MATERIAL SAFETY DATA SHEET

SECTION 1: CHEMICAL SUBSTANCE

PRODUCT NAME: Myleran® Tablets
COMMON NAME: busulfan
CHEMICAL NAME: 1,4-Butandiol dimethanesulfonate
SYNONYMS: Myleran® (busulfan) Tablets; Myleran Tablets; GW274383X; 340C50
SUBSTANCE CLASS: Bifunctional alkylating agent.

SECTION 2: HAZARDOUS INGREDIENTS

<table>
<thead>
<tr>
<th>NAME</th>
<th>CAS/EINECS/ELINCS #</th>
<th>% w/v or w/w</th>
<th>GW LIMITS (mcg/m³)</th>
<th>OTHER LIMITS (mcg/m³)</th>
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</thead>
<tbody>
<tr>
<td>busulfan</td>
<td>55-98-1</td>
<td></td>
<td>1.0 mcg/m³ (pure substance)</td>
<td>Not established</td>
</tr>
</tbody>
</table>

SECTION 3: HAZARDS IDENTIFICATION

Busulfan, the active agent in Myleran® Tablets, is a potent cytotoxic (cell-killing) agent. Myleran® (busulfan) is toxic if swallowed, in contact with skin, and if inhaled. Irritating to eyes and skin. Busulfan is listed by IARC (International Agency for Research on Cancer) and NTP (US National Toxicology Program) as a human carcinogen. Busulfan may cause heritable genetic damage. Adverse reactions noted in medicinal use include weakness, severe fatigue, anorexia, weight loss, nausea, and vomiting. Busulfan in sufficient dose may result in anemia (decreased numbers of red blood cells), leukopenia (decreased numbers of white blood cells), and thrombocytopenia (decreased numbers of platelets). Busulfan may cause fetal harm and produces human infertility.

See also Section 11: “Toxicological Information”.

SECTION 4: FIRST AID MEASURES

If in Eyes: Flush thoroughly with large amounts of water. Obtain medical attention.
SECTION 4: FIRST AID MEASURES (cont’d)

If On Skin: Remove contaminated clothing. Wash all affected areas thoroughly with soap and water. Obtain medical attention.

If Inhaled: If breathing is difficult or ceases, give oxygen or cardiopulmonary resuscitation. Remove to fresh air. Obtain medical attention.

If Ingested: Rinse mouth with water if conscious (awake). Do not give water if unconscious. Obtain medical attention.

Note to Physicians: Administration of activated charcoal would be indicated if ingestion was recent. Daily blood counts are necessary for at least 4 weeks. At first sign of bone marrow depression, prednisone in full dosage is indicated. Transfusions of fresh blood, antibiotics, and barrier nursing would be indicated according to condition of the bone marrow.

SECTION 5: FIRE / EXPLOSION HAZARDS & FIRE-FIGHTING MEASURES

FLASHPOINT / TEST METHOD: Unknown.

LEL / UEL: Unknown.

STORAGE OR HANDLING CONDITIONS TO BE AVOIDED: Heating may give rise to toxic or irritant fumes.

EXTINGUISHING MEDIA: Water Spray, foam or Multipurpose Dry Chemical.

FIRE-FIGHTING PROCEDURES: Wear full protective clothing and use self-contained breathing apparatus (SCBA).

SECTION 6: SPILL AND LEAK PROCEDURES

SPILL RESPONSE PROCEDURES (Liquid, Solid, Gas/Vapor):

Protective equipment may be necessary for spills. (See Section 8, “Exposure Controls / Personal Protection” for guidance).

For small quantities associated with normal therapeutic use, collect spillage and transfer to a closed waste container for disposal. For large or bulk quantities, collect spillage by carefully sweeping or wiping and place in a labeled, sealed container for disposal. Wash spill area (floor or other contact surfaces) with a suitable cleaning solvent, like dilute caustic soda and sodium hypochlorite solution, then wash down area with soap and water. (NOTE: Discharge of resulting high pH wash water may be illegal. Collect and treat before discharge.)

SECTION 7: HANDLING AND STORAGE

HANDLING: Avoid exposure by any route. Use only in well-ventilated area with limited access. Restrict access to designated work area and prevent exposure of those not equipped with protective equipment. Properly identify (signage and labeling) potential hazards in designated work areas.

No open handling of powders or uncoated tablets unless precautions have been taken to prevent exposure. Handling of solids and solutions should be conducted in designated areas to minimize surface contamination. Aerosol-generating procedures should be conducted in a laboratory fume hood or with other suitable local exhaust ventilation.

STORAGE: Store at 15°C to 25°C (59°C to 77°F) in a dry place. Keep in original container tightly closed. Protect from light.

