PRODUCT MONOGRAPH

PrLEUSTATIN®*

cladribine for Injection

1 mg/mL

Antineoplastic/Chemotherapeutic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Infusion	Liquid for Injection / 1mg/mL	Not Applicable *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

LEUSTATIN® (cladribine) for Injection will be referenced as LEUSTATIN® and/or cladribine throughout the Product Monograph.

INDICATIONS AND CLINICAL USE

LEUSTATIN® (cladribine) for Injection is indicated for:

- Treatment of patients with Hairy Cell Leukemia.

LEUSTATIN® should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

Geriatrics (>65 years of age):
See **WARNINGS AND PRECAUTIONS, Special Populations**.

Pediatrics, adolescents and young adults (<21 years of age):
Safety and effectiveness in children have not been established (see **WARNINGS AND PRECAUTIONS, Special Populations**).

CONTRAINDICATIONS

- LEUSTATIN® is contraindicated in those patients who are hypersensitive to this drug or any of its components (For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING).**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

LEUSTATIN® should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

- Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent
- Significant and prolonged lymphopenia has been noted
- Serious neurological toxicity (including irreversible paraparesis and quadriparesis) has been reported in patients who received LEUSTATIN® by continuous infusion at high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia)
- Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens
- Acute nephrotoxicity has been observed with high doses of LEUSTATIN® (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies

General

LEUSTATIN® is a potent antineoplastic agent with potentially significant toxic side effects. It should be administered only under the supervision of a physician experienced with the use of cancer chemotherapeutic agents. Patients undergoing therapy should be closely observed for signs of hematologic and non-hematologic toxicity. Careful hematologic monitoring (assessment of peripheral blood counts), particularly during the first 4 to 8 weeks post-treatment, is recommended to detect the development of anemia, neutropenia and thrombocytopenia and for early detection of any potential sequelae (e.g., infection or bleeding). Since fever is a frequently observed side effect during the first month on therapy, patients should be kept well hydrated. As with other potent chemotherapeutic agents, monitoring of renal and hepatic function is also recommended, especially in patients with underlying kidney or liver dysfunction (see **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Tumour Lysis Syndrome: Rare cases of Tumour Lysis Syndrome have been reported in patients treated with LEUSTATIN® with other hematologic malignancies having a high tumour burden.

Administration of LEUSTATIN®: LEUSTATIN® must be diluted in designated intravenous solution prior to administration (see **DOSAGE AND ADMINISTRATION**).

Benzyl alcohol as a Diluent: Benzyl alcohol is a constituent of the recommended diluent for the 7-day infusion solution. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants (see **DOSAGE AND ADMINISTRATION**).

Carcinogenesis and Mutagenesis

As expected for compounds in this class, the actions of cladribine yield DNA damage (see ***Product Monograph Part II*: TOXICOLOGY, Carcinogenesis and Mutagenesis**).

Hematologic

Bone Marrow Suppression: Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia, has been commonly observed in patients treated with LEUSTATIN®, especially at high doses. The myelosuppressive effects of LEUSTATIN® were most notable during the first month following treatment. Forty-four percent (44%) of patients received transfusions with RBCs and 14% received transfusions with platelets during Month 1. Careful hematologic monitoring (assessment of peripheral blood counts), particularly during the first 4 to 8 weeks post-treatment, is recommended. Most patients in the clinical studies had hematologic impairment as a manifestation of active Hairy Cell Leukemia. Consequently care should be taken to distinguish disease-related bone marrow suppression from that which may result following treatment with LEUSTATIN®. (During the first two weeks after treatment initiation, Mean Platelet Count, Absolute Neutrophil Count (ANC), and Hemoglobin concentration declined and subsequently increased with normalization of mean counts by Day 12, Week 5 and Week 8, respectively). Proceed carefully in patients with severe bone marrow impairment of any etiology since further suppression of bone marrow function should be anticipated (see **Monitoring and Laboratory Tests** and **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions)**.

Due to the known genotoxicity of cladribine and the prolonged immunosuppression associated with the use of nucleoside analogues like LEUSTATIN®, secondary malignancies are a potential risk.

Hepatic/Biliary/Pancreatic

There are inadequate data on dosing of patients with hepatic insufficiency. Therefore, caution is advised when administering LEUSTATIN® to patients with known or suspected hepatic insufficiency.

Immune

Fever: Fever (T≥37.8°C or 100°F) was associated with the use of LEUSTATIN® in approximately two-thirds of patients (131/196) in the first month of therapy. Virtually all of these patients were treated empirically with parenteral antibiotics. Overall, 47% (93/196) of all patients had fever in the setting of neutropenia (ANC≤1000 x 10^6/L), including 62 patients (32%) with severe neutropenia (ANC≤500 x 10^6/L) (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions**).

Opportunistic infections have occurred in the acute phase of treatment due to the immunosuppression mediated by LEUSTATIN®.

Neurologic

Neurotoxicity was observed in patients, undergoing bone marrow transplantation for acute leukemia. High doses (4 to 9 times the recommended dose for Hairy Cell Leukemia), in conjunction with cyclophosphamide and total body irradiation as preparation for bone marrow transplantation, have been associated with severe, irreversible, neurologic toxicity (paraparesis/quadriparesis) and/or acute renal insufficiency. These toxicities occurred in 45% of patients treated for 7-14 days.

Axonal peripheral polyneuropathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for Hairy Cell Leukemia) in patients not receiving cyclophosphamide or total body irradiation. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Renal

Acute renal insufficiency has developed in some patients receiving high doses of LEUSTATIN®. In one study, following a one-hour infusion, the recovery of cladribine in the urine over a 24-hour period was between 10-30% of the administered dose. There are inadequate data on dosing of patients with renal insufficiency. Therefore, caution is advised when administering LEUSTATIN® to patients with known or suspected renal insufficiency.

High doses (4 to 9 times the recommended dose for Hairy Cell Leukemia), in conjunction with cyclophosphamide and total body irradiation as preparation for bone marrow transplantation, have been associated with severe, irreversible, neurologic toxicity (paraparesis/quadriparesis) and/or acute renal insufficiency. These toxicities occurred in 45% of patients treated for 7-14 days. In patients with Hairy Cell Leukemia treated with the recommended dose (0.09 mg/kg/day for 7 days), no nephrotoxicity has been reported. Deviations from the dosing regimen recommended for Hairy Cell Leukemia are not advised.

Sexual Function/Reproduction

Impairment of Fertility: The effect on human fertility is unknown. When administered intravenously to Cynomolgus monkeys, cladribine has been shown to cause suppression of rapidly generating cells, including testicular cells.

Men being treated with LEUSTATIN® should be advised not to father a child up to 6 months after the last LEUSTATIN® dose.

Special Populations

Pregnant Women: Although there is no evidence of teratogenicity due to LEUSTATIN® in humans, other drugs that inhibit DNA synthesis (e.g. methotrexate and aminopterin) have been reported to be teratogenic in humans. LEUSTATIN® has been shown to be embryotoxic in mice when given at doses equivalent to the recommended dose.

LEUSTATIN® should not be given during pregnancy. Women of childbearing potential must use effective contraception during treatment with LEUSTATIN® and for 6 months after the last LEUSTATIN® dose.

There are no adequate and well-controlled studies in pregnant women. If LEUSTATIN® 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.

