PDR®

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PHYSICIANS' DESK REFERENCE®

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$\times 10^{-7}$ M, the doses of leucovorin should be increased to 100 mg/m^2 q 3 hours IV until the MTX level is $< 10^{-8}$ M When such doses are administered, a non-preserved diluent should be used (see WARNINGS). The rate of injection of leucovorin calcium should not exceed 17 5 mL (175 mg leucovorin) per minute.

Megaloblastic Anemia: No more than or up to 1 mg daily. There is no evidence that doses > 1 mg daily have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg

Instructions for Reconstitution: Read WARNINGS for considerations in choice of diluent. The contents of each vial should be reconstituted with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) or with Sterile Water for Injection, USP as follows

Contents of Vial	Amount of Diluent
25 mg	2.5 mL
50 mg	5 mL
100 mg	10 mL

The resulting solution in each case contains 10 mg leucovorin per mL

When reconstituted with Bacteriostatic Water for Injection, the resulting solution must be used within 7 days. If reconstituted with Sterile Water for Injection, use immediately and discard any unused portion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

HOW SUPPLIED

25 mg/vial, Box of 1 (NDC 0081-0636-93); 50 mg/vial, Box of 1 (NDC 0081-0637-93), 100 mg/vial, Box of 1 (NDC 0081-0638-93).

Store dry powder and reconstituted solution at controlled room temperature 15° to 30°C (59° to 86°F) Protect from light

LEUKERAN® ℞
[lū 'kŭh-răn]
(Chlorambucil)
2 mg Sugar-coated Tablets

WARNING: Leukeran (chlorambucil) can severely suppress bone marrow function. Chlorambucil is a carcinogen in humans Chlorambucil is probably mutagenic and teratogenic in humans. Chlorambucil produces human infertility. See "WARNINGS" and "PRECAUTIONS" sections.

DESCRIPTION

Leukeran (chlorambucil) was first synthesized by Everett *et al.*[1] It is a bifunctional alkylating agent of the nitrogen mustard type that has been found active against selected human neoplastic diseases Chlorambucil is known chemically as 4-[bis(2-chlorethyl)amino]benzenebutanoic acid.

Chlorambucil hydrolyzes in water and has a pKa of 5.8.

Leukeran (chlorambucil) is available in tablet form for oral administration. Each sugar-coated tablet contains 2 mg chlorambucil and the inactive ingredients corn and wheat starch, gum acacia, lactose, magnesium stearate, polysorbate 60, sucrose, and talc

CLINICAL PHARMACOLOGY

Chlorambucil is rapidly and completely absorbed from the gastrointestinal tract. After single oral doses of 0.6–1.2 mg/kg, peak plasma chlorambucil levels are reached within one hour and the terminal half-life of the parent drug is estimated at 1.5 hours. Chlorambucil undergoes rapid metabolism to phenylacetic acid mustard, the major metabolite, and the combined chlorambucil and phenylacetic acid mustard urinary excretion is extremely low—less than 1% in 24 hours The peak plasma levels of chlorambucil and phenylacetic acid mustard are similar, approximating 1 μg/ml; however, the metabolite's half-life is 1.6 times greater than the parent drug.[2,3]

Chlorambucil and its metabolites are extensively bound to plasma and tissue proteins *In vitro*, chlorambucil is 99% bound to plasma proteins, specifically albumin.[4] Cerebrospinal fluid levels of chlorambucil have not been determined. Evidence of human teratogenicity suggests that the drug crosses the placenta.[5,6]

Chlorambucil is extensively metabolized in the liver primarily to phenylacetic acid mustard which has antineoplastic activity.[2,3] Chlorambucil and its major metabolite spontaneously degrade *in vivo* forming monohydroxy and dihydroxy derivatives [2] After a single dose of radiolabeled chlorambucil (^{14}C) approximately 15% to 60% of the radioactivity appears in the urine after 24 hours. Again, less than 1% of the urinary radioactivity is in the form of chlorambucil or phenylacetic acid mustard.[2] In summary, the pharmacokinetic data suggest that oral chlorambucil undergoes rapid gastrointestinal absorption and plasma clearance and that it is almost completely metabolized, having extremely low urinary excretion.

INDICATIONS AND USAGE

Leukeran (chlorambucil) is indicated in the treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma and Hodgkin's disease. It is not curative in any of these disorders but may produce clinically useful palliation.