Minimize generation and accumulation of dusts and mists containing this substance.
SECTION 8: EXPOSURE CONTROLS / PERSONAL PROTECTION

ENGINEERING CONTROLS: Provide local exhaust ventilation at the source of dust generation. Facilities storing or utilizing this substance should be equipped with eyewash and safety shower.

PERSONAL PROTECTION: Full protective equipment including respirator, gloves, eye protection, and protective clothing should be worn where there is potential for skin exposure or risk of dust or mist inhalation.

Respiratory: For dusty processes, in the absence of local exhaust ventilation, use NIOSH-approved particulate respirator. A powered air-purifying respirator with a high-efficiency particulate filter or supplied-air respirators should be used. Respiratory protection should include a full hood or a full face piece and a separate head covering.

Eye: Workers should wear adequate eye protection to prevent eye contact.

Clothing: Adequate protective clothing should be worn to prevent occupational skin contact.

Gloves: Protective gloves should be worn at all times to prevent skin contact.

WORK PRACTICES: Special care should be taken to ensure that contaminated clothing, equipment, and work surfaces are properly cleaned or disposed of after use. Wash hands and other areas of skin contact thoroughly after handling this material.

SECTION 9: PHYSICAL / CHEMICAL PROPERTIES

APPEARANCE AND ODOR: Busulfan is a white almost odorless crystalline powder. Myleran® Tablets are white, scored tablets containing 2 mg busulfan, imprinted with “MYLERAN” and “K2A” on each tablet.

PHYSICAL STATE (liquid/solid/gas): Solid.

MELTING POINT (deg. C): 115 - 118⁰ C.

SOLUBILITY/MISCIBILITY (% w/v): Not determined for Myleran® Tablets. Busulfan, the active ingredient in Myleran® Tablets, is insoluble in water.

SECTION 10: STABILITY AND REACTIVITY

CHEMICAL STABILITY: Stable.

CONDITIONS TO AVOID: Not determined.

INCOMPATIBILITY WITH OTHER MATERIALS: Not determined for Myleran® Tablets. No known incompatibilities have been identified for busulfan, the active ingredient in Myleran® Tablets.

HAZARDOUS DECOMPOSITION PRODUCTS: Hazardous decomposition products of Myleran® Tablets have not been determined. Thermal decomposition products of busulfan, the active ingredient in Myleran® Tablets, include toxic and/or corrosive oxides of sulfur.

HAZARDOUS POLYMERIZATION: Not determined.
SECTION 11: TOXICOLOGICAL INFORMATION

THE RISK OF HEALTH HAZARDS MAY BE REDUCED WHEN MYLERAN\textsuperscript{\textregistered} TABLETS ARE HANDLED IN UNIT DOSAGE FORM.

PHARMACOLOGICAL ACTIVITY: Busulfan, the active agent in MYLERAN\textsuperscript{\textregistered} Tablets, is a bifunctional alkylating agent with cytotoxic (cell-killing) activity. Busulfan is indicated for the palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia. Although not curative, busulfan relieves symptoms of the disease and improves the clinical state of the patient. The anti-neoplastic actions of busulfan are thought to result, at least in part, from interaction of busulfan with DNA.

OCCUPATIONAL EXPOSURE LIMITS: For busulfan, the active ingredient in Myleran\textsuperscript{\textregistered} Tablets, the Glaxo Wellcome estimated safe working level is an eight hour time-weighted average (TWA) of 1 mcg/m\textsuperscript{3}.

ACUTE TOXICITY: Busulfan is a powerful cytotoxic (cell-killing) drug and may depress bone marrow function and formation of the formed elements of the blood. It is toxic in contact with skin, and if swallowed or inhaled. The oral LD\textsubscript{50} = 1.86 mg/kg in the rat and 110 mg/kg in the mouse. Overexposure to busulfan in the occupational setting may result in the same adverse effects which have been observed in experimental studies or when this substance is used medicinally. Acute exposure in sufficient dose may result in anemia (decreased numbers of red blood cells), leukopenia (decreased numbers of white blood cells), and thrombocytopenia (decreased numbers of platelets). Other adverse reactions include weakness, severe fatigue, anorexia, weight loss, nausea, and vomiting. (See “Repeat Dose Toxicity”, and “Clinical Safety”, below.)

REPEAT DOSE TOXICITY: In the occupational setting, repeated overexposure to busulfan may result in the same adverse effects which have been observed when this substance is used medicinally (see “Acute Toxicity”, above, and “Clinical Safety”, below.). Long term animal studies have been reviewed by both the US National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) and demonstrate toxic, teratogenic and carcinogenic effects of busulfan. See “Clinical Safety”, below, for long term effects and precautions in medicinal use.