Fetotoxicity: Cladribine is teratogenic in mice and rabbits and consequently has the potential to cause fetal harm when administered to a pregnant woman. A significant increase in variations of fetal growth/development (i.e. increases in cervical ribs, irregularly-shaped exoccipital bones, and variations in sternal ossification) was observed in mice receiving 1.5 mg/kg/day (4.5 mg/m^2) and increased resorptions, reduced litter size and increased fetal malformations were observed when mice received 3.0 mg/kg/day (9 mg/m^2). Fetal death and malformations were observed in rabbits that received 3.0 mg/kg/day (33.0 mg/m^2). No fetal effects were seen in mice at 0.5 mg/kg/day (1.5 mg/m^2) or in rabbits at 1.0 mg/kg/day (11.0 mg/m^2).

Breastfeeding: It is not known whether this drug is excreted in human milk. Breastfeeding should not be undertaken during treatment with LEUSTATIN®.

Pediatrics, Adolescents, and Young Adults (1-21 years of age): In a Phase I study involving patients 1-21 years old with relapsed acute leukemia, LEUSTATIN® was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m^2/day for 5 days (one-half to twice the dose recommended in Hairy Cell Leukemia). In this study, the dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose (10.7 mg/m^2/day), 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted in this study (see **INDICATIONS AND CLINICAL USE**).

Geriatrics (>65 years of age): Clinical studies of LEUSTATIN® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients (see **INDICATIONS AND CLINICAL USE**).

Monitoring and Laboratory Tests

During and following treatment, the patient's hematologic profile should be monitored regularly to determine the degree of hematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the Mean Platelet Count reached 100×10^9/L by Day 12, the Mean Absolute Neutrophil Count reached 1500×10^6/L by Week 5 and the Mean Hemoglobin reached 12 g/dL by Week 8. After peripheral counts have normalized, bone marrow aspiration and biopsy should be performed to confirm response to treatment with LEUSTATIN®. Febrile events should be investigated with appropriate laboratory and radiologic studies. Periodic assessment of renal function and hepatic function should be performed as clinically indicated.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Safety data are based on 196 patients with Hairy Cell Leukemia: the original cohort of 124 patients plus an additional 72 patients enrolled at the same 2 centres after the original enrolment cut-off. Of the 196 patients with Hairy Cell Leukemia entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious etiology, including 3 pneumonias, and 2 occurred in the first month following LEUSTATIN® therapy. Of the 8 deaths, 6 occurred in previously treated patients who were refractory to α-interferon.

In Month 1 of the clinical trials for Hairy Cell Leukemia, severe neutropenia was noted in 70% of patients, fever in 69%, and infection was documented in 28%. Other adverse experiences reported frequently during the first 14 days after initiating treatment included: fatigue (45%), nausea (28%), rash (27%), headache (22%) and injection site reactions (19%). Most of the non-hematologic adverse experiences were mild to moderate in severity.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Myelosuppression: Myelosuppression was frequently observed during the first month after starting treatment. Neutropenia (ANC<500×10^6/L) was noted in 70% of patients, compared with 26% in whom it was present initially. Severe anemia (Hemoglobin <8.5 g/dL) developed in 37% of patients, compared with 10% initially, and thrombocytopenia (Platelets <20×10^9/L) developed in 12% of patients, compared with 4% in whom it was noted initially. During the first month, 54 of 196 patients (28%) exhibited documented evidence of infection: serious infections (e.g. septicemia, pneumonia) were reported in 6% of all patients; the remainder were mild or moderate. Several deaths were attributable to infection and/or complications related to the underlying disease. During the second month, the overall rate of documented infection was 6%; these infections were mild to moderate and no severe systemic infections were seen. After the third month, the monthly incidence of infection was either less than or equal to that of the months immediately preceding LEUSTATIN® therapy.

Infection: Documented infections were noted in fewer than one-third of febrile episodes. Of the 196 patients studied, 19 were noted to have a documented infection in the month prior to treatment. In the month following treatment, there were 54 episodes of documented infection: 23 (42%) were bacterial, 11 (20%) were viral and 11 (20%) were fungal. Seven of 8 documented episodes of herpes zoster occurred during the month following treatment. Fourteen of 16 episodes of documented fungal infections occurred in the first two months following treatment. Virtually all of these patients were treated empirically with antibiotics.

Effects on Lymphocytes: Analysis of lymphocyte subsets indicates that treatment with cladribine is associated with prolonged depression of the CD4 counts and transient suppression of CD8 counts. Prior to treatment, the mean CD4 count was 766/µL. The mean CD4 count nadir, which occurred 4 to 6 months following treatment, was 272/µL. Fifteen months after treatment, mean CD4 counts remained below 500/µL. CD8 counts decreased initially, though increasing counts were observed after 9 months. In a study of 46 patients, the median time to reach a normal absolute CD4+ lymphocyte count was 40 months. Although depletion of these cells may contribute to the risk of opportunistic infection, no direct correlation has been reported between the CD4+ count and the incidence of infection. The clinical significance of the prolonged CD4 lymphopenia is unclear.

Bone Marrow Hypocellularity: Another event of unknown clinical significance includes the observation of prolonged bone marrow hypocellularity. Bone marrow hypocellularity (<35%) was noted after 4 months in 42 of 124 patients (34%) treated in the two pivotal trials. This hypocellularity was noted as late as Day 1010. It is not known whether the hypocellularity is the result of disease-related marrow fibrosis or if it is the result of cladribine toxicity. There was no apparent clinical effect on the peripheral blood counts.

Adverse experiences related to intravenous administration: Injection site reactions (9%; i.e. redness, swelling, pain), Thrombosis (2%), Phlebitis (2%) and a Broken Catheter (1%). These appear to be related to the infusion procedure and/or indwelling catheter, rather than the medication or the vehicle.

Skin: The vast majority of rashes were mild and occurred in patients who were receiving or had recently been treated with other medications (e.g. allopurinol or antibiotics) known to cause rash.

Gastrointestinal: Most episodes of nausea were mild, not accompanied by vomiting, and did not require treatment with antiemetics. In patients requiring antiemetics, nausea was easily controlled, most frequently with chlorpromazine.

Fever: Fever was a frequently observed side effect during the first month on study. During the first month, 11% of patients experienced severe fever (i.e. ≥40°C or 104°F). Since fever may be accompanied by increased fluid loss, patients should be kept well hydrated during treatment. Since the majority of fevers occurred in neutropenic patients, patients should be closely monitored during the first month of treatment and empiric antibiotics should be initiated as clinically indicated. Although 69% of patients developed fevers, less than 1/3 of febrile events were associated with documented infection. Given the known myelosuppressive effects of LEUSTATIN®, practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections (see **WARNINGS AND PRECAUTIONS**).

Adverse reactions reported during the first 2 weeks following treatment initiation (regardless of relationship to drug) by ≥5% of patients are listed in the following table.

Table 1.1: Adverse Reactions Reported by ≥5% of Patients During the First 2 Weeks Following Treatment Initiation *(regardless of relationship to drug)*

Body System	Adverse Event
Body as a Whole	Fever, chills, fatigue, asthenia, malaise, trunk pain, diaphoresis
Gastrointestinal System	Nausea, decreased appetite, constipation, vomiting, diarrhea, abdominal pain
Hemic/Lymphatic System	Purpura, petechiae, epistaxis
Nervous System	Headache, dizziness, insomnia
Cardiovascular System	Edema, tachycardia
Respiratory System	Abnormal breath sounds, abnormal chest sounds, cough, shortness of breath
Skin/Subcutaneous Tissue	Rash, injection site reactions, pruritus, pain, erythema
Musculoskeletal System	Myalgia, arthralgia

From Day 15 to the last follow-up visit, the only events reported by ≥5% of patients were: Fatigue (11%), Rash (10%), Headache (7%), Cough (7%), and Malaise (5%).

