SAFETY DATA SHEET

in accordance with Directive 93/112/EEC

1. IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

Product name: Busulfex® (busulfan) Injection
Synonyms: Busulfan injectable
Company: Otsuka Pharmaceutical Co., Ltd.
Second Tokushima Factory
Address: 224-18 Ebisuno Hiraishi Kawauchi-cho Tokushima, Japan
Department: Bulk Pharmaceutical Chemicals Dep.

Busulfex® injection formulation is an alkylating agent for the treatment of cancer dissolved in N,N-dimethylacetamide and Polyethylene Glycol 400. The product is intended for dilution with 0.9% sodium chloride injection or 5% dextrose injection prior to intravenous infusion.

2. COMPOSITION/INFORMATION ON INGREDIENTS

Component(s): % (by wt)
Busulfan (CAS # 55-98-1) < 1
Formulated with:
N,N-dimethylacetamide (DMA) (CAS # 127-19-5) approx. 33
Polyethylene Glycol 400 (PEG-400) (CAS # 25332-68-3) approx. 67

Classification and Labeling: T
R39/26/27/28, R62, R63, R45, R46

3. HAZARDS IDENTIFICATION

WARNING STATEMENT

CAUTION: Product contains busulfan, a potent and toxic active pharmaceutical ingredient, which is intended for research and clinical use only. This product should be handled by technically qualified individuals knowledgeable in the handling of potentially hazardous or potent pharmaceutical products. Repeated overexposure may cause effects on the hematological system (anemia and decreased platelets), with symptoms of increased risk of bleeding and tiredness. The active ingredient is considered a potential reproductive toxicant (affects fertility), a potential teratogen and developmental toxicant (affects the developing fetus and causes birth defects) and a potential carcinogen (causes cancer). Avoid skin contact, eye contact, and inhalation.

Routes of Absorption
Skin contact, eye contact, inhalation, and accidental ingestion.

Eye and Skin
No data available on eye or skin irritation potential of product or busulfan. N,N-dimethylacetamide (DMA), which is a solvent in the formulation is considered to be an irritant to the skin and eyes.
Busulfex-01-00

**Product name:**  Busulfex® (busulfan) Injection

**Systemic**

**Acute**
At the injectable clinical dose for busulfan, almost all patients have profound myelosuppression, including anemia (decrease in red blood cells), leukopenia (decrease in white blood cells), and thrombocytopenia (decrease in platelets). Other effects consistent with cytotoxic agents have also been reported, including: alopecia (hair loss), mucositis (inflammation of the stomach lining), nausea and vomiting and increased risk of infection. Other systems or organs effected by clinical doses include the nervous system (insomnia, anxiety, and dizziness), liver (hepatic vein occlusive effects), and pulmonary system (shortness of breath). It is also considered a developmental and reproductive toxicant (see further information below).

DMA is considered a liver toxicant if exposures exceed the recommended standards (see further under Occupational Exposure Limits) and a potential developmental toxicant (at high doses in laboratory animals)

Although these reported effects are from direct clinical administration or in the case of DMA from industrial scale use, because of its potency and toxicity, the handler/user of this product should protect against the potential effects on the hematological system, reproductive system, liver, and potential effects on the developing fetus.

Exposure will potentially occur during administration to patients, mixing / preparation activities, and if spilled or released from the ampoule.

**Chronic**
Chronic effects should be similar to those potentially occurring from acute exposure. The active ingredient, busulfan is considered a potential human carcinogen.

**Reproductive Toxicity**
The active ingredient is considered a reproductive toxicant based on studies in laboratory animals and human experience (see following section on effects during pregnancy and Section 11 for further detail of effects on fertility).

**Developmental Toxicity**
The active ingredient and DMA are considered potential teratogens (potential to cause birth defects) and developmental toxicants (affects the developing fetus).

**Mutagenicity**
The active ingredient is considered a mutagen and genotoxicant (see Section 11).

**Carcinogenicity**
Busulfan is a carcinogen in mice, and several cases of cancer have been reported in patients taking the drug. Busulfan is considered carcinogenic to humans by NTP, IARC and OSHA.

