



Glaxo Wellcome Inc.
PO Box 13398
5 Moore Drive
RTP, NC 27709

(919) 483-2100
(919) 483-2700 (24 hour contact)

Effective Date: 05/03/2000

MATERIAL SAFETY DATA SHEET

SECTION 1: CHEMICAL SUBSTANCE

PRODUCT NAME: Alkeran[®] (melphalan) 2 mg Scored Tablets
COMMON NAME: Melphalan
CHEMICAL NAME: 4-[bis(2-chloroethyl)amino]-L-phenylalanine
SYNONYMS: Alkeran[®](melphalan); Alkeran[®] Tablets; Alkeran Tablets; L-phenylalanine mustard; phenylalanine mustard; L-PAM; L-sarcolysin; 7P56
SUBSTANCE CLASS: Anti-neoplastic

SECTION 2: HAZARDOUS INGREDIENTS

NAME	CAS/EINECS/ELINCS #	% w/v or w/w	GW LIMITS (mcg/m ³)	OTHER LIMITS (mcg/m ³)
Melphalan	148-82-3		1.0 mcg/m ³ OEL	Not established

SECTION 3: HAZARDS IDENTIFICATION

THE RISK OF HEALTH HAZARDS MAY BE REDUCED WHEN ALKERAN[®] TABLETS ARE HANDLED IN UNIT DOSAGE FORM.

Melphalan is a powerful cytotoxic (cell killing) agent.

This substance is very toxic if swallowed and is likely to be toxic by inhalation or through skin contact.

Melphalan is known to react with DNA and as such may pose a carcinogenic, mutagenic and teratogenic risk.

May cause heritable genetic damage and reduce fertility.

May cause skin reactions and sensitization (allergy) by contact.

See also Section 11: Toxicological Information.

SECTION 4: FIRST AID MEASURES

If in Eyes: Flush with large amounts of cool water for at least 15 minutes. Obtain medical attention.

If On Skin: Wash affected areas with soap and water after removing contaminated clothing. Obtain medical attention if contamination is significant and/or a skin reaction is evident.

TO THE BEST OF OUR KNOWLEDGE THE INFORMATION CONTAINED HEREIN IS ACCURATE AS OF THE DATE HEREOF. ANY DETERMINATION AS TO THE SUITABILITY OF THE PRODUCT FOR ANY PARTICULAR PURPOSE, ITS SAFE USE OR DISPOSAL SHALL BE THE RESPONSIBILITY OF THE USER. THE INFORMATION CONTAINED HEREIN IS IN NO WAY INTENDED TO SUPPLEMENT, MODIFY OR SUPERSEDE THE INFORMATION PROVIDED IN THE PRODUCT PACKAGE INSERT WITH RESPECT TO THE USE OF THE PRODUCT FOR MEDICAL PURPOSES. PLEASE REFER TO THE PRODUCT PACKAGE INSERT FOR INFORMATION REGARDING THE USE OF THE PRODUCT FOR MEDICAL PURPOSES.

SECTION 4: FIRST AID MEASURES (cont'd)

If Inhaled: If not breathing, give artificial respiration or CPR. If breathing is difficult, give oxygen. Obtain medical attention and remove to fresh air.

If Ingested: If awake and able to swallow, rinse mouth with water. Never give anything by mouth if unconscious or having convulsions. Obtain medical attention.

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

FLASHPOINT/TEST METHOD: Not determined.

LEL / UEL: Not determined.

EXTINGUISHING MEDIA: Water Spray, Multipurpose Dry Chemical.

SPECIAL 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 wet wiping or HEPA vacuuming and place in a labeled, sealed container for disposal. Wash spill area (floor or other contact surfaces) with a suitable cleaning solvent, like 5% caustic soda solution, then wash down area with water. (NOTE: Discharge of resulting high pH wash water may be illegal. Collect and treat before discharge.)

SECTION 7: HANDLING AND STORAGE

HANDLING: Avoid contact with eyes, skin, and clothing. Dispense in glass.

STORAGE: Store at 59° to 77° F in a dry place protected from light.

SECTION 8: EXPOSURE CONTROLS / PERSONAL PROTECTION

ENGINEERING CONTROLS: No special ventilation requirements for normal dosage and administration. In areas of high dust concentration, provide good general exhaust ventilation to keep airborne concentrations below the occupational exposure limit (OEL).

PERSONAL PROTECTION:

Respiratory: Respiratory protective equipment should be worn when workers are exposed to high dust levels. Recommendations for respiratory selection issued by the National Institute for Occupational Safety and Health (NIOSH), the American National Standard Practices for Respiratory Protection (ANSI Z88.2) and the respiratory equipment manufacturer should be followed.

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

Alkeran® Tablets
Clothing:

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

SECTION 8: EXPOSURE CONTROLS / PERSONAL PROTECTION (cont'd)

Gloves: Impermeable (e.g., latex) gloves should be worn.

WORK PRACTICES: Special care should be taken to ensure that contaminated clothing and equipment is properly cleaned after use. Wash hands and other areas of skin contact thoroughly with soap and water after handling this material. Contaminated clothing should be cleaned or disposed of.

SECTION 9: PHYSICAL / CHEMICAL PROPERTIES

APPEARANCE AND ODOR: Alkeran® (melphalan) Tablets are supplied as white, scored tablets imprinted with "ALKERAN" AND "A2A".

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

MELTING POINT (deg. C): Alkeran decomposes at 177° C.

BOILING POINT (deg. C): Not determined.

SOLUBILITY/MISCIBILITY (% w/v): Not determined for Alkeran® Tablets. Melphalan, the active ingredient in Alkeran®, is practically insoluble in water and ethanol; slightly soluble in .1N NaOH and HCl; and soluble in 1.0N HCl.