Effects of High Doses: In a Phase I investigational study using LEUSTATIN® in high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia) as part of a bone marrow transplant

conditioning regimen, which also included high dose cyclophosphamide and total body irradiation, acute nephrotoxicity and delayed onset neurotoxicity were observed.

Thirty-one poor-risk patients with drug-resistant acute leukemia in relapse (29 cases) or non-Hodgkins lymphoma (2 cases) received doses of LEUSTATIN® for 7 to 14 days prior to bone marrow transplantation. During LEUSTATIN® infusion, 8 patients experienced gastrointestinal symptoms. While the bone marrow was initially cleared of all hematopoietic elements, including tumour cells, leukemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with LEUSTATIN®, 6 patients (19%) developed manifestations of renal dysfunction (i.e., acidosis, anuria, elevated serum creatinine, etc.) and 5 required dialysis. Several of these patients were also being treated with other medications having known nephrotoxic potential. Renal dysfunction was reversible in 2 of these patients. In the 4 patients whose renal function had not recovered at the time of death, autopsies were performed; in 2 of these, evidence of tubular damage was noted. Eleven patients (35%) experienced delayed onset neurologic toxicity. In the majority, this was characterized by progressive irreversible motor weakness (paraparesis/quadriparesis) of the upper and/or lower extremities, first noted 35 to 84 days after starting high dose therapy with LEUSTATIN®. Non-invasive testing (electromyography and nerve conduction studies) was consistent with demyelinating disease.

Axonal peripheral polyneuropathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for Hairy Cell Leukemia) in patients not receiving cyclophosphamide or total body irradiation. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens (see **WARNINGS AND PRECAUTIONS, Neurologic** and **Renal**).

Post-Market Adverse Drug Reactions

The following additional adverse reactions have been reported since the drug became commercially available. These adverse reactions have been reported primarily in patients who received multiple courses of LEUSTATIN®.

Infections and infestations*:* Septic shock. Opportunistic infections have occurred in the acute phase of treatment.

Blood and lymphatic system disorders: bone marrow suppression with prolonged pancytopenia, including some reports of aplastic anemia; hemolytic anemia (including autoimmune hemolytic anemia), which was reported in patients with lymphoid malignancies, occurring within the first few weeks following treatment; hypereosinophilia. Cases of myelodysplastic syndrome have been reported.

Immune system disorders: Hypersensitivity.

Metabolism and nutrition disorders: Tumour lysis syndrome.

Psychiatric disorders: Confusion (including disorientation).
Neoplasms: secondary malignancies.

Nervous system disorders: Depressed level of consciousness, neurological toxicity (including peripheral sensory neuropathy, motor neuropathy (paralysis), polyneuropathy, paraparesis); however, severe neurotoxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Eye disorders: Conjunctivitis.

Respiratory thoracic and mediastinal disorders: Pulmonary interstitial infiltrates (including lung infiltration, interstitial lung disease, pneumonitis and pulmonary fibrosis); in most cases, an infectious etiology was identified.

Hepatobiliary disorders: Reversible, generally mild, increases in bilirubin and transaminases.

Skin and tissue disorders: Urticaria. In isolated cases, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients who were receiving or had recently been treated with other medications (e.g. allopurinol or antibiotics) known to cause these syndromes.

Renal and urinary disorders: Renal failure (including renal failure acute, renal impairment).

For a description of adverse reactions associated with the use of high doses in non-Hairy Cell Leukemia patients see **WARNINGS AND PRECAUTIONS**.

DRUG INTERACTIONS

Overview

There are no known drug interactions with LEUSTATIN®. Caution should be exercised if LEUSTATIN® is administered before, after or in conjunction with other drugs known to cause immunosuppression or myelosuppression (see **WARNINGS AND PRECAUTIONS**).

Due to increased risk of infection in the setting of immunosuppression with chemotherapy including LEUSTATIN®, it is not recommended to administer live attenuated vaccines to patients receiving LEUSTATIN®.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

High doses of LEUSTATIN® have been associated with:

- Irreversible neurologic toxicity (paraparesis/quadriparesis)
- Acute nephrotoxicity
- Severe bone marrow suppression resulting in neutropenia, anemia and thrombocytopenia

Recommended Dose and Dosage Adjustment

The recommended dose and schedule of LEUSTATIN® for Hairy Cell Leukemia is a single course given by continuous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day. Deviations from this dosage regimen are not advised. If the patient does not respond to the initial course of LEUSTATIN® for Hairy Cell Leukemia, it is unlikely that they will benefit from additional courses. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs (see **WARNINGS AND PRECAUTIONS**).

Specific risk factors predisposing to increased toxicity from LEUSTATIN® have not been defined. In view of the known toxicities of agents of this class, it would be prudent to proceed carefully in patients with known or suspected renal insufficiency or severe bone marrow impairment of any etiology. Patients should be monitored closely for hematologic or non-hematologic toxicity (see **WARNINGS AND PRECAUTIONS**).

Acute renal insufficiency has developed in some patients receiving high doses of LEUSTATIN®. In one study, following a one-hour infusion, the recovery of cladribine in the urine over a 24-hour period was between 10-30% of the administered dose. In addition, there are inadequate data on dosing of patients with renal or hepatic insufficiency. Therefore, caution is advised when administering LEUSTATIN® to patients with known or suspected renal or hepatic insufficiency (see **WARNINGS AND PRECAUTIONS**).

Administration

Reconstitution

Parenteral Products: LEUSTATIN® must be diluted with the designated diluent prior to administration. **Since the drug product does not contain any antimicrobial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of LEUSTATIN® solutions.**

Preparation of a Single Daily Dose: Add the calculated dose (0.09 mg/kg or 0.09 mL/kg) of LEUSTATIN® to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP. Infuse continuously over 24 hours. Repeat daily for a total of 7 consecutive days. **The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine.** Admixtures of LEUSTATIN® are chemically and physically stable for at least 24 hours at room temperature under normal room fluorescent light in Baxter Viaflex™† PVC infusion containers.

Table 1.2: 24-Hour Infusion Method

Dose of LEUSTATIN®	Recommended Diluent	Quantity of Diluent
0.09 mg/kg 1(day) X 0.09 mg/kg	0.9% Sodium Chloride Injection	500 mL

Preparation of a 7-Day Infusion: The 7-day infusion solution should only be prepared with Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol preserved). In order to minimize the risk of microbial contamination, both LEUSTATIN® and the diluent should be passed through a sterile 0.22µ disposable hydrophilic syringe filter as each solution is being introduced into the infusion reservoir. First add the calculated dose of LEUSTATIN® (7 days x 0.09 mg/kg) to the infusion reservoir through the sterile filter. Then add a calculated amount of Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol preserved) also through the filter to bring the total volume of the solution to 100 mL. After completing solution preparation, clamp off the line, disconnect and discard the filter. Aseptically aspirate air bubbles from the reservoir as necessary using the syringe and a dry second sterile filter or a sterile vent filter assembly. Reclamp the line and discard the syringe and filter assembly. Infuse continuously over 7 days. Solutions prepared with Bacteriostatic Sodium Chloride injection for individuals weighing more than 85 kg may have reduced preservative effectiveness due to greater dilution of the benzyl alcohol preservative. Admixtures for the 7-day infusion have demonstrated acceptable chemical and physical stability for at least 7 days in SIMS Deltec Inc. MEDICATION CASSETTES™‡.

