Chlorambucil

- (klor-am-byoo-sil)
- Leukeran®
- Immunosuppressant/Antineoplastic

**Prescriber Highlights**

- Nitrogen mustard derivative immunosuppressant & antineoplastic in dogs, cats, and horses.
- Caution: Preexisting bone marrow depression, infection.
- Potential teratogen.
- Adverse Effects primarily myelosuppression & GI toxicity.

**Uses/Indications**

Chlorambucil may be useful as part of multi-drug protocols or as a solo metronomic agent (Leach et al. 2012; Schrempp et al. 2013) in a variety of neoplastic diseases, including lymphocytic leukemia, multiple myeloma, polycythemia vera, macroglobulinemia, and ovarian adenocarcinoma. It may also be useful as adjunctive therapy for some immune-mediated conditions (e.g., inflammatory bowel disease, non-erosive arthritis, or immune-mediated skin disease).

**Pharmacology/Actions**

Chlorambucil is a cell-cycle nonspecific alkylating antineoplastic/immunosuppressive agent. Its cytotoxic activity stems from cross-linking with cellular DNA. Immunosuppressive effects may not be noted until 2-4 weeks after starting the drug.

**Pharmacokinetics**

Chlorambucil is rapidly and nearly completely absorbed after oral administration; peak levels occur in about one hour. It is highly bound to plasma proteins. While it is not known whether it crosses the blood-brain barrier, neurological side effects have been reported. Chlorambucil crosses the placenta, but it is not known whether it enters maternal milk. Chlorambucil is extensively metabolized in the liver, primarily to phenylacetic acid mustard, which is active. Phenylacetic acid mustard is further metabolized to other metabolites that are excreted in the urine.

**Contraindications/Precautions/Warnings**
Chlorambucil is contraindicated in patients that are hypersensitive to it or have demonstrated resistance to its effects. It should be used with caution in patients with preexisting bone marrow depression or infection, or susceptible to bone marrow depression or infection.

**Adverse Effects**

The most commonly associated major adverse effects seen with chlorambucil therapy is myelosuppression manifested by anemia, leukopenia, and thrombocytopenia and gastrointestinal toxicity (e.g., vomiting, diarrhea, etc.). A greater likelihood of toxicity occurs with higher dosages. This may occur gradually with nadirs occurring usually within 7-14 days of the start of therapy. Recovery generally takes from 7-14 days. Severe bone marrow depression can result in pancytopenia that may take months to years for recovery. Alopecia and delayed regrowth of shaven fur have been reported in dogs; Poodles or Kerry blues are reportedly more likely to be affected than other breeds. Lower dose metronomic therapy (4 mg/m² once daily) in dogs, is associated with a lower incidence of adverse effects.

One case report in cat of neurotoxicity (e.g., facial twitching, myoclonus, agitation, seizures) after chlorambucil therapy has been reported (Benitah et al. 2003). In another report in a dog, chlorambucil was suspected of causing seizures (Giuliano 2013).

In humans, bronchopulmonary dysplasia with pulmonary fibrosis, neurotoxicity, and uric acid nephropathy have been reported. These effects are uncommon and generally associated with chronic, higher dose therapy. Hepatotoxicity has been reported rarely in humans.

**Reproductive/Nursing Safety**

Chlorambucil’s teratogenic potential remains poorly documented, but it may potentially cause a variety of fetal abnormalities. It is generally recommended to avoid the drug during pregnancy, but because of the seriousness of the diseases treated with chlorambucil, the potential benefits to the mother must be considered. Chlorambucil has been documented to cause irreversible infertility in male humans, particularly when given during pre-puberty and puberty. In humans, the FDA categorizes this drug as category D for use during pregnancy *(There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as class: C *(These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks.)*

**Overdosage/Acute Toxicity**
The oral LD$_{50}$ in mice is 123 mg/kg. There have been limited experiences with acute overdoses in humans. Doses of up to 5 mg/kg resulted in neurologic (seizures) toxicity and pancytopenia (nadirs at 1-6 weeks post ingestion). All patients recovered without long-term sequelae. Treatment should consist of gut emptying when appropriate (beware of rapidly changing neurologic status if inducing vomiting). Monitoring of CBC’s several times a week for several weeks should be performed after overdoses and blood component therapy may be necessary.

