

Product Monograph

PrLEUKERAN[®]

Chlorambucil Tablets USP
2 mg

Antineoplastic Agent

Triton Pharma Inc.
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Date of Preparation:
November 29, 2010

Submission Control No: 143125

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Chlorambucil Tablets USP
2 mg

Antineoplastic Agent

CAUTION - LEUKERAN[®] (CHLORAMBUCIL) IS A POTENT DRUG PRODUCT AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS. BLOOD COUNTS SHOULD BE TAKEN ONCE OR TWICE WEEKLY. DISCONTINUE OR REDUCE THE DOSAGE UPON EVIDENCE OF ABNORMAL DEPRESSION OF THE BONE MARROW. (SEE CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS).

Clinical Pharmacology

LEUKERAN[®] (chlorambucil) is an aromatic nitrogen mustard derivative which acts as a bifunctional alkylating agent. Alkylation takes place through the formation of a highly reactive ethylenimonium radical. A probable mode of action involves cross-linkage of the ethylenimonium derivative between two strands of helical DNA and subsequent interference with replication.

After oral administration of carbon-14 labelled chlorambucil, maximum plasma radioactivity occurs between 40 and 70 minutes later. Studies have shown that chlorambucil disappears from the plasma with a mean terminal phase half-life of 1.5 hours and that its urinary excretion is low. A high level of urinary radioactivity after oral or intravenous administration of carbon-14 labelled chlorambucil indicates that the drug is well absorbed after oral dosage.

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

Chlorambucil is extensively metabolized in the liver primarily to phenylacetic acid mustard which has antineoplastic activity. Chlorambucil and its major metabolite spontaneously degrade *in vivo* forming monohydroxy and dihydroxy derivatives. After a single dose of radiolabelled chlorambucil (carbon-14), approximately 15% to 60% of the radioactivity appears in the urine after 24 hours. Less than 1% of the urinary radioactivity is in the form of chlorambucil or phenylacetic acid mustard. 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 Clinical Use

LEUKERAN[®] (chlorambucil) is indicated as monotherapy in the treatment of chronic lymphocytic leukemia. It is also indicated as monotherapy or in combination with other agents in non-Hodgkin's lymphomas including follicular lymphoma, indolent lymphoma, MALT-lymphoma, mantle-cell lymphoma; Waldenstrom's macroglobulinemia and Hodgkin's disease. It is not curative but produces remissions.

Contraindications

LEUKERAN[®] (chlorambucil) should not be administered to patients who are resistant to the drug or who have developed hypersensitivity to it. There may be cross-hypersensitivity (skin rash) between chlorambucil and other alkylating agents.

Chlorambucil should not be used within four weeks of a full course of radiation or chemotherapy.

Warnings

LEUKERAN[®] (chlorambucil), a derivative of nitrogen mustard, is a potent drug. It is for use only under the direction of physicians experienced in the administration of cancer chemotherapeutic drugs.

Rare instances of skin rash progressing to erythema multiforme, toxic epidermal necrolysis, or Stevens-Johnson syndrome have been reported. Chlorambucil should be discontinued promptly in patients who develop skin reactions.

Use in Pregnancy

The use of chlorambucil should be avoided whenever possible during pregnancy. However, when cytotoxic drugs are used in pregnancy, the possible teratogenic effect on the fetus should be kept in mind. It is therefore advisable to delay treatment with these drugs as long as possible and certainly until after the first three months of pregnancy. In any individual case, the potential hazard to the fetus must be balanced against the expected benefit to the mother.

Use in Lactation

Mothers receiving LEUKERAN[®] should not breast feed.

Vaccination

Immunisation using a live organism vaccine has a potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Precautions

General

Since LEUKERAN[®] (chlorambucil) is capable of producing irreversible bone marrow depression, blood counts should be monitored once or twice weekly in patients under treatment.

