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Effective Date: 07/18/97

MATERIAL SAFETY DATA SHEET

SECTION 1: CHEMICAL SUBSTANCE

PRODUCT NAME: Leukeran[®] (chlorambucil) 2 mg Sugar-coated Tablets
COMMON NAME: chlorambucil
CHEMICAL NAME: 4-[bis(2-chlorethyl)amino]benzenebutanoic acid
SYNONYMS: Leukeran[®] (chlorambucil) Tablets; Leukeran[®]; Leukeran Tablets; Chlorambucil; 3P55
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)
Chlorambucil	305-03-3		0.5 mcg/m ³ (pure substance) OEL	

SECTION 3: HAZARDS IDENTIFICATION

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

Chlorambucil, the active agent in Leukeran[®] Tablets, is a potent cytotoxic (cell-killing) agent.

Leukeran[®] (chlorambucil) is toxic if swallowed, in contact with skin, and if inhaled.

Irritating to eyes and skin.

Chlorambucil is listed by IARC (International Agency for Research on Cancer) as very likely to be carcinogenic in humans and as a human carcinogen by NTP (US National Toxicology Program).

Chlorambucil may cause heritable genetic damage.

Adverse reactions include hyperactivity, ataxia, convulsions and coma, nausea, vomiting and bone marrow toxicity.

Chlorambucil may cause fetal harm and produces human infertility.

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.

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 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.
- 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.
- Notes to Physicians: No known antidotes exist for chlorambucil, and general supportive care, monitoring of the blood pressure, and appropriate blood transfusions should be given if necessary.

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

- FLASHPOINT / TEST METHOD: Not determined.
- LEL / UEL: Not determined.
- STORAGE OR HANDLING CONDITIONS TO BE AVOIDED: Not determined.
- EXTINGUISHING MEDIA: Water Spray, 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, minimizing dust generation, and transfer to a closed waste container for disposal. For large or bulk quantities, collect spillage by carefully sweeping or wiping (minimizing dust generation) 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 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 LEUKERAN® (chlorambucil) Tablets at 15° to 25° C (59° to 77° F) in a dry place. Keep in original container tightly closed.

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 facepiece and a separate head covering.
- Eye, Clothing, Gloves: Use eye protection, impermeable gloves (*double latex*) and lab coats.
- WORK PRACTICES: Change or wash gloves after handling powder. Dispose of work clothing properly.

SECTION 9: PHYSICAL / CHEMICAL PROPERTIES

- APPEARANCE AND ODOR: LEUKERAN[®] (chlorambucil) Tablets are odorless, white sugar-coated tablets printed with "635" in black ink.
- PHYSICAL STATE (liquid/solid/gas): Solid.
- MELTING POINT (deg. C): 64-66°C (chlorambucil).
- SOLUBILITY/MISCIBILITY (% w/v): Not determined for Leukeran[®]. The solubility of chlorambucil, the active ingredient in Leukeran[®] Tablets is <0.1 mg/ml in water, ≥100 mg/ml in DMSO, ≥100 mg/ml in 95% ethanol, and ≥100 mg/ml in 95% acetone.

SECTION 10: STABILITY AND REACTIVITY

- CHEMICAL STABILITY: Not determined.
- CONDITIONS TO AVOID: Not determined.
- INCOMPATIBILITY WITH OTHER MATERIALS: Not determined for Leukeran[®] Tablets. No known incompatibilities have been identified for chlorambucil, the active ingredient in Leukeran[®].
- HAZARDOUS DECOMPOSITION PRODUCTS: Hazardous decomposition products of Leukeran[®] Tablets have not been determined. Thermal decomposition products of chlorambucil, the active ingredient in Leukeran[®], include toxic and/or corrosive chloride vapors and oxides of nitrogen and chlorine.

SECTION 11: TOXICOLOGICAL INFORMATION

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

- PHARMACOLOGICAL ACTIVITY: Leukeran[®] (chlorambucil) is a cytotoxic (cell-killing) drug used in treating certain cancers. Chlorambucil is indicated in the treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease.¹

SECTION 11: TOXICOLOGICAL INFORMATION (cont'd)

PHARMACOLOGICAL ACTIVITY (cont'd): Chlorambucil is a bifunctional alkylating agent which most likely exerts its anti-neoplastic activity by causing cytotoxicity related to inter-strand cross-linking within DNA, probably by binding at the N⁷ position of guanine.

OCCUPATIONAL EXPOSURE LIMITS: For chlorambucil the active ingredient in Leukeran® Tablets, the Glaxo Wellcome estimated safe working level is an eight hour time-weighted average (TWA) of 0.5 mcg/m³.