**DRUG INTERACTIONS**

The following drug interactions have either been reported or are theoretical in humans or animals receiving chlorambucil and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **Myelosuppressive Drugs** *(e.g., other antineoplastics, chloramphenicol, flucytosine, amphotericin B, or colchicine)*: Bone marrow depression may be additive.
- **Immunosuppressive Drugs** *(e.g., azathioprine, cyclophosphamide, cyclosporine, corticosteroids)*: Use with other immunosuppressant drugs may increase the risk of infection.

**LABORATORY CONSIDERATIONS**

- Chlorambucil may raise serum uric acid levels. Drugs such as allopurinol may be required to control hyperuricemia in some patients.

**DOSES**

**NOTE**: Because of the potential toxicity of this drug to patients, veterinary personnel and clients, and since chemotherapy indications, treatment protocols, monitoring and safety guidelines often change, the following dosages should be used only as a general guide. Consultation with a veterinary oncologist and referral to current veterinary oncology references *[e.g., (Withrow et al. 2012); (Dobson et al. 2011); (Henry et al. 2009); (North et al. 2009); (Argyle et al. 2008)]* are strongly recommended.

Dosages are commonly listed as mg/m$^2$. Do not confuse with mg/kg dosages.

**Dogs:**

- **As an immunosuppressant** *(extra-label)*: Dosage recommendations vary. Commonly dosed at 0.1 – 0.2 mg/kg (corresponds approximately to 2 – 6 mg/m$^2$) once daily initially. Dosages are generally rounded to the nearest 2 mg. When remission occurs, attempt to
dose every other day; use lowest dosage that will control condition. Often used in conjunction with prednisolone.

- **For adjunctive therapy of lymphoreticular neoplasms, macroglobulinemia, and polycythemia vera** (extra-label): For first level treatment of dogs of canine lymphoma where clients cannot afford, or will not accept combination chemotherapy due to risks of toxicity: Prednisone alone 40 mg/m² (NOT mg/kg) PO daily for 7 days then every other day or in combination with chlorambucil at 6 – 8 mg/m² (NOT mg/kg) PO every other day. Perform a CBC every 2-3 weeks. (Ogilvie 2006)

- **For metronomic treatment of cancer** (extra-label): 4 mg/m² (NOT mg/kg) PO once daily. For dogs weighing >8 kg, the dose is rounded to the nearest 2 mg; dogs weighing ≤8 kg, dose is compounded to 4 mg/m² (Leach et al. 2012; Schrempp et al. 2013). **Note:** In the second reference (Schrempp et al. 2013), dogs enrolled in the study had bladder transitional cell carcinoma. 70% of dogs either had a partial remission (1/30) or stable disease (20/30).

**Cats:**

- **For low-grade gastrointestinal lymphosarcoma** (extra-label): Several protocols using chlorambucil with prednisolone have had a relatively high degree of efficacy, including:
  - **As an immunosuppressant** (extra-label): Chlorambucil is generally considered a second-line immunosuppressant (after glucocorticoids) in cats and often used in conjunction with prednisolone. Anecdotal chlorambucil dosing recommendations vary and the commercial tablet size (2 mg) may make precise dosing difficult without compounding. For immune-mediated conditions it is commonly dosed initially at 0.1 – 0.2 mg/kg (approximately 1.5 – 4 mg/m²; ¼ of a 2 mg tablet for larger cats or a compounded dosage form) PO once daily. If using the whole 2 mg tablets, it is dosed in a practical manner every 48 hours for cats weighing more than 4 kg, and every 72 hours for cats weighing less than 4 kg. Once remission occurs the dosage is reduced or the dosage interval (often every 3-4 days) is extended to where the condition is still controlled.
    a. Chlorambucil 15 mg/m² PO once daily for 4 days; repeated every 3 weeks and prednisolone initially at 3 mg/kg PO once daily. (Lingard et al. 2009)
    b. Chlorambucil 20 mg/m² (rounded to nearest 2 mg) PO once every 2 weeks and prednisolone 2 mg/kg PO once daily. (Stein et al. 2010)
    c. Chlorambucil 2 mg per cat PO every 2-3 days (q48-72h) and prednisolone 5 – 10 mg per cat PO q12-24h. (Kiselow et al. 2008)