At therapeutic dosage, LEUKERAN[®] depresses lymphocytes and has less effect on neutrophil and platelet counts and on hemoglobin levels. Discontinuation of LEUKERAN[®] is not necessary at the first sign of a fall in neutrophils but it must be remembered that the fall may continue for 10 days or more after the last dose.

When lymphocytic infiltration of the bone marrow is present, or the bone marrow is hypoplastic, the daily dose should not exceed 0.1 mg/kg body weight.

Patients with nephrotic syndrome, patients prescribed high pulse dose regimens and patients with a history of seizure disorder, should be closely monitored following administration of chlorambucil, as they 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.

Use in Children

The safety and effectiveness in children have not been established.

Patients with Impaired Renal Function

Patients with evidence of impaired renal function should be carefully monitored as they are prone to additional myelosuppression associated with azotemia.

Patients with Impaired Hepatic Function

Consideration should be given to dose reduction in patients with gross hepatic dysfunction.

Carcinogenicity

Acute secondary hematologic malignancies (especially leukemia and myelodysplastic syndrome) have been reported, particularly after long term treatment (see ADVERSE EVENTS).

A comparison of patients with ovarian cancer who received alkylating agents with those who did not, showed that the use of alkylating agents including chlorambucil, significantly increased the incidence of acute leukemia.

Acute myelogenous leukemia has been reported in a small proportion of patients receiving chlorambucil as long-term adjuvant therapy for breast cancer.

The leukemogenic risk must be balanced against the potential therapeutic benefit when considering the use of chlorambucil.

Impairment of Fertility, Teratogenic Effects, Mutagenesis

Chlorambucil may cause suppression of ovarian function. Amenorrhea has been reported following chlorambucil therapy.

Azoospermia has been observed as a result of therapy with chlorambucil although it is estimated that a total dose of at least 400 mg is necessary.

Varying degrees of recovery of spermatogenesis have been reported in patients with lymphoma following treatment with chlorambucil in total doses of 410 to 2600 mg.

As with other cytotoxic agents LEUKERAN[®] is potentially teratogenic.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving chlorambucil.

Chlorambucil has been shown to cause chromatid or chromosome damage in man.

Drug Interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see WARNINGS).

Animal studies indicate that patients who receive phenylbutazone may require a reduction of the standard chlorambucil doses because of the possibility of enhanced chlorambucil toxicity.

Adverse Reactions

Leucopenia, neutropenia, thrombocytopenia, pancytopenia, anemia or bone marrow suppression is very common. 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.

Acute secondary hematologic malignancies (especially leukemia and myelodysplastic syndrome) are common, particularly after long term treatment.

Gastrointestinal disturbances such as nausea and vomiting, diarrhea and oral ulceration occur infrequently. Other side effects may be encountered but usually only when the therapeutic dosage has been exceeded.

Severe interstitial pulmonary fibrosis has occasionally been reported in patients with chronic lymphocytic leukemia on long-term chlorambucil therapy. Pulmonary fibrosis may be reversible on withdrawal of chlorambucil.

Allergic reactions to LEUKERAN[®] (chlorambucil) such as urticaria and angioneurotic oedema have been rarely reported following initial or subsequent dosing. Skin hypersensitivity (including rare reports of skin rash progressing to erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome) has been reported (see WARNINGS).

Other reported adverse reactions include hepatotoxicity and jaundice, drug fever, peripheral neuropathy, interstitial pneumonia, sterile cystitis, infertility, leukemia, and secondary malignancies (see PRECAUTIONS).

Seizures have occurred in children with nephrotic syndrome treated with chlorambucil. Rare, focal and/or generalised seizures have been reported to occur in children and adults receiving therapeutic daily doses or high pulse dosing regimens of chlorambucil. Patients with a history of seizure disorder may be particularly susceptible (see PRECAUTIONS).

Movement disorders including tremor, twitching and myoclonia in the absence of convulsions have also been reported.