CONTRAINDICATIONS

Chlorambucil should not be used in patients whose disease has demonstrated a prior resistance to the agent. Patients who have demonstrated hypersensitivity to chlorambucil should not be given the drug.[7] There may be cross-hypersensitivity (skin rash) between chlorambucil and other alkylating agents [8]

WARNINGS

Because of its carcinogenic properties, chlorambucil should not be given to patients with conditions other than chronic lymphatic leukemia or malignant lymphomas. Convulsions,[9] infertility,[10] leukemia[11,12] and secondary malignancies[13] have been observed when chlorambucil was employed in the therapy of malignant and non-malignant diseases.

There are many reports of acute leukemia arising in patients with both malignant[15] and non-malignant[16] diseases following chlorambucil treatment In many instances, these patients also received other chemotherapeutic agents or some form of radiation therapy. The quantitation of the risk of chlorambucil-induction of leukemia or carcinoma in humans is not possible. Evaluation of published reports of leukemia developing in patients who have received chlorambucil (and other alkylating agents) suggests that the risk of leukemogenesis increases with both chronicity of treatment and large cumulative doses However, it has proved impossible to define a cumulative dose below which there is no risk of the induction of secondary malignancy. The potential benefits from chlorambucil therapy must be weighed on an individual basis against the possible risk of the induction of a secondary malignancy

Chlorambucil has been shown to cause chromatid or chromosome damage in man [17,18] Both reversible and permanent sterility have been observed in both sexes receiving chlorambucil

A high incidence of sterility has been documented when chlorambucil is administered to prepubertal and pubertal males.[19] Prolonged or permanent azoospermia has also been observed in adult males [20] While most reports of gonadal dysfunction secondary to chlorambucil have related to males, the induction of amenorrhea in females with alkylating agents is well documented and chlorambucil is capable of producing amenorrhea. Autopsy studies of the ovaries from women with malignant lymphoma treated with combination chemotherapy including chlorambucil have shown varying degrees of fibrosis, vasculitis, and depletion of primordial follicles.[21,22]

Pregnancy: "*Pregnancy Category D*": Chlorambucil can cause fetal harm when administered to a pregnant woman Unilateral renal agenesis has been observed in two offspring whose mothers received chlorambucil during the first trimester.[5,6] Urogenital malformations including absence of a kidney were found in fetuses of rats given chlorambucil [14] There are no adequate and well-controlled studies in pregnant women. 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. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General: Many patients develop a slowly progressive lymphopenia during treatment. The lymphocyte count usually rapidly returns to normal levels upon completion of drug therapy Most patients have some neutropenia after the third week of treatment and this may continue for up to ten days after the last dose. Subsequently, the neutrophil count usually rapidly returns to normal. Severe neutropenia appears to be related to dosage and usually occurs only in patients who have received a total dosage of 6.5 mg/kg or more in one course of therapy with continuous dosing. About one-quarter of all patients receiving the continuous-dose schedule, and one-third of those receiving this dosage in eight weeks or less may be expected to develop severe neutropenia.[23]

While it is not necessary to discontinue chlorambucil at the first evidence of a fall in neutrophil count, it must be remembered that the fall may continue for ten days after the last dose and that as the total dose approaches 6 5 mg/kg there is a risk of causing irreversible bone marrow damage The dose of chlorambucil should be decreased if leukocyte or platelet counts fall below normal values and should be discontinued

Chlorambucil should **not** be given at full dosages before four weeks after a full course of radiation therapy or chemotherapy because of the vulnerability of the bone marrow to damage under these conditions. If the pretherapy leukocyte or platelet counts are depressed from bone marrow disease process prior to institution of therapy, the treatment should be instituted at a reduced dosage.

Persistently low neutrophil and platelet counts or peripheral lymphocytosis suggest bone marrow infiltration If confirmed by bone marrow examination, the daily dosage of chlorambucil should not exceed 0.1 mg/kg. Chlorambucil appears to be relatively free from gastrointestinal side effects or other evidence of toxicity apart from the bone marrow depressant action. In humans, single oral doses of 20 mg or more may produce nausea and vomiting.

Children with nephrotic syndrome[9] and patients receiving high pulse doses of chlorambucil[24] may have an increased risk of seizures. As with any potentially epileptogenic drug, caution should be exercised when administering chlorambucil to patients with a history of seizure disorder, head trauma or receiving other potentially epileptogenic drugs.