**Medical Conditions Aggravated by Exposure**
None known or reported.

**Occupational Exposure Limit**
None currently established by OSHA, ACGIH or Protein Design Laboratories for busulfan. N,N-dimethylacetamide has an OSHA PEL and ACGIH TLV of 10 ppm as a time-weighted average.
4. FIRST-AID MEASURES

General instruction:
Show this MSDS to the physician.

Skin contact:
Immediately wash thoroughly with soap and water for 15 minutes. If an irritation develops, contact medical personnel and notify supervisor.

Eye contact:
Immediately flush eyes thoroughly with water for at least 15 minutes. Notify medical personnel and supervisor.

Inhalation:
Immediately move to fresh air and notify medical personnel and supervisor.

Ingestion:
Immediately notify medical personnel and supervisor. Drink 2-3 glasses of water and contact medical personnel.

5. FIRE-FIGHTING MEASURES

Suitable extinguishing media:
Water mist, Carbon dioxide, Powder, Foam

Extinguishing media to avoid:
Jet of water

Special exposure hazards arising from combustion products:
COx, NOx, SOx

Protective equipment for fire-fighters:
Wear protective clothing and self contained breathing apparatus.

Special extinguishing instructions:
Use water spray to cool the fire exposed containers as well as for protection of people.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions:
Wear personal protective equipment (goggles and gloves).

Environmental protection:
Prevent spillage from directly entering ground or navigable waters.

Methods for cleaning up:
Absorb to cloth or sand promptly and deposit in suitable containers for disposal. Remove to permitted waste disposal. Follow local regulations for chemical waste.

7. HANDLING AND STORAGE

7.1 Handling
Technical measures and precautions:
Avoid release to ground or navigable waters.

Precautions for safe handling:
Use local exhaust ventilation. Use personal protective equipment (protective clothes, goggles and latex gloves).

7.2 Storage
Technical measures/conditions for safe storage:
Store in air tight and unbreakable containers, at 2 to 4°C. in well ventilated areas. Avoid substance outside the container.

Incompatible materials: None known.
**8. EXPOSURE CONTROL/PERSONAL PROTECTIVE EQUIPMENT**

**Airborne exposure limits:**
- Occupational Exposure Limit (OEB) recommended:
  Category 3: 0.001-0.05 mg/m³ (for active pharmaceutical ingredient “Busulfan”)

**Technical measures:**
Substance should only be handled in well ventilated areas.

**Personal protection:**
- **Respiratory protection:**
  If ventilation insufficient, wear a half-face organic vapor respirator.
- **Hand protection:**
  Wear latex gloves.
- **Eye protection:**
  Use safety goggles or face protection.
- **Skin protection:**
  Protective clothing.
- **Hygiene measures:**
  Wash hands after handling

**9. PHYSICAL AND CHEMICAL PROPERTIES**

- **Appearance:** Viscous liquid
- **Color:** Clear
- **Melting point:** Not applicable
- **Boiling point:** No data
- **Specific gravity:** 1.06
- **Vapor pressure:** Negligible
- **Water solubility:** Soluble
- **Partition coefficient:** Not applicable
- **Flammability:** Not flammable
- **Explosive properties:** Not explosive
- **Relative self ignition:** Not autoflammable

**10. STABILITY AND REACTIVITY**

- **Stability:**
  Stable under storage conditions (at 2 to 4°C, avoid direct sunlight).
- **Conditions to avoid:**
  High temperatures
- **Materials to avoid:**
  Strong oxidizers, strong acids, and halogenated compounds in the presence of iron.
- **Hazardous substances produced upon decomposition:**
  COx, NOx, SOx

**11. TOXICOLOGICAL INFORMATION**

- **Acute toxicity:** Busulfan is considered toxic orally, with an oral LD50 values of 110 mg/kg in the mouse. PEG-400 is not considered toxic orally and DMA is also not toxic orally with an LD50 of 5000 mg/kg.
- **Irritation/Sensitization:** DMA is considered an irritant. PEG-400 is not considered an irritant and no data available on busulfan.
- **Repeated dose studies:** See Carcinogenicity.
Busulfan produced teratogenic changes in the offspring of mice, rats and rabbits when given during gestation. Malformations and anomalies included significant alterations in the musculoskeletal system, body weight gain, and size. In pregnant rats, busulfan produced sterility in both male and female offspring due to the absence of germinal cells in the testes and ovaries.