Symptoms and Treatment of Overdosage

Reversible pancytopenia was the main finding of inadvertent overdose of chlorambucil. Neurological toxicity ranging from agitated behaviour and ataxia to multiple grand mal seizures has also occurred. As there is no known antidote, the blood picture should be closely monitored and general supportive measures should be instituted together with appropriate blood transfusion if necessary. Chlorambucil is not dialyzable. The physician should consider contacting a poison centre for additional information on the treatment of any overdose.

Dosage and Administration

Chronic Lymphocytic Leukemia

Treatment with LEUKERAN[®] (chlorambucil) is usually started after the patient has developed symptoms or when there is evidence of impaired bone marrow function (but not marrow failure) as indicated by the peripheral blood count.

Initially, LEUKERAN[®] is given at the dose of 0.15 mg/kg/day until the total leukocyte count is formed to 10 000 per μ L. Treatment may be resumed four weeks after the end of the first course and continued at a dosage of 0.1 mg/kg/day.

In a proportion of patients, usually after about two years of treatment, the blood leukocyte count is reduced to the normal range, enlarged spleen and lymph nodes become impalpable and the proportion of lymphocytes in the bone marrow is reduced to less than 20%.

Patients with evidence of bone marrow failure should first be treated with prednisolone and evidence of marrow regeneration should be obtained before commencing treatment with LEUKERAN[®].

Non-Hodgkin's Lymphoma

Used as a single agent, the usual dosage is 0.1 to 0.2 mg/kg/day for 4-8 weeks initially. Maintenance therapy is then given either by a reduced daily dosage or intermittent courses of treatment.

LEUKERAN[®] is useful in the management of patients with advanced lymphocytic lymphoma and those who have relapsed after radiotherapy.

There is no significant difference in the overall response rate obtained with chlorambucil as a single agent and combination chemotherapy in patients with advanced non-Hodgkin's lymphocytic lymphoma.

Hodgkin's Disease

Used as a single agent in the palliative treatment of advanced disease, a typical dosage is 0.2 mg/kg/day for 4-8 weeks. LEUKERAN[®] is usually included in combination therapy and a number of regimes have been used. LEUKERAN[®] may also be used as an alternative to nitrogen mustard with a reduction in toxicity but similar therapy results.

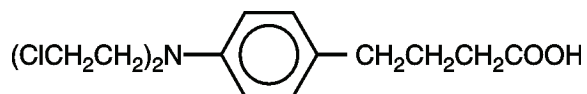
Pharmaceutical Information

Drug Substance

Proper Name: Chlorambucil

Chemical Name: Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]

Structural Formula:



Molecular Formula: C₁₄H₁₉Cl₂NO₂

Molecular Weight: 304.22

pKa: 5.8

Description: Flattened needles from petroleum ether. Melting point of 64-66°C. Soluble at 20°C in 1.5 parts alcohol, in 2.5 parts chloroform, in 2 parts acetone. Practically insoluble in water.

Composition

Each LEUKERAN[®] (chlorambucil) Tablet contains 2 mg chlorambucil and the non-medicinal ingredients anhydrous lactose, colloidal silicon dioxide, microcrystalline cellulose and stearic acid. The tablet coating contains: hydroxy propylmethylcellulose, macrogol, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide.

Stability and Storage Recommendations

LEUKERAN[®] (chlorambucil) 2 mg Tablets should be stored in a refrigerator, 2°C to 8°C.

Special Instructions

Tablets should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging those materials for transport.

All materials which have come in contact with cytotoxic drugs should be segregated and incinerated at 1000°C or more. Sealed containers may explode.

Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

Provided the outer coating is intact, there is no risk to handling. LEUKERAN[®] Tablets should not be divided.

Availability of Dosage Forms

LEUKERAN[®] (chlorambucil) Tablets 2 mg are brown film-coated, round, biconvex tablets engraved "GX EG3" on one face and "L" on the other face. Bottles of 25 tablets.

