic to natural rubber latex should select gloves made from one of the other materials.

Special Clothing: Wear impervious disposable coveralls with closed front, long sleeves and elastic cuffs, and shoe covers or boots to protect from dusts, splashes, or sprays. Disposable sleeve covers can also be used, in addition to the lab coat and gloves, for additional skin protection. Remove disposable clothing prior to leaving the work area.

Hygiene: Wash hands, forearms, and face thoroughly after handling compounds and before eating, smoking, using lavatory, and at the end of day.

*Note: NIOSH approves respirators in the United States.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance/Physical State/Color: White crystalline powder packaged in vials.

Boiling point: Not available.

Evaporation rate: Not available



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PHYSICAL AND CHEMICAL PROPERTIES (CONTINUED)

Flash point: Not applicable.

Freezing point/Melting point (degrees C): 49-50.5.

Octanol/water partition coefficient: Not available.

Odor (threshold): Not available.

pH: Not applicable.

Solubility in water: Freely soluble in water.

Specific gravity: Not available.

Vapor density: Not available.

Vapor Pressure: Not available.

Viscosity: Solid material.

10. STABILITY AND REACTIVITY

Stability: Stable under normal conditions (77 degrees F and below).

Incompatibilities: None known.

Conditions of Reactivity: None known.

Hazardous Decomposition Products: May include CO, CO₂, Cl₂, HCl, NO_x, PO_x and possibly some carcinogenic compounds.

Hazardous Polymerization: Will not occur at normal temperatures. May occur at temperatures above 120 degrees F.

Explosion data relative to mechanical impact: No specific data.

Explosion data relative to static discharge: No specific data.

11. TOXICOLOGICAL INFORMATION (for ifosfamide)

RTECS NUMBER (U.S.): RP6050000.

ACUTE

LD 50:

Acute oral LD50 (rat) = 143 mg/kg;

Acute oral LD50 (mouse) = 1005 mg/kg.

Acute ip LD50 (rat) = 140 mg/kg;

Acute ip LD50 (mouse) = 397 mg/kg.

Acute sc LD50 (rat) = 160 mg/kg;

Acute sc LD50 (mouse) = 656 mg/kg.

Acute iv LD50 (rat) = 190 mg/kg;

Acute iv LD50 (mouse) = 338 mg/kg.

LC 50: No information.



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TOXICOLOGICAL INFORMATION (CONTINUED)

CHRONIC

Carcinogenicity: Ifosfamide is a carcinogen in laboratory animals. Administration of this compound has been associated with leiomyosarcomas and mammary fibroadenomas in female rats. It is a potential human carcinogen.

Mutagenicity: Ifosfamide was reported to cause mutations in genetic toxicity studies. Compounds that are mutagens may have potential to cause carcinogenicity and/or adverse developmental effects.

Teratogenicity: Ifosfamide can cause fetal damage when administered to pregnant women. The drug is embryotoxic and teratogenic in mice, rats and rabbits at doses 0.05-0.075 times the human dose.

Reproductive Effects: Ifosfamide is used to treat germ cell testicular cancer. It has been shown to induce mutagenic effects in mice germ cells. It may adversely affect the male reproductive system. Ifosfamide is excreted in breast milk.

Toxicological synergistic products: Ifosfamide may potentiate the toxicity of other antineoplastic agents and vice versa. Mesnex (2-mercaptoethane sulfonic acid monosodium salt) antagonizes the hemorrhagic cystitis effects of ifosfamide.

12. ECOLOGICAL INFORMATION

Ecotoxicological Information: No information.

Chemical Fate Information: Ifosfamide has been shown to be non-biodegradable in laboratory-scale sewage treatment studies.

13. DISPOSAL CONSIDERATIONS

Disposal: Dispose of in accordance with National, State, Local and applicable country regulations. Treat product and contaminated materials as a hazardous material. Incineration at an approved facility is recommended.

14. TRANSPORT INFORMATION

Proper shipping name: Medicines, solid, toxic, n.o.s., (ifosfamide) 6.1, UN 3249.

15. REGULATORY/STATUTORY INFORMATION -- not meant to be all inclusive.

Material is considered to be hazardous under OSHA's Hazard Communication Standard.

International: See EC labeling below.

EC Labeling: The following risk phrases refer to the active pharmaceutical ingredient (ifosfamide)- R25, R40, R46, R48, R60, R61, R64.

California: Product contains ifosfamide which is subject to California Proposition 65 reproductive toxin warning and release requirements.



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16. OTHER INFORMATION

June 9, 2004: The MSDS for Ifex for Injection, dated June 4, 2004 was revised to add the R64 phrase in section 16.

June 4, 2004: The MSDS for Ifex for Injection, dated November 20, 2000 was revised to change telephone contact numbers, and revise and or add information in sections 1, 2, 3, 4, 6, 7, 8, 9, 11, 14, and 15.

Federal law prohibits dispensing without prescription. See package insert for recommended medical use.

Therapeutic agents are intended for use under direction of a physician and/or under the conditions of use described on the label. As a general precaution, personnel who handle drug substances should avoid contact (ingestion, inhalation, skin and eye contact) with these substances.

This material safety data sheet is intended for use by personnel who handle this material as part of their job responsibilities. It does not address the therapeutic use of this material. Information concerning the therapeutic use of this drug substance should be obtained from formulated product package inserts and other appropriate references.

The information contained in this MSDS is believed to be accurate and represents the best information available at the time of preparation. However, we make no warranty, express or implied, with respect to such information, and we assume no liability from its use.

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