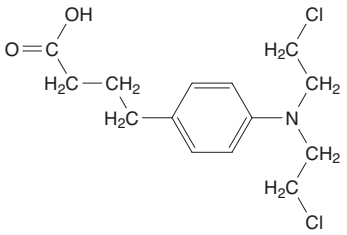
Chlorambucil

CAS No. 305-03-3

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 4-[*p*-[bis(2-chloroethyl)amino]phenyl]butyric acid



Carcinogenicity

Chlorambucil is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports have linked treatment with chlorambucil, either alone or in combination with other therapies, with development of cancer, primarily acute nonlymphocytic leukemia, in patients who were treated for other types of cancer or other (nonmalignant) diseases. In addition, a few small epidemiological studies found excesses of cancer in patients treated with chlorambucil. In a randomized clinical trial with 431 polycythemia vera patients, the incidence of acute nonlymphocytic leukemia was 13-fold higher in patients treated with chlorambucil plus phlebotomy than in patients treated with phlebotomy alone, and the risk of leukemia increased with increasing dose and duration of treatment (IARC 1981, 1987).

Cancer Studies in Experimental Animals

Chlorambucil administered by intraperitoneal injection caused tumors of the hematopoietic system in mice of both sexes (lymphosarcoma) and in male rats (lymphosarcoma, myelogenous leukemia, and reticulum-cell sarcoma). In mice, it also caused lung tumors in both sexes and ovarian tumors in females. In an initiation-promotion study, chlorambucil acted as a skin-tumor initiator when croton oil was used as the promoter (IARC 1981, 1987). The Internatioal Agency for Research on Cancer (IARC 1987) concluded that there was sufficient evidence for the carcinogenicity of chlorambucil in experimental animals.

Properties

Chlorambucil is a nitrogen mustard that acts as a bifunctional alkylating agent and is used as a pharmaceutical agent (IARC 1987). It exists at room temperature as an off-white granular powder with a slight odor. It is soluble in ethanol, chloroform, ethyl acetate, benzene, and ether, and readily soluble in acid or alkaline solutions. In water, the free acid is insoluble, but the sodium salt is soluble. Chlorambucil is sensitive to oxidation and moisture (IARC 1981). Physical and chemical properties of chlorambucil are listed in the following table.

Property	Information
Molecular weight	304.2[a]
Melting point	64°C to 66°C[a]
Log K_{ow}	1.47 at pH 7.4[a]
Water solubility	12.4 g/L at 25°C[b]
Vapor pressure	5.7×10^{-8} mm Hg at 25°C[a]
Dissociation constant (pK_a)	5.75[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Chlorambucil is used primarily as an antineoplastic agent to treat cancer of the blood and lymphatic system, such as Hodgkin and non-Hodgkin lymphoma, chronic lymphocytic leukemia, and primary (Waldenström) macroglobulinemia. It is also used as a chemotherapeutic agent for Kaposi sarcoma and cancer of the breast, lung, cervix, ovary, and testis. Chlorambucil is an immunosuppressive agent that has been used to treat rheumatoid arthritis, systemic lupus erythematosus, acute and chronic glomerulonephritis, nephrotic syndrome, psoriasis, Wegener granulomatosis, chronic active hepatitis, and cold agglutinin disease (IARC 1981). It is also used in veterinary medicine to treat cancer and immune-mediated diseases, including lymphocytic leukemia, multiple myeloma, ovarian cancer, lymphoma, polycythemia rubra vera, pemphigus diseases, eosinophilic granuloma complex, inflammatory bowel disease, feline infectious peritonitis, immune-mediated hemolytic anemia, and immune-mediated platelet destruction (Brooks 2009).

Production

All of the chlorambucil used in the United States is imported from the United Kingdom (HSDB 2009). However, the drug has been formulated in the United States since 1957. Annual U.S. sales of chlorambucil in the mid 1970s were estimated at less than 20 kg (44 lb) (IARC 1975). In 2009, chlorambucil was available from six U.S. suppliers (ChemSources 2009), and one product approved by the U.S. Food and Drug Administration contained chlorambucil as the active ingredient (FDA 2009). Annual U.S. imports of chlorambucil were 32 to 34 kg (71 to 75 lb) in the early 1970s, increasing slightly to 48 kg (106 lb) in 1978 (IARC 1981, HSDB 2009).

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. Chlorambucil is available in 2-mg tablets. The initial daily dose is 0.1 to 0.2 mg/kg of body weight (for a total daily dose of 4 to 10 mg) for 3 to 6 weeks. If clinical improvement or bone-marrow toxicity occurs, the dose is reduced. A daily maintenance dose of 2 mg may be required (IARC 1981, FDA 2009). Occupational exposure to chlorambucil may occur through dermal contact or inhalation of dust during formulation, packaging, and administration of the drug product. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 3,719 workers, including 2,018 women, potentially were exposed to chlorambucil (NIOSH 1990). No more recent estimates of exposure were found.

Regulations

Consumer Product Safety Commission (CPSC)

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

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of chlorambucil = U035.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Chlorambucil is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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