ACUTE TOXICITY: Experimental studies indicate that high doses of chlorambucil may be harmful when ingested. It is also possible that inhalation of chlorambucil or absorption of this substance through the skin and mucous membranes may cause adverse effects. Overexposure to chlorambucil 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. Approximate median lethal doses (MLD) of chlorambucil following single intraperitoneal (ip) administration in rats and oral administration in mice were¹:

Male and female rats (ip): 12.5 mg/kg
Male and female mice (oral): 123 mg/kg

Lethal doses of chlorambucil in rats caused symptoms including labored breathing, salivation, and convulsions. Overdose in humans has resulted in neurological toxicity including agitation, ataxia, and grand mal seizures; reversible pancytopenia is the main finding with chlorambucil.¹

REPEAT DOSE TOXICITY: In the occupational setting, repeated overexposure to chlorambucil may result in the same adverse effects which have been observed when this substance is used medicinally (see "Pharmacologic Activity" and "Acute Toxicity", above, and "Clinical Safety", below.). In medicinal use, bone marrow suppression is the most significant toxicity associated with repeated use of chlorambucil in most patients. Depressed platelet count, hemoglobin, white blood cell count, and altered differential blood cell counts (indications of thrombocytopenia and/or leukopenia) are indications to withhold further therapy.¹ Long-term use of chlorambucil is associated with development of leukemia and other cancers.

SENSITIZATION: The clinical presentation and history of cases of chlorambucil use suggests that it is an allergenic hazard. Allergic responses range from mild (e.g., skin rash) to severe (including possible anaphylaxis, a allergic response which may include tightness of the chest, difficult breathing, sudden decrease in blood pressure, loss of consciousness, and in severe cases, death).

REPRODUCTIVE EFFECTS: Both reversible and permanent sterility have been observed in both sexes receiving chlorambucil. In experimental studies, chlorambucil was embryotoxic and teratogenic causing delayed fetal development, deformation of the brain, cleft palate, deformed appendages and other deformities. Occupational studies investigating potential effects of exposure to cytotoxic compounds similar to chlorambucil among nurses in the clinical setting suggest a reproductive hazard for this class of compounds.^{3,4} For recommended dosage and administration, Leukeran® is classified as "Pregnancy Category D"; Leukeran® can cause fetal harm when

SECTION 11: TOXICOLOGICAL INFORMATION (cont'd)

REPRODUCTIVE EFFECTS (cont'd):	administered to a pregnant woman. Use of Leukeran® in pregnancy should be avoided. 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. It is not known whether this 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 chlorambucil, 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:	Chlorambucil is mutagenic in animals and humans.
CARCINOGENICITY:	Chlorambucil is carcinogenic in animals, and may increase risk of cancer in humans. It is listed as a carcinogen by the US National Toxicology Program (NTP) and likely to be a carcinogen by the International Agency for Research on Cancer (IARC). ²
CLINICAL SAFETY:	The hazards of both acute and repeated chlorambucil exposure have been documented by observation and investigation of adverse effects in relatively long-standing medicinal use. ¹ The immediate effects of overdose by ingestion are severe nausea and vomiting. Decreased consciousness, convulsions, ataxia and hyperactivity may occur due to effects on the central nervous system. Severe mucositis, stomatitis, colitis, and diarrhea can occur. The principal toxic effect in therapeutic use is bone marrow aplasia (loss of functional marrow), resulting in pancytopenia (pronounced decreases in numbers of formed elements (cells) of the blood).

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.
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SECTION 13: WASTE DISPOSAL

ROUTINE:	For disposal purposes, Chlorambucil is listed as hazardous by the EPA; EPA Waste Number-U035. Arrange for incineration or burial at an approved hazardous waste facility.
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: LEUKERAN® Tablets

US Department of Transportation

Proper Shipping Name: Not Regulated

IATA/ICAO

Proper Shipping Name: Not Regulated

SECTION 14: TRANSPORTATION INFORMATION (cont'd)**IMDG**

Proper Shipping Name: Not Regulated

RQ of Chlorambucil: 10 pounds (4.54 kg) Marine Pollutant: No

SECTION 15: REGULATORY INFORMATION

EC PACKAGING AND LABELING FOR SUPPLY: Not determined.

OTHER LEGISLATION: Not determined.

SECTION 16: OTHER INFORMATION

¹ GlaxoWellcome. 1996. LEUKERAN (chlorambucil) 2 mg Sugar-coated Tablets. p. 1133-1135. In Physicians Desk Reference (PDR). Medical Economics Co. Montvale, NJ.

² IARC working group. 1981. Some Antineoplastic and Immunosuppressive Agents. Chlorambucil:115-136.

³ OSHA. 1995. Controlling occupational exposure to hazardous drugs. p. 21-1 to 21-34. In OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Occupational Health and Safety Administration, Washington.

⁴ Shortridge-McCauley, L. A. 1995. Reproductive hazards: An overview of exposures to health care workers. Amer. Assoc. Occu. Health Nurses J. 43:614-620.

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