IRRITATION: Busulfan is an irritant to the skin and mucous membranes. In rats, busulphan has been reported to induce cataracts (permanent opacity of the lens of the eye) and cataract formation is a rare complication of busulfan use in humans.

SENSITIZATION: Clinical cases of hypersensitivity to busulfan have been reported.

REPRODUCTIVE EFFECTS: In female patients, busulfan may cause suppression of ovarian function and amenorrhea. Busulfan interferes with spermatogenesis in experimental animals, and there have been clinical reports of sterility, azoospermia and testicular atrophy in male patients receiving this drug.

In pregnant rats, busulfan produces sterility in both male and female offspring due to the absence of germinal cells in testes and ovaries. Germinal cell aplasia or sterility in offspring of mothers receiving busulfan during pregnancy has not been reported in humans. There are few reports of human birth defects caused by medicinal use of busulfan. However, there are no adequate and well-controlled studies of busulfan in pregnant women. Busulfan may cause fetal harm when administered to a pregnant woman. If this drug 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. For recommended dosage and administration, Myleran\textsuperscript{\textregistered} Tablets are classified as “Pregnancy Category D”. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of
SECTION 11: TOXICOLOGICAL INFORMATION (cont’d)

REPRODUCTIVE EFFECTS (cont’d): the potential for serious adverse reactions in nursing infants from busulfan, precautions should be taken to limit exposure to this substance while pregnant or nursing; medical evaluation of exposure and attention to compliance with standard operating procedures and/or other workplace health and safety directives is advised.

GENOTOXICITY: Busulfan is mutagenic in mice and humans. Reports of chromosomal abnormalities and other variations in the genetic material in a variety of tissues have been observed in medicinal use.

CARCINOGENICITY: This substance has been demonstrated to be a carcinogen in animal studies as well as causing tumors in medicinal use in humans. Busulfan is listed by the US National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) as a substance known to be carcinogenic.

CLINICAL SAFETY: There is a risk of severe bone marrow hypoplasia in medicinal use of busulfan and a warning to monitor any decrease of the formed elements of the blood. This most common toxic effect is manifested by anemia, leukopenia, and thrombocytopenia. Adverse reactions include weakness, severe fatigue, anorexia, weight loss, nausea, and vomiting. Busulfan treatment has been associated with an increased risk of developing leukemia. A rare but important complication of long term busulfan therapy is development of bronchopulmonary dysplasia with pulmonary fibrosis.

SECTION 12: ECOLOGICAL INFORMATION

ENVIRONMENTAL FATE: Environmental testing is currently in progress. Until environmental effects have been determined, dispose of unused compound or process wastes by incineration.

ENVIRONMENTAL EFFECTS: Environmental testing is currently in progress.

ENVIRONMENTAL TEST RESULTS: Environmental testing is currently in progress.

<table>
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<tr>
<th>STUDY NAME</th>
<th>RESULTS</th>
<th>COMMENTS</th>
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<td>Water Solubility:</td>
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<td>Hydrolysis Rate:</td>
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<td>Vapor Pressure:</td>
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<td>UV/Visible Spectrum:</td>
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<td>Soil Absorption/Desorption:</td>
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<tr>
<td>Acute toxicity to Daphnia:</td>
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SECTION 13: WASTE DISPOSAL

ROUTINE: Unused product should be disposed of at an approved facility in accordance with federal, state and local regulations.

ACCIDENTAL RELEASE: Clean up spills immediately, observing precautions in Section 8 - “Personal Protection”. Remove or decontaminate all residues in accordance with federal, state and local regulations.
SECTION 14: TRANSPORTATION INFORMATION

Component 1 or Formulation 1: Myleran® Tablets

**US Department of Transportation**
Proper Shipping Name: Not Regulated

**IATA/ICAO**
Proper Shipping Name: Not Regulated

**IMDG**
Proper Shipping Name: Not Regulated

RQ: None
Marine Pollutant: No

SECTION 15: REGULATORY INFORMATION

EC PACKAGING AND LABELING FOR SUPPLY: Not applicable.

OTHER LEGISLATION: Not determined.

SECTION 16: OTHER INFORMATION

Physicians Desk Reference, Medical Economics Co., Inc., Oradell, NJ  Edward R. Barnhart, Publisher


Work Practice Guidelines For Personnel Dealing With Cytotoxic (Antineoplastic) Drugs, January, 1986, Office of Occupational Medicine, Occupational Safety and Health Administration, U.S. Dept. of Labor

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SUPERSEDES: 1/28/97