Table 1.3: 7-Day Infusion Method

Dose of LEUSTATIN®	Recommended Diluent	Quantity of Diluent
7(days) x 0.09 mg/kg	Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol)	q.s. to 100 mL

N.B. - use sterile 0.22µ filter when preparing infusion solution

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised. Solutions containing LEUSTATIN® should not be mixed with other intravenous drugs or additives, or infused simultaneously via a common intravenous line, since

† *Viaflex containers, manufactured by Baxter Healthcare Corporation*
‡ *MEDICATION CASSETTES® (available in Canada through SIMS Canada Ltd)*

compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates (see **WARNINGS AND PRECAUTIONS, Special Populations**).

If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed with a compatible diluent before and after infusion of LEUSTATIN®.

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of LEUSTATIN® should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than 8 hours prior to start of administration. Vials of LEUSTATIN® are for single use only. Any unused portion should be discarded in an appropriate manner.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of LEUSTATIN® to low temperatures; it may be resolubilized by allowing the solution to warm naturally to room temperature and by shaking vigorously. **Do not heat or microwave.**

OVERDOSAGE

There is no known specific antidote to overdosage. Treatment of overdosage consists of discontinuation of LEUSTATIN®, careful observation and appropriate supportive measures. It is not known whether cladribine can be removed from the circulation by any form of dialysis or hemofiltration.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

LEUSTATIN® (also commonly known as 2-chloro-2'-deoxy-β-D-adenosine) is a synthetic antineoplastic agent. The selective toxicity of cladribine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase, and deoxynucleotidase. Like some other deoxypurine nucleosides, cladribine crosses the cell membrane passively. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2'-deoxy-β-D-adenosine monophosphate (2-CdAMP). Since cladribine is resistant to deamination by adenosine deaminase and there is little deoxynucleotidase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2'-deoxy-β-D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by cladribine as toxic deoxynucleotides accumulate intracellularly.

Cells containing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus cladribine can be distinguished from other chemotherapeutic agents affecting purine metabolism in that it is cytotoxic to both actively dividing and quiescent lymphocytes and monocytes, inhibiting both DNA synthesis and repair.

Pharmacokinetics

Absorption: In a clinical investigation, 17 patients with Hairy Cell Leukemia and normal renal function were treated for 7 days with the recommended treatment regimen of LEUSTATIN® (0.09 mg/kg/day) by continuous intravenous infusion. The mean steady-state serum concentration was estimated to be 5.7 ng/mL with a systemic clearance of 663.5 mL/hr/kg. Accumulation of cladribine over the seven day treatment period was not noted.

In a study using two (2) hour infusion of LEUSTATIN® at 0.14 mg/kg (8 patients with hematologic malignancies), the mean end-of-infusion plasma cladribine concentration was 48±19 ng/mL. For 5 of the 8 patients with hematologic malignancies, the disappearance of cladribine could be described by either a biphasic or triphasic decline. The mean harmonic terminal half-life for both studies was 5.4 hours, with mean values for clearance and steady-state volume of distribution represented as 978±422 mL/hr/kg and 4.52±2.82 L/kg, respectively. In patients with Hairy Cell Leukemia, there does not appear to be a relationship between serum concentrations and ultimate clinical outcome.

Plasma cladribine concentrations were reported to decline multi-exponentially after intravenous infusions. In one study, thirteen patients with B-cell CLL and low-grade NHL were treated with LEUSTATIN® for 5 consecutive days. LEUSTATIN® was administered as a 2-hour IV infusion (0.14 mg/kg), SC (0.14 mg/kg), or orally (0.28 mg/kg) with alternate order between patients. Cladribine declined bi-exponentially after the IV administration with α and β half-lives ranging from 0.24 to 2.33 hours (mean±SD = 0.70±0.60 hours) and 4.5 to 21.8 hours (mean±SD = 9.9±4.6 hours), respectively. The mean±SD C_{max}, clearance, and apparent volume of distribution of cladribine when the 2-hour infusion was administered as the initiate dose were 213±193 nmol/L (n=3), 29.5±8.3 L/h/m^2 (n=6), and 67.6±28.9 L/m^2 (n=6), respectively. In another study, twelve patients with lymphoproliferative diseases were treated with LEUSTATIN® at a dose of 0.14 mg/kg for 5 consecutive days. LEUSTATIN® was administered as a 2-hour IV infusion on Days 1, 3, 4 and 5 and as a 24-hour IV infusion on Day 2. Cladribine declined bi-exponentially after the first IV dose with α and β half-lives ranging from 19 to 58 minutes (mean±SD = 35±12 minutes) and 2.8 to 12.1 hours (mean±SD = 6.7±2.5 hours), respectively. The mean±SD C_{max} and apparent volume of distribution of cladribine after the first IV dose was 198±87 nmol/L and 9.2±5.4 L/kg, respectively. There was no apparent difference in area under the plasma concentration time curve between the first 2-hour infusion dose and the second 24-hour IV infusion dose, suggesting the disposition of cladribine is independent of infusion rate ranging from 6 to 70 mg/kg/h. The mean half-life of cladribine in leukemic cells has been reported to be 23 hours.

Distribution: Cladribine is bound approximately 20% to plasma proteins and penetrates into cerebrospinal fluid. One report indicates that the CSF concentrations are approximately 25% of those in plasma.

Metabolism: In man, following a 2 hour infusion, the terminal half-life of cladribine has been estimated at ~5.4 hours. Except for limited understanding of the mechanism of cellular toxicity and route of excretion, no other information is available on the metabolism of cladribine in man.

Excretion: An average of 18% of the administered dose has been reported to be excreted in urine of patients with solid tumours during a 5-day continuous intravenous infusion of 3.5-8.1mg/m^2/day of cladribine. Other investigators reported approximately 30% of urinary recovery of cladribine during the first 24 hour post-infusion period during a 5-day 2-hour intravenous infusion of 3.5-10.5 mg/m^2/day of cladribine in patients with solid tumours and during 5-day 2-hour intravenous infusion of 6-12 mg/m^2/day of cladribine in 10 patients with leukemia or lymphoma. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

STORAGE AND STABILITY

When vials and infusion solutions are stored between 2°C to 8°C protected from light, unopened vials of LEUSTATIN® are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. **DO NOT** heat or microwave. Once thawed, the vial of LEUSTATIN® is stable until expiry if refrigerated. **DO NOT** refreeze. Once diluted, solutions containing LEUSTATIN® should be administered promptly or stored in the refrigerator (2°C to 8°C) for no more than 8 hours prior to administration.

Store refrigerated between 2°C to 8°C.

Protect from light during storage.

SPECIAL HANDLING INSTRUCTIONS

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering LEUSTATIN®. The use of disposable gloves and protective garments is recommended. If LEUSTATIN® comes in contact with the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published. Refer to your institution's guidelines for disposal of cytotoxic waste.

