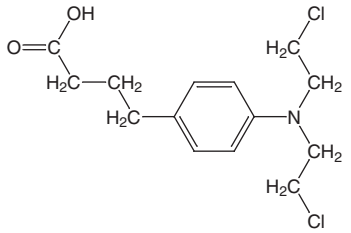
Chlorambucil
CAS No. 305-03-3

Known to be a human carcinogen
First Listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Chlorambucil is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. Excesses of cancer, primarily acute nonlymphocytic leukemia, were reported in a number of case reports and a few small epidemiological studies in which chlorambucil, either alone or in combination with other therapies, was used in treating nonmalignant and malignant diseases. A randomized clinical trial showed a 13-fold increase in the incidence of acute nonlymphocytic leukemia in 431 polycythemia vera patients treated with chlorambucil plus phlebotomy compared to patients treated with phlebotomy alone. The risk increased with increasing dose and time of treatment (IARC 1981, 1987).

The finding in humans is supported by studies in animals demonstrating that chlorambucil is tumorigenic in rats and mice. When administered by intraperitoneal injection, chlorambucil increased incidences of lymphosarcomas and lung tumors in mice of both sexes, ovarian tumors in female mice, hematopoietic tumors (lymphosarcomas, myelogenous leukemia and reticulum cell sarcomas) in male rats, and hematopoietic and lymphatic tumors in female rats (IARC 1981, 1987). Chlorambucil acted as an initiator when used with croton oil as the promoter in a two-stage skin carcinogenesis study in mice. IARC (1987) concluded that there is sufficient evidence of carcinogenicity of chlorambucil in experimental animals (IARC 1987).

Properties

Chlorambucil is an alkylating agent and is a derivative of nitrogen mustard. It has a molecular weight of 304.2 and is a white crystalline powder with a slight odor and low vapor pressure (5.7×10^{-8} mm Hg at 25°C). The melting point is 64°C to 66°C and the log octanol-water partition coefficient is 1.47. It is insoluble in water but is soluble in ethanol, chloroform, acetone, benzene, ether, acid, and alkali. The sodium salt is soluble in water. It undergoes hydrolysis in aqueous and alkaline solutions to produce the hydroxyl form. Chlorambucil is sensitive to oxidation and moisture (IARC 1981, HSDB 2003).

Use

Chlorambucil is used primarily as an antineoplastic agent to treat chronic lymphocytic leukemia, and primary (Waldenström's) macroglobulinemia. It also is an immunosuppressive agent that has been used to treat systemic lupus erythematosus, acute and chronic glomerular nephritis, nephrotic syndrome, psoriasis, Wegener's granulomatosis, chronic active hepatitis, and cold agglutinic disease (IARC 1981, Chabner *et al.* 2001).

Production

All of the chlorambucil used in the United States is imported from the United Kingdom (HSDB 2003). However, the drug has been formulated in the United States since 1957, and three current U.S. suppliers were identified (ChemSources 2003). One U.S. pharmaceutical company with drug products approved by the U.S. Food and Drug Administration (FDA) containing chlorambucil as the active ingredient was identified (FDA 2003). U.S. imports in the early 1970s were approximately 32 to 34 kg (71 to 75 lb) per year and increased slightly to 48 kg (106 lb) in 1978 (IARC 1981, HSDB 2003). Estimates of U.S. sales in the mid 1970s were less than 20 kg (44 lb) per year (IARC 1975).

Exposure

The primary routes of potential human exposure to chlorambucil are ingestion, inhalation, and dermal contact. Continuous and intermittent oral treatment schedules are employed for patients treated with chlorambucil. The initial daily dose is 0.1 to 0.2 mg/kg body weight (total daily dose of 4 to 10 mg) for 3 to 6 weeks. If clinical improvement or bone marrow toxicity occurs, the dosage is reduced. A maintenance dose of 2 mg/day may be required. Chlorambucil is available in 2 mg tablets (FDA 2003).

Potential occupational exposure may occur from skin contact or inhalation of dust during the formulation, packaging, and administration of the pharmaceutical. The National Occupational Exposure Survey, conducted by NIOSH from 1981 to 1983 reported that 3,719 workers, including 2,018 women, were potentially exposed to chlorambucil (NIOSH 1984). More recent estimates of worker or patient exposure were not available.

Regulations

CPSC

Any orally-administered, prescription drug for human use requires child-resistant packaging

EPA

Comprehensive Environmental Response, Compensation, and Liability Act
- Reportable Quantity (RQ) = 10 lb

Resource Conservation and Recovery Act
- Listed as a Hazardous Constituent of Waste
- Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - U035

FDA

Chlorambucil is a prescription drug subject to labeling and other requirements

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