Pharmacology

LEUKERAN[®] (chlorambucil) is a derivative of nitrogen mustard first synthesized by Everett, Roberts and Ross (1953).

Haddow discovered that the substance was a powerful inhibitor of the transplanted Walker rat tumor 256, and has the pharmacological effects of nitrogen mustard compounds. Subsequent clinical investigation showed that the drug was of value in producing remissions in chronic lymphocytic leukemia and in treatment of malignant lymphomas and Hodgkin's disease. It acts as a bifunctional alkylating agent. Alkylation takes place through the formation of a highly reactive ethylenimmonium radical. A

probable mode of action involves crosslinkage of the ethylenimonium derivative between two strands of helical DNA and subsequent interference with replication.

The metabolism of chlorambucil in man appears to be similar to that in laboratory animals and involves β -oxidation of the butyric acid side chain. Bis-2-chloroethyl-2(4-aminophenyl) acetic acid (or phenylacetic mustard) is a major metabolite of chlorambucil; its peak plasma concentration occurs within 2-4 hours of administration of the parent drug, it has a longer terminal phase half-life than chlorambucil and it contributes significantly to the alkylating activity of the drug.

Toxicology

Pharmacologic studies in rats showed that oral absorption is good, being slightly less than intraperitoneal absorption. A single dose of 12.5 mg/kg intraperitoneally produces typical nitrogen mustard effects. These include loss of weight the first three days, atrophy of intestinal mucosa and of lymphoid organs, severe lymphopenia becoming maximal in four days, transient mild anemia lasting ten days, and thrombocytopenia. Rapid recovery occurs, commonly within 72 hours, and the animal appears normal in about one week, although the bone marrow and blood may not become completely normal for about three weeks. An intraperitoneal dose of 18.5 mg/kg kills about 50% of the rats, with the development of convulsions. As much as 50 mg/kg has been given orally to rats as a single dose with recovery. Chlorambucil is only partially radiomimetic, producing chiefly the lymphoid effects of x-radiation as contrasted with MYLERAN (busulfan) which produces mainly the myeloid effects.

In human subjects, single oral doses of 20 mg or more may produce nausea and vomiting. In therapeutic doses, the depressant effect on the bone marrow is only moderate and rapidly reversible. Patients with lymphomas are more sensitive to the drug and smaller doses are indicated and are therapeutically useful. With excessive doses or prolonged therapy amounting to a total accumulated dosage approaching 6.5 mg/kg (about 450 mg

per patient) patients may develop pancytopenia with possible irreversible bone marrow damage. Patients will usually respond to considerably less total dosage of drug than this if they are to respond at all.

References

1. Barone C, Cassano A, Astone A. Toxic epidermal necrolysis during chlorambucil therapy in chronic lymphocytic leukaemia. *Eur J Cancer* 1990; 26(11/12):1262.
2. Calamera JC, Morgenfeld MC, Mancini RE, Vilar O. Biochemical changes of the human semen produced by chlorambucil, testosterone propionate and human chorionic gonadotropin administration. *Andrologia* 1979; 11(1):43-50.
3. Catovsky D, Galton DAG. Myelomonocytic leukemia supervening on chronic lymphocytic leukemia. *Lancet* 1971; 1(7697):478-479.
4. Cheviakoff S, Calamera JC, Morgenfeld M, Mancini RE. Recovery of spermatogenesis in patients with lymphoma after treatment with chlormabucil. *J Reprod Fertil* 1973; 33:155-157.
5. Cole SR, Myers TJ, Klatsky AU. Pulmonary disease with chlorambucil therapy. *Cancer* 1978; 41(2):455-459.
6. Daoud D, Tan J, Fox N. Sterile cystitis associated with chlorambucil. *Drug Intell Clin Pharm* 1977; 11:491.
7. De Vita VT. Summary of Symposium. *Cancer Treatm Rep* 1977; 61(6):1223-1227.
8. Enck RE, Bennett JM. Inadvertent chlorambucil overdose in adult. *NY State J Med* 1977; 77(9):1480-1485.
9. Godard P, Marty JP, Michel FB. Interstitial pneumonia and chlorambucil. *Chest* 1979; 76(4):471-473.
10. Kaye SB, Juttner CA, Smith IE, Barrett A, Austin DE, Peckham MJ et al. Three years experience with ChlVPP (a combination of drugs of low toxicity) for the treatment of Hodgkin's disease. *Br J Cancer* 1979; 39(2):168-174.
11. Knisley RE, Settipane GA, Albala MM. Unusual reaction to chlorambucil in a patient with chronic lymphocytic leukemia. *Arch Dermatology* 1971; 104(1):77-79.
12. Knopse WH, Loeb V, Jr., Huguley CM, Jr. Bi-weekly chlorambucil in the treatment of chronic lymphocytic leukemia. *Cancer* 1974; 33(2):555-562.