LEUSTATIN® must be diluted with the designated intravenous solutions prior to administration. **Since the drug product does not contain any antimicrobial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of LEUSTATIN® solutions.**

DOSAGE FORMS, COMPOSITION AND PACKAGING

LEUSTATIN® is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine in a single-use clear flint glass 20 mL vial. LEUSTATIN® is available in individually boxed vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

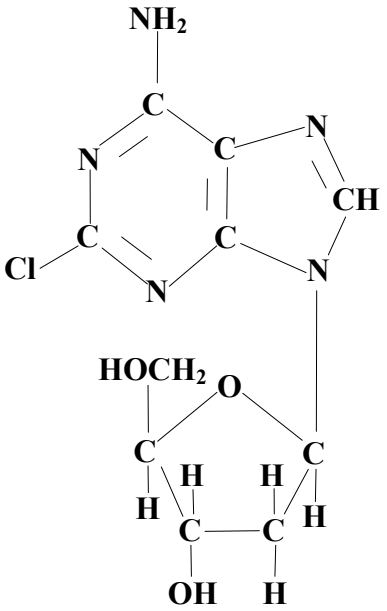
Drug Substance

Proper name: cladribine

Chemical name: 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine

Molecular formula and molecular mass: $C_{10}H_{12}N_5O_3Cl$ / 285.7

Structural formula:



Physicochemical properties: cladribine is a white non-hygroscopic, crystalline powder.

LEUSTATIN® (cladribine) for Injection is available in single-use vials containing 10 mg (1 mg/mL) of cladribine, a chlorinated purine nucleoside analog. Each milliliter of LEUSTATIN® contains 1 mg of the active ingredient, cladribine, and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient.

LEUSTATIN® is a synthetic antineoplastic agent for continuous intravenous infusion. It is a clear, colourless, sterile, preservative-free, isotonic solution.

The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to 6.3 ± 0.3.

CLINICAL TRIALS

Two single-center open studies of LEUSTATIN® have been conducted in patients with Hairy Cell Leukemia with evidence of active disease requiring therapy. In the study conducted at the Scripps Clinic and Research Foundation (Study A), 89 patients were treated with a single course of LEUSTATIN® given by continuous intravenous infusion for 7 days at a dose of 0.09 mg/kg/day. In the study conducted at the M.D. Anderson Cancer Center (Study B), 35 patients were treated with a 7-day continuous intravenous infusion of LEUSTATIN® for Injection at a comparable dose of 3.6 mg/m^2/day.

A complete response (CR) required clearing of the peripheral blood and bone marrow of hairy cells and recovery of the Hemoglobin to 12 g/dL, platelet count to 100×10^9/L, and absolute neutrophil count to 1500×10^6/L. A good partial response (GPR) required the same hematologic parameters as a complete response, and that fewer than 5% hairy cells remain in the bone marrow. A partial response (PR) required that hairy cells in the bone marrow be decreased by at least 50% from baseline and the same response for hematologic parameters as for complete response. A pathologic relapse was defined as an increase in bone marrow hairy cells to 25% of pretreatment levels. A clinical relapse was defined as the recurrence of cytopenias, specifically decreases in Hemoglobin ≥ 2 g/dL, ANC≥25% of pretreatment levels or platelet counts $\geq50\times10^9$/L. Patients who met the criteria for a complete response but subsequently were found to have evidence of bone marrow hairy cells (<25% of pretreatment levels) were reclassified as partial responses and were not considered to be complete responses with relapse.

Among patients evaluable for efficacy (N=106), using the hematologic and bone marrow response criteria described above, the complete response rates were 65% and 68% for Study A and Study B, respectively, yielding a combined complete response rate of 66%. Overall response rates (i.e., Complete plus Partial Responses) were 89% and 86% in Study A and Study B, respectively, for a combined overall response rate of 88%.

Using an intent-to-treat analysis (N=123) and further requiring no evidence of splenomegaly as a criterion for CR (i.e., no palpable spleen on physical examination and ≤ 13 cm on CT scan), the complete response rates for Study A and Study B were 54% and 56%, respectively, giving a combined CR rate of 54%. The overall response rates (CR + GPR + PR) were 90% and 85%, for Studies A and B respectively, yielding a combined overall response rate of 89%.

Table 2.1: Response rates to LEUSTATIN® Treatment in Patients with Hairy Cell Leukemia

	Complete Response	Overall Response
Evaluable Patients (N=106)	66%	88%
Intent-to-treat Population (N=123)	54%	89%

In these studies, 60% of the patients had not received prior chemotherapy for Hairy Cell Leukemia or had undergone splenectomy as the only prior treatment and were receiving LEUSTATIN® as a first-line treatment. The remaining 40% of the patients received

LEUSTATIN® as a second-line treatment, having been treated previously with other agents, including α-interferon and/or deoxycoformycin. The overall response rate for patients without prior chemotherapy was 92%, compared with 84% for previously treated patients. LEUSTATIN® is active in previously treated patients; however, retrospective analysis suggests that the overall response rate is decreased in patients previously treated with splenectomy or deoxycoformycin and in patients refractory to α-interferon.

Table 2.2: Overall Response Rates (CR + GPR+ PR) to LEUSTATIN® Treatment in Patients with Hairy Cell Leukemia

	OVERALL RESPONSE (N = 123)	**NR + RELAPSE**
No Prior Chemotherapy	68/74 92%	6 + 4 14%
Any Prior Chemotherapy	41/49 84%	8 + 3 22%
Previous Splenectomy	32/41* 78%	9 + 1 24%
Previous Interferon	40/48 83%	8 + 3 23%
Interferon Refractory	6/11* 55%	5 + 2 64%
Previous Deoxycoformycin	3/6* 50%	3 + 1 66%

NR = No Response
* $P < 0.05$

After a reversible decline, normalization of peripheral blood counts (Hemoglobin ≥12.0 g/dL, Platelets 100×10^9/L, Absolute Neutrophil Count (ANC) $\geq 1500 \times 10^6$/L) was achieved by 92% of evaluable patients. The median time to normalization of peripheral counts was 9 weeks from the start of treatment (Range: 2 to 72). The median time to normalization of platelet count was 2 weeks, the median time to normalization of ANC was 5 weeks and the median time to normalization of Hemoglobin was 8 weeks. With normalization of Platelet Count and Hemoglobin, requirements for platelet and RBC transfusions were abolished after Months 1 and 2, respectively, in those patients with a complete response. Platelet recovery may be delayed in a minority of patients with severe baseline thrombocytopenia. Corresponding to normalization of ANC, a trend toward a reduced incidence of infection was seen after the third month, when compared to the months immediately preceding LEUSTATIN® therapy (see **WARNINGS AND PRECAUTIONS**, and **ADVERSE REACTIONS**).

Table 2.3: LEUSTATIN® Treatment in Patients with Hairy Cell Leukemia: Time to Normalization of Peripheral Counts

Parameter	Median Time to Normalization of Count*
Platelet Count	2 Weeks
Absolute Neutrophil Count	5 Weeks
Hemoglobin	8 Weeks
ANC, Hemoglobin and Platelet Count	9 Weeks

***** Day 1 = First day of infusion

For patients achieving a complete response, the median time to response (i.e., absence of hairy cells in bone marrow and peripheral blood together with normalization of peripheral blood parameters), measured from treatment start, was approximately 4 months. Since bone marrow aspiration and biopsy were frequently not performed at the time of peripheral blood normalization, the median time to complete response may actually be shorter than that which was recorded. At the time of the data cut-off, the median duration of complete response was greater than 8 months and ranged to 25+ months. Among 93 responding patients, 7 had shown evidence of disease progression at the time of the data cut-off. In 4 of these patients, disease was limited to the bone marrow without peripheral blood abnormalities (pathologic progression), while in 3 patients there were also peripheral blood abnormalities (clinical progression). Seven patients who did not respond to a first course of LEUSTATIN® therapy received a second course of therapy. In the five patients who had adequate follow-up, additional courses did not appear to improve their overall response.