SECTION 10: STABILITY AND REACTIVITY

CHEMICAL STABILITY: Stable.

CONDITIONS TO AVOID: Not determined.

INCOMPATIBILITY WITH OTHER MATERIALS: No known incompatibilities have been identified for Alkeran® Tablets.

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

SECTION 11: TOXICOLOGICAL INFORMATION

THE RISK OF HEALTH HAZARDS MAY BE REDUCED WHEN ALKERAN® TABLETS ARE HANDLED IN UNIT DOSAGE FORM.

PHARMACOLOGICAL ACTIVITY: Alkeran® (melphalan) is an anti-neoplastic drug with significant data on adverse effects in the clinical and occupational setting. The mechanism by which melphalan exerts its anti-neoplastic activity against certain human cancers is most likely due to cytotoxicity related to interstrand cross-linking within DNA, probably by binding at the N⁷ position of guanine. As a bifunctional alkylating agent it is active against both resting and rapidly dividing tumor cells. Alkeran® is indicated for patients with multiple myeloma, or non-resectable epithelial carcinoma of the ovary.

OCCUPATIONAL EXPOSURE LIMITS: For melphalan, the active ingredient in Alkeran® Tablets, the Glaxo Wellcome estimated safe working level is an eight hour time-weighted average (TWA) of 1 mcg/m³.

SECTION 11: TOXICOLOGICAL INFORMATION (cont'd)

- ACUTE TOXICITY:** Experimental studies indicate that high doses of melphalan may be harmful following exposure by ingestion. It is also possible that inhalation of melphalan or absorption of this substance through the skin and mucous membranes may cause adverse effect. The approximate median lethal dose (MLD) of melphalan following single oral administration were:
- | | |
|-----------------------|------------------------|
| Male and female mice: | 10.2 mg/kg body weight |
| Male and female rats: | 4.7 mg/kg body weight |
- Lethal doses of melphalan in mice and rats caused symptoms including unkempt appearance, ataxia, hypoactivity, and gross pathology of hemorrhage in the intestine. Melphalan causes reduction in hematopoietic / blood cells through toxicity to bone marrow progenitor cells (precursors for hematopoietic/blood cells).
- REPEAT DOSE TOXICITY:** In dogs, symptoms including weight loss, hemorrhage in the gastrointestinal tract and mesentery, congestion and lymphoid hypoactivity, bone marrow hypocellularity and decreased spermatogenesis were observed at one or more treatment levels. In medicinal use, bone marrow suppression is the most significant toxicity associated with melphalan in most patients. Monitoring of platelet count, hemoglobin, white blood cell count, and differential blood cell counts for indications of thrombocytopenia and/or leukopenia are indications to withhold further therapy .
- IRRITATION:** Adverse irritation reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis, vasculitis, and alopecia.
- SENSITIZATION:** The clinical presentation and history of cases of melphalan use suggests that it is an allergenic hazard. Allergic responses range from mild (e.g., skin rash) to severe (including possible anaphylaxis).
- REPRODUCTIVE EFFECTS:** In experimental studies in rats, melphalan was embryotoxic and teratogenic, causing lag in development, deformation of the brain, eyes, mandible and other deformities. Occupational studies investigating potential effects of exposure to cytotoxic compounds similar to melphalan among nurses in the clinical setting suggest a reproductive hazard for this class of compounds. However, there are no adequate and well controlled studies of melphalan in pregnant women. For recommended dosage and administration, Alkeran® is classified as "Pregnancy Category D"; Alkeran® may cause fetal harm when administered to a pregnant women. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from melphalan, it is recommended that nursing be discontinued in women who are receiving therapy with Alkeran®. Precautions should be taken to limit exposure to Alkeran® 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/CARCINOGENICITY: Melphalan is mutagenic in animals and humans, carcinogenic in animals, and may increase risk of neoplasia in humans. It is listed as a carcinogen by both the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) listing of carcinogens .

CLINICAL SAFETY: The hazards of both acute and repeated melphalan exposure have been documented by observation and investigation of adverse effects in relatively

SECTION 11: TOXICOLOGICAL INFORMATION (cont'd)

CLINICAL SAFETY (cont'd): long-standing medicinal use. In medicinal use an overdose of 290 mg/m² (normalization of dose to body surface area) resulted in death. The immediate effects of overdose are severe nausea and vomiting . Decreased consciousness, convulsions, cholinomimetic effects and muscular paralysis are less frequently seen. Severe mucositis, stomatitis, colitis, diarrhea and hemorrhage of the gastrointestinal tract can occur at doses exceeding 100 mg/m². The principal toxic effect in therapeutic use is bone marrow aplasia, resulting in pronounced decreases in numbers of formed elements (cells) of the blood (pancytopenia). No antidotes exist for melphalan, but administration of autologous bone marrow or hematopoietic growth factors (GM-CSF, G-CSF) may shorten the period of pancytopenia.

SECTION 12: ECOLOGICAL INFORMATION

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

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: Alkeran® (melphalan) 2 mg Scored Tablets

US Department of Transportation

Proper Shipping Name: Not Regulated in Transportation

IATA/ICAO

Proper Shipping Name: Not Regulated in Transportation

IMDG

Proper Shipping Name: Not Regulated in Transportation

RQ: None Marine Pollutant: No

SECTION 15: REGULATORY INFORMATION

EC PACKAGING AND LABELING FOR SUPPLY: Not determined.

OTHER LEGISLATION: Not determined.

SECTION 16: OTHER INFORMATION

REVISION DATE: 05/03/00

SUPERSEDES: 07/18/97