**Horses:**
For adjunctive therapy in treating lymphoma using the LAP protocol (extra-label):
Cytarabine 200 – 300 mg/m\(^2\) (NOT mg/kg) SC or IM once every 1-2 weeks; Chlorambucil 20 mg/m\(^2\) (NOT mg/kg) PO every 2 weeks (alternating with cytarabine) and Prednisone 1.1 – 2.2 mg/kg PO every other day. If this protocol is not effective (no response seen in 2-4 weeks) add vincristine at 0.5 mg/m\(^2\) (NOT mg/kg) IV once a week. Side effects are rare. (Couto 1994)

**MONITORING**

- Efficacy.
- CBC, Platelets once weekly (or once stable, every other week) during therapy; once stable, dogs may require only monthly monitoring. If neutrophils are <3,000/microL hold drug until recovered and reduce dose by 25% or increase dosing interval. Other references recommend CBCs at 0, 1, 2, 4, 8, & 12 weeks and then every 3-6 months (Mueller 2000) or in cats, CBCs at 2 to 3 weeks after starting therapy and every 3-6 months thereafter (Ashley 2009).
- Uric acid, liver enzymes; if warranted.

**CLIENT INFORMATION**

- Give this drug with food.
- Chlorambucil is a chemotherapy (cancer) drug. The drug and its byproducts can be hazardous to other animals and people that come in contact with it. On the day your animal gets the drug and then for a few days afterward, all bodily waste (urine, feces, litter), blood, or vomit should only be handled while wearing disposable gloves. Seal the waste in a plastic bag and then place both the bag and gloves in with the regular trash.
- Chlorambucil can be very toxic to the gastrointestinal tract and cause vomiting and gastrointestinal upset.
- Contact your veterinarian immediately if you notice abnormal bleeding, bruising, depression, infection, shortness of breath, bloody diarrhea, etc.

**CHEMISTRY/SYNONYMS**

A nitrogen mustard derivative antineoplastic agent, chlorambucil occurs as an off-white, slightly granular powder. It is very slightly soluble in water.

Chlorambucil may also be known as: CB-1348, NSC-3088, WR-139013, chlorambucilum, chloraminophene, chlorbutinum, Chloraminophene®, Leukeran®, or Linfolysin®.

**STORAGE/Stability**
Chlorambucil tablets should be stored in light-resistant, well-closed containers under refrigeration (2-8°C; 36-46°F). Tablets can be stored at a maximum of 30°C (86°F) up to one week. An expiration date of one year after manufacture is assigned to the commercially available tablets.

**Compatibility/Compounding Considerations**

**Compounded preparation stability:** Chlorambucil oral suspension compounded from commercially available tablets has been published (Dressman et al. 1983). Triturating six (6) chlorambucil 2 mg tablets with 2 mL Cologel® and qs ad to 6 mL with simple syrup yields a 2 mg/mL oral suspension that retains 90% potency for 7 days at 5°C. Suspensions of chlorambucil stored at room temperature rapidly decompose with losses >15% in one day. Chlorambucil is rapidly hydrolyzed independently of pH, but minimal hydrolysis occurs at pH 2. Refrigeration also slows hydrolysis.

**Dosage Forms/Regulatory Status**

**Veterinary-Labeled Products:** None.

**Human-Labeled Products:**

Chlorambucil Oral Tablets (film-coated): 2 mg; *Leukeran®*; (Rx)

**Revisions/References**

*Monograph revised/updated October 2013.*