Deaths: Of the 196 patients with Hairy Cell Leukemia entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious etiology, including 3 pneumonias, and 2 occurred in the first month following LEUSTATIN® therapy. Of the 8 deaths, 6 occurred in previously treated patients who were refractory to α-interferon.

DETAILED PHARMACOLOGY

Nonclinical Pharmacodynamics

In vitro: The following table summarizes the data for the effects of cladribine on human cell lines and peripheral blood cells. The IC50 or ID50 values (CEM cells) may vary with experimental protocols and duration of drug exposure.

Table 2.4: Inhibition of the Growth of Various Human Cells Treated with Cladribine

Cell Line or Cells	Cell Type	IC50 or ID50 (nM)
CEM	T-lymphoblast	14
MOLT-3	T-lymphoblast	24
MOLT-4	T-lymphoblast	55
HL60	Myeloid	20
THP-1	Myeloid	24
U937	Myeloid	23
RAJI	B-lymphoblast	27
SB	B-lymphoblast	--
K562	Myeloid Progenitor	256
WI-38	Fibroblast	--
CCRF-CEM	T-lymphoblast	3
WI-L2	B-lymphoblast	35
WI-L2 (AKase deficient)	B-lymphoblast	35
WI-L2 (dCKase deficient)	B-lymphoblast	>2000
Monocytes*	Monocyte	27
Lymphocytes*	Lymphocyte	20
GM 01380	Fibroblast	--

AKase - adenosine kinase dCKase - deoxycytidine kinase
-- No concentration inhibited 50% * Isolated Peripheral Blood Cells

Freshly isolated human peripheral blood monocytes and lymphocytes and normal human GM 01380 fibroblasts were cultured for 5 days with various concentrations of cladribine. Viable monocytes and fibroblasts were measured by the MTT[3-(4,5-dimethylthiazol-2yl)-2,5diphenyl tetrazoliumbromide] reduction assay, and viable lymphocytes were enumerated by dye exclusion. The data indicate that lymphocytes and monocytes are sensitive to the cytotoxic effects of cladribine, *in vitro*, at nanomolar concentrations, whereas the fibroblast line, GM 01380, is unaffected. This cytotoxicity of both peripheral blood cell populations is substantially prevented by deoxycytidine. However, contrasting lymphocytes, monocyte lysis is not prevented by nicotinamide or 3-aminobenzamide, inhibitors of poly (ADP ribose) synthetase, suggesting that the cytotoxic mechanism differs in these two cell types.

Utilizing a human tumour colony-forming assay, the cytotoxic activity of cladribine toward several human solid tumours was assessed. Overall, cladribine, at concentrations of 1.0 µg/mL and 10.0 µg/mL, reduced the tumour survival rate (defined as <50% survival of tumour colony-forming units) by 8% and 23% respectively, when given in a 1-hour pulse; and by 11% and 31% respectively when given as a continuous exposure. The data indicate that cladribine is much less active against solid tumours than against leukemic lymphoblasts.

Whereas lymphoblasts are sensitive to nanomolar concentrations of cladribine, the solid tumours required at least 100-fold greater concentrations. The data suggest that some solid tumours may respond to cladribine therapy *in vivo*, but the concentration of drug required to kill these tumour cells may be considerably higher than the concentrations required to kill lymphoid cells.

Cladribine has been examined *in vitro* for cytotoxic effects against normal bone marrow and a number of human leukemia and lymphoma cells. In these studies, the effects of the cladribine on spontaneous thymidine uptake by 40 leukemic or 20 normal human bone marrow suspensions were monitored. Twelve of 20 acute lymphoblastic leukemia (ALL) cell suspensions bearing the common acute lymphocytic leukemia antigen (CALLA+) and 4 of 5 T and pre-T acute lymphoblastic leukemia cell preparations were more sensitive to the inhibitory effects of cladribine (ID50$\leq$5nM) than any normal bone marrow. The pre-B-cell acute lymphocytic leukemias and the acute myelocytic leukemias (AML) varied greatly in their sensitivity to cladribine (2 nM to >50 nM). These studies indicate that the CALLA-positive ALL specimens and the T and pre-T ALL specimens are significantly more sensitive to cladribine than normal bone marrow. The data suggest that cladribine inhibits the proliferation and survival of malignant T- and non-T, non-B lymphocytes at concentrations that spare normal bone marrow cells and other cell types.

Cladribine showed curative therapeutic activity (50% of mice were cured; i.e. survived >60 days) in mice bearing L1210 leukemia, when administered at 15 mg/kg every 3 hrs on days 1, 5, and 9 after tumour inoculation. Increase in the lifespan of dying mice was dose-dependent. Cladribine was most effective when administered via a multiple dosage schedule on days 1, 5, and 9 after tumour implantation. Neither single treatment nor a daily dose of 50 mg/kg over 6 days produced cures (survival beyond 60 days).

The degree of cladribine binding to plasma proteins has been investigated in normal rat (male; Sprague-Dawley), dog (female; Beagle), monkey (male; cynomolgus) and human (male; fasted, no caffeine consumption for 24 hours prior to blood donation and not on any medication) plasma. For all species, heparin was used as the anticoagulant. In humans, the degree of cladribine binding to serum proteins was also investigated. Cladribine solutions (spiked with ^{3}H-2-CdA) were added to plasma/serum to achieve concentrations of 6.1 ng, 61.1 ng or 6.1 µg/mL and dialyzed to equilibrium at 37°C.

Cladribine was minimally bound to plasma proteins in all species (~10 to 20%) at each drug concentration tested. At the same cladribine concentrations, human plasma and serum yielded similar results, indicating that the anticoagulant (heparin) did not compete with cladribine binding sites.

Nonclinical Pharmacokinetics

In Vivo: In a pilot study, female Sprague-Dawley rats had cannulas implanted in both the femoral (administration) and jugular (sampling) veins. Cladribine (spiked with ^{3}H-2-CdA) was administered, at 1 mg/kg, either by bolus (2 rats) or by a constant 1-hour infusion (2 rats). Immediately following bolus dosing, the total plasma radioactivity concentration was

~1.2 µg-eq/mL. Since this sample was drawn immediately post dose, the radiolabelled concentration is likely to equate to the cladribine concentration. In this case, cladribine would distribute into an initial volume ~0.8 L/kg. At 1 hour, circulating radioactivity concentrations were ~0.5 µg-eq/mL and remained essentially constant at that concentration for 96 hours. Following the end of the constant infusion, the plasma radioactivity concentration was ~0.6 µg-eq/mL, and, as from bolus administration, showed minimal decline over 96 hours.

Since the above concentrations are based on radioactivity measurements, it can be assumed that this elimination profile does not reflect the actual decline of cladribine from rat plasma. In man, following a 2 hour infusion, the terminal half-life of cladribine has been estimated at ~5.4 hours.

In a pilot study in rats treated with radiolabelled cladribine, approximately 41% to 44% of the administered label was recovered in the urine in the first 6 hours from a 1 mg/kg bolus or infusion. Only small amounts of radioactivity were recovered after 6 hours. Less than 1% of the administered radioactivity was excreted in the feces following a bolus dose to rats. From preliminary profiling of the 0-6 hour urine in one rat, it would appear that three of the radioactivity peaks were associated with intact cladribine, 2-CdAMP and 2-CA. Since it is recognized that 2-CA can be a degradation product of cladribine, it is possible that its detection in rat urine may be an artifact, as the samples were stored at -20°C for about 4 to 6 weeks prior to assay. Quantitatively, ~37 to 46% of the urinary radioactivity was associated with 2-CdA, which would infer that in the Sprague-Dawley rat cladribine does undergo biotransformation to some extent.