Information for Patients: Patients should be informed that the major toxicities of chlorambucil are related to hypersensitivity, drug fever, myelosuppression, hepatotoxicity, infertility, seizures, gastrointestinal toxicity, and secondary malignancies Patients should never be allowed to take the drug without medical supervision and should consult their physician if they experience skin rash, bleeding, fever, jaundice, persistent cough, seizures, nausea, vomiting, amenorrhea, or unusual lumps/masses. Women of childbearing potential should be advised to avoid becoming pregnant.

Laboratory Tests: Patients must be followed carefully to avoid life-endangering damage to the bone marrow during treatment. Weekly examination of the blood should be made to determine hemoglobin levels, total and differential leukocyte counts, and quantitative platelet counts. Also, during the first 3 to 6 weeks of therapy, it is recommended that white blood cell counts be made 3 or 4 days after each of the weekly complete blood counts. Galton *et al* [23] have suggested that in following patients it is helpful to plot the blood counts on a chart at the same time that body weight, temperature, spleen size, etc., are recorded It is considered dangerous to allow a patient to go more than two weeks without hematological and clinical examination during treatment.

Drug Interactions: There are no known drug/drug interactions with chlorambucil.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS section for information on carcinogenesis, mutagenesis and impairment of fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category D: See WARNINGS section.

Nursing Mothers: 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Pediatric Use: The safety and effectiveness in children have not been established

ADVERSE REACTIONS

Hematologic: The most common side effect is bone marrow suppression.[25] Although bone marrow suppression frequently occurs, it is usually reversible if the chlorambucil is withdrawn early enough. However, irreversible bone marrow failure has been reported [26,27]

Gastrointestinal: Gastrointestinal disturbances such as nausea and vomiting, diarrhea and oral ulceration occur infrequently.

CNS: Tremors, muscular twitching, confusion, agitation, ataxia, flaccid paresis and hallucinations have been reported as rare adverse experiences to chlorambucil which resolve upon discontinuation of drug. Rare, focal and/or generalized seizures have been reported to occur in both children[9,28,29] and adults[24,30–33] at both therapeutic daily doses, pulse dosing regimens and in acute overdose (see PRECAUTIONS-General).

Miscellaneous: Other reported adverse reactions include: pulmonary fibrosis, hepatotoxicity and jaundice, drug fever, skin hypersensitivity, peripheral neuropathy, interstitial pneumonia, sterile cystitis, infertility, leukemia and secondary malignancies (see WARNINGS).

OVERDOSAGE

Reversible pancytopenia was the main finding of inadvertent overdoses of chlorambucil.[34,35] Neurological toxicity ranging from agitated behavior and ataxia to multiple grand mal seizures has also occurred.[28,34] As there is no known antidote, the blood picture should be closely monitored and general supportive measures should be instituted, together with appropriate blood transfusions if necessary. Chlorambucil is not dialyzable.

Continued on next page

Burroughs Wellcome—Cont.

Oral LD_{50} single doses in mice are 123 mg/kg In rats, a single intraperitoneal dose of 12.5 mg/kg of chlorambucil produces typical nitrogen-mustard effects; these include atrophy of the intestinal mucous membrane and lymphoid tissues, severe lymphopenia becoming maximal in four days, anemia and thrombocytopenia. After this dose, the animals begin to recover within three days and appear normal in about a week although the bone marrow may not become completely normal for about three weeks. An intraperitoneal dose of 18 5 mg/kg kills about 50% of the rats with development of convulsions. As much as 50 mg/kg has been given orally to rats as a single dose, with recovery. Such a dose causes bradycardia, excessive salivation, hematuria, convulsions, and respiratory dysfunction.

DOSAGE AND ADMINISTRATION

The usual oral dosage is 0.1 to 0.2 mg/kg body weight daily for three to six weeks as required This usually amounts to 4 to 10 mg a day for the average patient. The entire daily dose may be given at one time These dosages are for initiation of therapy or for short courses of treatment. The dosage must be carefully adjusted according to the response of the patient and must be reduced as soon as there is an abrupt fall in the white blood cell count Patients with Hodgkin's disease usually require 0.2 mg/kg daily whereas patients with other lymphomas or chronic lymphocytic leukemia usually require only 0.1 mg/kg daily. When lymphocytic infiltration of the bone marrow is present, or when the bone marrow is hypoplastic, the daily dose should not exceed 0.1 mg/kg (about 6 mg for the average patient).