13. Latta K, von Schnakenburg C, Ehrich JHH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatric Nephrology*. 2001;16(3):271-82.
14. Lawler SD, Lele KP. Chromosomal damage induced by chlorambucil in chronic lymphocytic leukemia. *Scand J Haemat* 1972; 9(6):603-612.
15. Lerner HJ. Acute myelogenous leukemia in patients receiving chlorambucil as long term adjuvant chemotherapy for stage II breast cancer. *Cancer Treat Rep* 1978; 62(8):1135-1138.
16. Lister TA, Cullen MH, Beard ME, Brearley RL, Whitehouse JM, Wrigley PF et al. Comparison of combined and single agent chemotherapy in non-Hodgkin's lymphoma of favourable histological type. *Br Med J* 1978; 1(6112):533-537.
17. McElwin TJ, Toy J, Smith E, Peckham MJ, Austin DE. A combination of chlorambucil, vinblastine, procarbazine and prednisolone for the treatment of Hodgkin's disease. *Br J Cancer* 1977; 36(2):276-280.
18. Millard LG, Rajah SM. Cutaneous reaction to chlorambucil. *Arch Dermatology* 1977; 113(9):1298.
19. Moore GE, Bross IDJ, Ausman R, Nadler S, Jones R, Slack N et al. Effects of chlorambucil (NSC-3088) in 374 patients with advanced cancer. *Cancer Chemother Rep*. 1968(PT1);52:661-66.
20. Naysmith A, Robson RH. Focal fits during chlorambucil therapy. *Postgrad Med J* 1979; 55(649):806-807.
21. Pietrantonio F, Moriconi L, Torino F, Romano A, Gargovich A. Unusual reaction to chlorambucil: a case report. *Cancer Lett* 1990; 54(3):109-111.
22. Portlock CS, Fischer DS, Cadman E, Lundberg WB, Levy A, Bobrow S et al. High-dose pulse chlorambucil in advanced low-grade non-Hodgkin's lymphoma. *Cancer Treatment Reports*. 1987;71(11):1029-31.
23. Reimer RR, Hoover R, Fraumeni JF, Jr., Young RC. Acute leukemia after alkylating-agent therapy of ovarian cancer. *New Engl J Med* 1977; 297(4):177-181.
24. Richter P, Calamera JC, Morgenfeld MC, Kierszenbaum AL, Lavieri JC, Mancini RE. Effect of chlorambucil on spermatogenesis in the human with malignant lymphoma. *Cancer* 1970; 25(5):1026-1030.