In addition, in an earlier pilot study, <1% of the administered radioactivity was excreted in the feces following bolus injection.

The metabolism of 2-chloro-2′-3′-dideoxyadenosine (2-CddA) has been investigated in mice. The total urinary excretion of unchanged CddA for 24 hours, after exposure to 24 mg/kg, was 3.4% of the delivered dose. At least two possible CddA metabolites were detected in mouse urine which did not co-elute with 2-chloro-2′-3′-dideoxyinosine, 2-CA or 2-chlorohypoxanthine.

TOXICOLOGY

Carcinogenesis and Mutagenesis

No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine. cladribine induced chromosomal effects when tested in both an *in vivo* bone marrow micronucleus assay in mice and an *in vitro* assay using CHO-WBL cells.

As expected for compounds in this class, the actions of cladribine yield DNA damage. In mammalian cells in culture, cladribine caused the accumulation of DNA strand breaks. Cladribine was also incorporated into DNA of human lymphoblastic leukemia cells. Cladribine was not mutagenic *in vitro* (Ames and Chinese hamster ovary cell gene mutation tests) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures. However, cladribine

was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test).

As expected for compounds in this class, the actions of cladribine have been shown to yield DNA damage. The mutagenicity studies are summarized below.

Table 2.5: Mutagenicitiy Studies with Cladribine

Assay	Species/Cell Line	Dose Levels	Control Groups	Results
Ames Test	*Salmonella Typhimurium strains* TA98, TA100, TA1535, TA1537, TA1538; *Escherichia coli* strain WP_2uvrA	10, 50, 100, 250, 500, and 1000 µg/plate, +/- S-9 mix	Vehicle: Saline Positives[1]: MNNG, 9-aminoacridine•HCl, 2-anthramine, sodium azide	cladribine negative for inducing mutations in bacteria
DNA Repair Assay	Primary rat hepatocyte cultures (in vitro assay)	1, 5, 10, 50, 75, 100, 150, and 200 µg/mL	Vehicle: Saline Positive: 2-AAF	cladribine negative for inducing unscheduled DNA synthesis
DNA Synthesis Inhibition	CCRF-CEM Cells (Human Lympho-blastic Cells)	0.3 µM	--[2]	cladribine incorporated into DNA; 90% reduction in DNA synthesis (0.3 µM); decreased levels of dNTPs
DNTP Imbalance; DNA Strand Breaks	Mouse mammary tumour FM3A cells (F28-7)	0.5, 1.0, 5.0, and 20.0 µM	--[2]	Intracellular dNTP imbalance; double strand DNA breaks; cell death
DNA Strand Breaks; NAD depletion	Human peripheral blood lymphocytes	0.1, 1, and 10 µM	--[2]	DNA strand breaks; inhibition of RNA synthesis; reduced intracellular NAD levels; reduced ATP pool; cell death[3]
DNA Repair Inhibition	Human peripheral blood lymphocytes	0.1, 1, 10, and 100 µM	γ-radiation	Blocked γ-radiation-induced unscheduled DNA synthesis (DNA repair)

[1] Choice of positive control dependent on strain and/or presence or absence of S-9 mix.
[2] No control groups identified
[3] Effects prevented by deoxycytidine, a competitive inhibitor of cladribine phosphorylation; nicotinamide (NAD precursor) and 3-aminobenzamide [both inhibitors of poly (ADP-ribose) synthetase] also protected the cells from cladribine toxicity.
KEY: S-9 mix = Aroclor® 1254-induced rat liver S-9 mix; MNNG = N-methyl-N-nitro-N′-nitrosoguanidine; 2-AAF = 2-acetylaminofluorene, dNTP = deoxynucleotide triphosphate

Toxicology Studies

Table 2.6: Acute Toxicity Studies with Cladribine

Strain/Species (# sex/group)	Age/Weight	Administration Route	Dose Groups	Observations	Results
Crl:CD-1® (ICR)BR, VAF/Plus® Mice (5 M,F/group)	6 wks/ M: 26 - 32 g F: 20 - 25 g	i.v.	25 mg/kg 2-CdA[a] 25 mg/kg 2-CdA + 2-chloroadenine[b] Vehicle: 0.9% NaCl	Clinical signs and symptoms. Mortality, body weight changes	No mortality. No treatment-induced signs of toxicity.
CDF1 Mice (3 or 4 F/group)	4 - 6 wks/ Wt NA	i.p.	30, 45, 60, 75, 90, 120, 150, 180, and 210 mg/kg[c] Vehicle: 0.9% NaCl	Mortality	MTD = 120 mg/kg LD_{50} = 150 mg/kg LD_{90} ≤180 mg/kg

[a] 1.0 mg/mL solution of 2-CdA in 0.9% NaCl at a dose volume of 25 mL/kg.
[b] 1.0 mg/mL 2-CdA + approximately 75 µg/mL 2-chloroadenine (breakdown product observed in clinical formulation under some storage conditions) in 0.9% NaCl at a dose volume of 25 mL/kg.
[c] Administered as a 0.1% solution in 0.9% NaCl.

KEY: wks = weeks; NA = not available; i.v. = intravenous; i.p. = intraperitoneal; MTD = maximum tolerated dose; Wt = weight.

Table 2.7: Repeated Dose Toxicity Studies with Cladribine (Subacute)

Strain/Species (# sex/group)	Age/ Weight	Duration of Trt.	Admin. Route	Dose Groups	Observations	Results
CDF1/Mice (4 F/group)	4 – 6 wks/ Wt NA	5 Days	i.p.	50, 75, 100, and 125 mg/kg/day[a] Vehicle: 0.9% NaCl	Clinical signs, mortality.	MTD = 50 mg/kg/day LD_{50} = 75 mg/kg/day $LD_{90} \leq$ 100 mg/kg/day
Cynomolgus Monkey/Macaca fascicularis (1 M/dose)	Age & Wt NA	7 - 10 Days	i.v. cont. infusion	#1: 1.0, 2.0 mg/kg/day[b] #2: 1.0 mg/kg/day (10 days)	Mortality, clinical signs, serum chemistry, necropsy and histopathology.	Moribund condition & mortality observed 2 - 3 days after end of treatment. Major signs of toxicity: anorexia, nausea & vomiting, seizures, ataxia, suppression of rapidly dividing tissues.
Cynomolgus Monkey/Macaca fascicularis (4 M,F/grp; 2 M,F/0.1 mg/kg group)	Age NA/ 1.8-4.9 kg	14 Days followed by 6-week recovery period	i.v. cont. infusion[c]	0.1, 0.3 & 0.6 mg/kg/day Vehicle: Saline	Mortality, clinical signs, body wt, food consumption, ECG, ophthalmoscopy, neurological exam, hematology & serum chemistry, FACS, necropsy and histopathology.	No mortality. Major signs of toxicity in **0.6 mg/kg/day** group: body wt loss, reduced motor activity, diarrhea in males; reduction in red & white cells (including lymphocyte & monocyte subsets). Marked suppression of proliferating tissues; cellular depletion of lymphoid tissues and bone marrow. Effects reversed following 6 weeks of recovery. **0.3 mg/kg/day** group: leukopenia. **0.1 mg/kg/day** group: no toxicity.