The solvent in the formulation, dimethylacetamide or DMA, at doses of 400 mg/kg/d given during organogenesis caused significant developmental anomalies. The most striking abnormalities included anasarca, cleft palate, vertebral anomalies, rib anomalies, and serious anomalies of the vessels of the heart. DMA is a significantly less potent teratogen than busulfan.

Busulfan depleted oocytes of female rats and induced sterility in male rats and hamsters. A DMA daily dose of 0.45 g/kg/d given to rats for nine days significantly decreased spermatogenesis in rats. A single subcutaneous dose of 2.2 g/kg four days after insemination terminated pregnancy in 100% of tested hamsters.

Busulfan is a mutagen and a clastogen. In vitro tests it caused mutations in Salmonella typhimurium and Drosophila melanogaster. Chromosomal aberrations induced by busulfan have been reported in vivo (rats, mice, hamsters, and humans) and in vitro (rodent and human cells).

The intravenous administration of busulfan (48 mg/kg given as biweekly doses of 12 mg/kg) has been shown to increase the incidence of thymic and ovarian tumors in mice. Four cases of acute leukemia occurred among 19 patients who became pancytopenic in a 243 patient study incorporating busulfan as adjuvant therapy following surgical resection of bronchogenic carcinoma.

**12.ECOLOGICAL INFORMATION**

Degradability:
Not available

Ecotoxicity:
Not available

**13.DISPOSAL CONSIDERATIONS**

Product:
Incinerate with high temperatures in accordance with local/national regulations.

Packaging:
Packages can be washed out with small amounts of water. The used water shall be discharged in an environmentally safe manner, (e.g., appropriately permitted municipal or on-site wastewater treatment facility).

**14.TRANSPORT INFORMATION**

Hazard Class
Toxic liquid, organic, n.o.s.

UN Number
2810
15. REGULATORY INFORMATION

Containers of this material should have affixed the following label (in addition to the identity label):

CAUTION: Product contains busulfan, a potent and toxic active pharmaceutical ingredient, which is intended for research and clinical use only. This product should be handled by technically qualified individuals knowledgeable in the handling of potentially hazardous or potent pharmaceutical products. Repeated overexposure may cause effects on the hematological system (anemia and decreased platelets), with symptoms of increased risk of bleeding and tiredness. The active ingredient is considered a potential reproductive toxicant (affects fertility), a potential teratogen and developmental toxicant (affects the developing fetus and causes birth defects) and a potential carcinogen (causes cancer). Avoid skin contact, eye contact, and inhalation. Read and understand the Material Safety Data Sheet before handling material.

The following regulatory information has been provided for customer and internal use. This information is not meant to be inclusive of all regulations that may apply in the handling of this material.

According to Directive 93/21 EEC the substances should be classified and labeled as:

Symbol: T Toxic
R-Sentences:
R39/26/27/28 Very toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.
R62 Possible risk of impaired fertility.
R63 Possible risk of harm to the unborn child.
R45 May cause cancer.
R46 May cause heritable genetic damage.

California Proposition 65
Busulfan is listed as a carcinogen and a developmental toxicant under this regulation.
CERCLA
Not listed.
SARA Hazard Categories Section 311 and 312
The product meets the following definitions under this regulation: An immediate health hazard, a delayed/chronic health hazard

16. OTHER INFORMATION

No additional information.

Abbreviations
ACGIH: American Conference of Governmental Industrial Hygienists
CAS#: Chemical Abstract Services Number
CERCLA: Comprehensive Environmental Response Compensation and Liability Act (Superfund)
CFR: Code of Federal Regulations
DOT: Department of Transportation
EU: European Union
IARC: International Agency for Research on Cancer
IATA: International Air Transport Association
OSHA: Occupational Safety and Health Administration
NTP: National Toxicology Program
SARA: Superfund Amendment and Reauthorization Act of 1986 (SARA Title III)
TSCA: Toxic Substances Control Act
Product name: Busulfex® (busulfan) Injection

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The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions.

No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is biologically active.