25. Robak J, Blonski JZ, Kasznicki M, Blasinska-Morawiec M, Krykowski E, Dmoszynska A et al. Cladribine with prednisone versus chlorambucil with prednisone as firstline therapy in chronic lymphocytic leukemia: report of a prospective, randomized, multicenter trial. *Blood*. 2000;96 (8):2723-29.
26. Rosenberg SA. Current concepts in cancer: non Hodgkin's lymphoma-selection of treatment on the basis of histological type. *New Engl J Med* 1979; 301(17):924-928.
27. Rosner F. Acute leukemia as a delayed consequence of cancer chemotherapy. *Cancer* 1976; 37(2 Suppl):1033-1036.
28. Rubio FA, Jr. Possible pulmonary effects of alkylating agents. *New Engl J Med* 1972; 287(22):1150-1151.
29. Rudd P, Fries JF, Epstein WV. Irreversible bone marrow failure with chlorambucil. *J Rheumatol* 1975; 2(4):421-429.
30. Salloum E, Khan KK, Cooper DL. Chlorambucil induced seizures. *Cancer* 1997; 79(5): 1009-1013
31. Sandler RM, Gonsalkorale M. Chronic lymphatic leukemia, chlorambucil and sensorimotor peripheral neuropathy. *Br Med J* 1977; 2(6097): 1265-1266.
32. Sawitsky A, Boklan BF, Benjamin Z. Drug fever produced by chlorambucil. *NY State J Med* 1971; 71(20):2434-2436.
33. Sieber SM, RH Adamson. Toxicity of antineoplastic agents in man; Chromosomal aberrations, antifertility effects, congenital malformations and carcinogenic potential. *Adv Cancer Res* 1975; 22:57-155.
34. Stevenson AC, Patel C. Effects of chlorambucil on human chromosomes. *Mutat Res* 1973 18(3):333-351.
35. Stout R, Todd IDH. The treatment of advanced and recurrent Hodgkin's disease with chlorambucil, vinblastine, procarbazine and prednisone in combination. *Cancer Treat Rev* 1979; 6 Suppl:107-113.
36. Summerfield GP, Taylor PRA, Mounter PJ, Proctor SJ. High-dose chlorambucil for the treatment of chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma. *British Journal of Haematology*. 2002;116(4):781-86.

37. Westin J. Chromosome abnormalities after chlorambucil therapy of polycythaemia vera. *Scand J Haemat* 1976; 17(3):197-204.
38. Williams SA, Makker SP, Grupe WE. Seizures: A significant side effect of chlorambucil therapy. *Pediatric Res* 1977; 11(4):559.
39. Wiltshaw E. Chemotherapy in chronic lymphocytic leukemia. *Clin Haematol* 1977; 6(1):223-235.

PART III: CONSUMER INFORMATION

Pr LEUKERAN[®] Tablets Chlorambucil tablets, USP

This leaflet is part III of a three-part "Product Monograph" published when LEUKERAN[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LEUKERAN[®]. Contact your doctor or pharmacist if you have any questions about the drug.

You may want to read this leaflet again. **Please Do Not Throw It Away** until you have finished your medicine.

ABOUT THIS MEDICATION

What the medication is used for:

LEUKERAN[®] is used to treat cancers of the blood:

- as a single agent to treat certain forms of leukemias
- alone or in combination with other agents to treat certain types of lymphomas.

What it does:

LEUKERAN[®] belongs to a group of medicines called cytotoxics. LEUKERAN[®] interferes with the growth of cancer cells which eventually are killed. Normal cells may also be affected which may lead to side effects.

When it should not be used:

Do not use LEUKERAN[®] if:

- You have previously experienced an allergic reaction to chlorambucil or any of the other ingredients in LEUKERAN[®].
- You are currently receiving, or have recently had, radiotherapy or other chemotherapy.

What the medicinal ingredient is:

The medicinal ingredient in LEUKERAN[®] is chlorambucil.

What the important nonmedicinal ingredients are:

Each LEUKERAN[®] Tablet contains anhydrous lactose, colloidal silicon dioxide, hydroxy propylmethylcellulose, macrogol, microcrystalline cellulose, stearic acid, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide.

What dosage forms it comes in:

Tablets. Each tablet contains 2 mg chlorambucil.

WARNINGS AND PRECAUTIONS

LEUKERAN[®] should be prescribed by a doctor who is experienced in the use of medicines to treat cancers.