[a] Administered as a 0.1% solution in 0.9% NaCl.
[b] 7 days for each, separated by a 7 day recovery period
[c] Infusion rate of 7.5 mL/kg/day.
KEY: i.v. = intravenous; i.p.= intraperitoneal; wt = weight; #/group = number of animals per group; Admin. = Administration; Trt = Treatment; NA = not available; cont. = continuous; wks = weeks; M = male; F = female; ECG = electrocardiogram; Wt = weight

Table 2.8: Reproductive Toxicity Studies with Cladribine

Strain/Species (# /group)[a]	Route/Duration of Administration	Dose Groups	Observations	Results
Mouse/Crl:CD-1®(ICR)(BR) (30/group)	i.v./Days 6-15 of gestation[b]	0.5, 1.5 & 3.0 mg/kg/day Vehicle: Saline	Maternal body weight and clinical signs. Number of corporea lutea/ implantations and early/late resorptions; fetal survival, fetal weight/sex; fetal alterations.	**3 mg/kg/day:** Mean maternal body weight sign. reduced, attributed to a sign. increase in number of resorptions and concomitant reduced number of live fetuses. Increases in incidence of fetal variations and malformations. **1.5 mg/kg/day:** Increase in skeletal variations. **0.5 mg/kg/day:** No effect on fetal development.
Rabbit/New Zealand White (Hra: (NZW) SPF) (18/group)	i.v./Days 7-19 of gestation[c]	0.3, 1.0 & 3.0 mg/kg/day Vehicle: Saline	Maternal body weight, food consumption & clinical signs. Number of corporea lutea/ implantations and early/late resorptions; fetal survival, fetal weight/sex; fetal alterations.	**3 mg/kg/day:** Mean fetal weight sign. reduced. Abnormalities of head, limbs and palate. **1.0 and 0.3 mg/kg/day:** No effect on fetal development.

[a] All animals were female.
[b] Dose volume of 10 mL/kg at an infusion rate of 1 mL/min.
[c] Administered as a bolus injection in dose volume of 2.5 mL/kg.

KEY: i.v. = intravenous; sign. = significant(ly); #/group = number of animals per group

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PART III: CONSUMER INFORMATION

PrLEUSTATIN®*

cladribine for Injection

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

ABOUT THIS MEDICATION

What the medication is used for:
LEUSTATIN® is used in the treatment of patients with Hairy Cell Leukemia, which is defined by very low blood counts, associated with abnormally shaped white blood cells.

What it does:
LEUSTATIN® passively crosses the cell membrane, accumulates within cells and is believed to reduce cellular metabolism and interrupt cell division of lymphocytes and monocytes.

When it should not be used:
Do not use LEUSTATIN® if you are allergic (hypersensitive) to cladribine or any of the other ingredients in LEUSTATIN®. If you have any concerns, discuss with your doctor.

What the medicinal ingredient is:
Cladribine

What the nonmedicinal ingredients are:
Sodium chloride
The reconstituted solution may also contain benzyl alcohol.

What dosage forms it comes in:
LEUSTATIN® is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine in a single-use clear flint glass 20 mL vial. LEUSTATIN® for Injection is available in individually boxed vials.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
LEUSTATIN® should be given under the supervision of a qualified doctor experienced in the use of cancer therapy.

- Suppression of bone marrow function: This is usually reversible and appears to be related to the amount of drug given;
- Significant and prolonged drop in white blood cell count (lymphopenia);
- Severe neurotoxicity (severe weakness in the limbs) has been reported in patients receiving 4 to 9 times the dose recommended for Hairy Cell Leukemia, and rarely at the recommended dose;
- Sudden abnormal kidney function has been seen at high doses, especially when given together with other kidney-damaging drugs/treatments.

BEFORE you use LEUSTATIN®, talk to your doctor or pharmacist if:

- you have or suspect abnormal kidney or liver function;
- you are pregnant or planning to get pregnant; LEUSTATIN should not be given during pregnancy;
- you are a nursing mother; It is advised that you do not breast-feed while you are receiving LEUSTATIN;
- you are a male patient and planning to father a child.

The safety and efficacy of LEUSTATIN® have not been established in patients under 21 years of age.

Before receiving any vaccine, check with your doctor.

Contraception and Pregnancy:
Both men and women must use effective contraception while receiving LEUSTATIN®, and for 6 months after their treatment. Pregnancy should be avoided during treatment, however, if it happens you should contact your doctor immediately.

INTERACTIONS WITH THIS MEDICATION

Interactions with other drugs, food, herbs, and laboratory tests have not been established. Tell your doctor about all medications, natural health products, vitamins, herbal medicines and/or therapies you have taken or currently participate in.

Since your immune system while receiving LEUSTATIN® is suppressed, it is not recommended that you receive live attenuated vaccines while being treated.

PROPER USE OF THIS MEDICATION

Usual dose:
A dose of 0.09 mg/kg/day is given by intravenous infusion for 7 days in a row as a single course of treatment.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, LEUSTATIN® can have side effects. If you experience any of the following side effects mentioned below, contact your doctor or nurse as soon as possible. Some of these effects may be serious. However, there might be ways to reduce discomfort of these effects.

The following are side effects observed in patients at the beginning of clinical trials:

Very common (≥ 10%) side effects

- very low white blood cell count;
- fever;
- infection;
- fatigue;
- nausea;
- rash;
- headache;
- reaction at the injection site: redness, swelling, pain.

The following are side effects reported during the first 2 weeks following treatment initiation**,** regardless of relationship to drug:

Common (≥5%) side effects

Body as a Whole: Fever, chills, fatigue *(malaise)*, loss of strength *(asthenia)*, trunk pain, profuse sweating *(diaphoresis)*

Gastrointestinal System: Nausea, decreased appetite, constipation, vomiting, diarrhea, abdominal pain

Blood/Lymphatic System: purplish bruising *(purpura)*, very small reddish/purplish spotting *(petechiae)*, nose bleed *(epistaxis)*

Nervous System: headache, dizziness, inability to obtain adequate sleep *(insomnia)*

Respiratory System: cough

Skin/Subcutaneous Tissue: rash, injection site reactions, itching *(pruritus)*, pain, redness of skin *(erythema)*

Musculoskeletal System: muscle pain *(myalgia)*, joint pain *(arthralgia)*

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

Symptom / effect		Talk with your doctor immediately
Blood and Lymphatic System	**Very Common**	
	Low white blood cell count *(neutropenia)*	✓
	Low platelet count *(thrombocytopenia)*	✓
	Common	
	low red blood cell count *(anemia)*	✓
Infections	Serious infections *(e.g. sepsis)*	✓
Cardiovascular System	swelling *(edema)*	✓
	rapid beating of the heart (*tachycardia)*	✓
Respiratory System	abnormal breath sounds	✓
	abnormal chest sounds	✓
	shortness of breath	✓

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

HOW TO STORE IT

When vials and infusion solutions are stored between 2°C to 8°C protected from light, unopened vials of LEUSTATIN® are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. **DO NOT** heat or microwave. Once thawed, the vial of LEUSTATIN® is stable until expiry if refrigerated. **DO NOT** refreeze. Once diluted, solutions containing LEUSTATIN® should be administered promptly or stored in the refrigerator (2°C to 8°C) for no more than 8 hours prior to administration.

Store refrigerated between 2°C to 8°C.

Protect from light during storage.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. 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.janssen.com
or by contacting the sponsor, Janssen Inc., at:
1-800-567-3331

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