Alternate schedules for the treatment of chronic lymphocytic leukemia employing intermittent, bi-weekly or once monthly pulse doses of chlorambucil have been reported.[36,37]

Intermittent schedules of chlorambucil begin with an initial single dose of 0 4 mg/kg. Doses are generally increased by 0.1 mg/kg until control of lymphocytosis or toxicity is observed. Subsequent doses are modified to produce mild hematologic toxicity. It is felt that the response rate of chronic lymphocytic leukemia to the bi-weekly or once monthly schedule of chlorambucil administration is similar or better to that previously reported with daily administration and that hematologic toxicity was less than or equal to that encountered in studies using daily chlorambucil.

Radiation and cytotoxic drugs render the bone marrow more vulnerable to damage and chlorambucil should be used with particular caution within four weeks of a full course of radiation therapy or chemotherapy However, small doses of palliative radiation over isolated foci remote from the bone marrow will not usually depress the neutrophil and platelet count. In these cases chlorambucil may be given in the customary dosage.

It is presently felt that short courses of treatment are safer than continuous maintenance therapy although both methods have been effective It must be recognized that continuous therapy may give the appearance of "maintenance" in patients who are actually in remission and have no immediate need for further drug. If maintenance dosage is used, it should not exceed 0.1 mg/kg daily and may well be as low as 0 03 mg/kg daily. A typical maintenance dose is 2 mg to 4 mg daily, or less, depending on the status of the blood counts. It may, therefore, be desirable to withdraw the drug after maximal control has been achieved since intermittent therapy reinstituted at time of relapse may be as effective as continuous treatment.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[38–44]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate

HOW SUPPLIED

White sugar-coated tablet containing 2 mg chlorambucil; bottle of 50 (NDC-0081-0635-35).

Store at 15°–25°C (59°–77°F) in a dry place

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Shown in Product Identification Section, page 407

MANTADIL® CRIM ℞

[*măn'tah-dĭl"*]

DESCRIPTION

Mantadil® Cream contains the antihistamine chlorcyclizine hydrochloride 2% and the corticosteroid hydrocortisone acetate 0.5%, with methylparaben 0.25% (added as a preservative) in a vanishing cream base The inactive ingredients are liquid and white petrolatum, emulsifying wax and purified water

Mantadil Cream is an ANTIPRURITIC-ANTI-INFLAMMATORY-ANESTHETIC for topical administration.

Chlorcyclizine hydrochloride is known chemically as 1-[(4-chlorophenyl)phenylmethyl]-4-methylpiperazine monohydrochloride.

Hydrocortisone acetate is the acetate ester of cortisol, known chemically as 21-(acetyloxy)-11β,17-dihydroxypregn-4-ene-3,20-dione.

The pH of this product is approximately 4.5.

CLINICAL PHARMACOLOGY

Chlorcyclizine hydrochloride is an H_1 histamine-receptor antagonist that will occupy receptor sites in effector cells to the exclusion of histamine. It blocks most of the effects of histamine mediated by H_1 receptors, including contraction of smooth muscle and increased capillary permeability. Absorption of chlorcyclizine hydrochloride into the skin is rapid following topical application, whereas systemic absorption from the skin is minimal Chlorcyclizine hydrochloride prevents local edema and provides local anesthetic and antipruritic action in the skin.

Hydrocortisone acetate administered topically suppresses most inflammatory and allergic responses in the skin. Following topical application, it is absorbed rapidly into the skin, where it reduces local heat, redness, swelling, and tenderness. A small part of the dose applied to broken skin is absorbed systemically and metabolized by the liver

INDICATIONS AND USAGE

Mantadil Cream is indicated for the treatment of pruritic skin eruptions and other dermatoses including: eczema (allergic, nuchal and nummular); dermatitis (atopic, lichenoid and seborrheic); contact dermatitis including poison ivy, poison oak and poison sumac; localized neurodermatitis; insect bites; sunburn, intertrigo; and anogenital pruritus.

CONTRAINDICATIONS

This preparation is contraindicated in patients who are hypersensitive to any of its components; in tuberculosis of the skin, vaccinia, varicella, and herpes simplex. As with other topical products containing hydrocortisone, the cream should not be used in bacterial infections of the skin unless antibacterial therapy is concomitant.

Not for ophthalmic use.

WARNINGS

Oral chlorcyclizine is teratogenic in animals. Long-term reproduction studies of topical chlorcyclizine have not been conducted in humans.

PRECAUTIONS

General: If signs of irritation develop with use of this cream, treatment should be discontinued and appropriate therapy instituted.

Any of the side effects reported following systemic use of corticosteroids, including adrenal suppression, may also