LEUKERAN[®] decreases the production of blood cells, which can lower your blood counts. Your blood counts should be measured regularly.

LEUKERAN[®] can cause an allergic reaction.

LEUKERAN[®] may harm an unborn fetus.

LEUKERAN[®] may cause secondary cancers.

LEUKERAN[®] can cause severe skin rash.

BEFORE you use LEUKERAN[®] talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in LEUKERAN[®].
- you have a history of seizures. You may have an increased risk of seizures when taking LEUKERAN[®].
- you are pregnant or likely to become pregnant or father a child. Reliable contraceptive precaution MUST be taken to avoid pregnancy whilst you or your partner is taking LEUKERAN[®].
- you are breastfeeding a baby.
- you have been vaccinated, or planning to be vaccinated with a live vaccine.
- you have kidney disease.
- you have liver problems.

If you need surgery, tell the doctor/anaesthetist that you are taking LEUKERAN[®].

INTERACTIONS WITH THIS MEDICATION

It is important that your doctor know about all your medication so that you get the best possible treatment. Tell your doctor about all the medicines you are taking including herbal products and those you have bought yourself.

Drugs may interact with LEUKERAN[®] include:

- phenylbutazone
- live organism vaccines

Ask your doctor before receiving any vaccination.

PROPER USE OF THIS MEDICATION

It is important to take your medicine at the right times. You must take it in the way your doctor has told you to.

Swallow your tablets whole with a glass of water. Do not break, crush or chew the tablets.

From time to time while you are taking LEUKERAN[®], your doctor will want you to have a blood test. This is to check your blood cell count and to change your dose if necessary.

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are same as yours.

Overdose:

If you take too much LEUKERAN[®] or if someone else takes your medicine by mistake, do not delay; ask your doctor what to do immediately, or contact your nearest hospital emergency department, or poison control centre.

Missed Dose:

If you forget to take a dose, ask your doctor or pharmacist for advice. DO NOT double your next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, LEUKERAN[®] can have side effects. The most common side effects with LEUKERAN[®] are:

- A temporary reduction in the amount of new blood cells and bone marrow cells produced by your body. In particular, a type of white blood cell which is important for your body to prevent and fight-off an infection.
- You may become temporarily anemic and tired or take longer for a minor injury to stop bleeding.

In addition, LEUKERAN[®] may cause the following side-effects:

- Diarrhea
- Nausea
- Vomiting
- Mouth ulcers
- In women, periods may stop. In men, sperm production may be reduced or stopped.
- Allergic reactions such as difficulty breathing, swelling of eyelids and mouth (refer to SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM)

Tell your doctor if any of the following happen to you while you are taking LEUKERAN[®]:

- if you feel sick, vomit or develop diarrhea or mouth ulcers
- if you notice any signs of jaundice (yellowing of the whites of the eyes or the skin)
- if you start feeling more tired than usual, or if you notice any signs of a rash, a fever or an infection such as cystitis
- if you have any unexpected bruising or bleeding
- if you have a convulsion
- if you develop a persistent cough or breathlessness
- if you notice numbness or weakness of your muscles

- if you experience jerking movements

Tell your pharmacist or doctor if you notice any other symptoms that you do not understand which are not mentioned here.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Side Effect/ Symptom	Talk with your Doctor or Pharmacist	Stop taking drug and call your doctor or pharmacist immediately
Rare	Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate		X
	Jaundice (yellowing of the whites of eyes or the skin)	X	
	Progressively increasing shortness of breath	X	

This is not a complete list of side effects. For any unexpected effects while taking LEUKERAN[®], contact your doctor or pharmacist.

HOW TO STORE IT

- Keep your LEUKERAN[®] tablets in a safe place, between 2°C and 8°C
- Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness
Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
<http://www.tritonpharma.ca> or by contacting the sponsor,

Triton Pharma Inc.
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This leaflet was prepared by Triton Pharma Inc.

Last revised: November 29, 2010

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