



451091B

December 2009

**Cladribine** for Injection  
Antineoplastic/Chemotherapeutic Agent

**SUMMARY PRODUCT INFORMATION**

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Liquid for injection/ 1 mg/mL	Dibasic Sodium Phosphate, USP Phosphoric Acid, USP Sodium Chloride, USP Water for Injection, USP <i>For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

**INDICATIONS AND CLINICAL USE**

Cladribine for Injection is indicated for:

- Treatment of patients with Hairy Cell Leukemia.

Cladribine for Injection 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**

Cladribine for Injection is contraindicated in those patients who are hypersensitive to this drug or any of its components. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

**WARNINGS AND PRECAUTIONS**

Serious Warnings and Precautions
<p>Cladribine for Injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.</p> <ul style="list-style-type: none"> <li>• Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent.</li> <li>• Significant and prolonged lymphopenia has been noted.</li> <li>• Serious neurological toxicity (including irreversible paraparesis and quadriparesis) has been reported in patients who received cladribine by continuous infusion at high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia).</li> <li>• Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.</li> <li>• Acute nephrotoxicity has been observed with high doses of cladribine (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies.</li> </ul>

**General**

Cladribine for Injection 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.**)

**Tumor Lysis Syndrome:** Rare cases of Tumor Lysis Syndrome have been reported in patients treated with cladribine with other hematologic malignancies having a high tumor burden.

**Administration of Cladribine for Injection:** Cladribine for Injection must be diluted in designated intravenous solutions 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.

**Hematologic**

**Bone Marrow Suppression:** Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia, has been commonly observed in patients treated with cladribine, especially at high doses. The myelosuppressive effects of cladribine 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 Cladribine for Injection. [During the first two weeks after treatment initiation, mean platelets 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.

**Hepatic/Biliary/Pancreatic**

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

**Immune**

**Fever:** Fever (T ≥ 37.8°C or 100°F) was associated with the use of cladribine 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<sup>6</sup>/L), including 62 patients (32%) with severe neutropenia (ANC ≤ 500 x 10<sup>6</sup>/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 cladribine.

**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 cladribine. 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 Cladribine for Injection 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.

**Special Populations**

**Pregnant Women:** Although there is no evidence of teratogenicity due to cladribine in humans, other drugs which inhibit DNA synthesis (e.g., methotrexate and aminopterin) have been reported to be teratogenic in humans. Cladribine has been shown to be

embryotoxic in mice when given at doses equivalent to the recommended dose. Cladribine for Injection should not be given during pregnancy. There are no adequate and well-controlled studies in pregnant women. If Cladribine for Injection is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

**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<sup>2</sup>) and increased resorptions, reduced litter size and increased fetal malformations were observed when mice received 3.0 mg/kg/day (9 mg/m<sup>2</sup>). Fetal death and malformations were observed in rabbits that received 3.0 mg/kg/day (33.0 mg/m<sup>2</sup>). No fetal effects were seen in mice at 0.5 mg/kg/day (1.5 mg/m<sup>2</sup>) or in rabbits at 1.0 mg/kg/day (11.0 mg/m<sup>2</sup>).

**Nursing Women:** It is not known whether this drug is excreted in human milk. Cladribine for Injection should not be given to a nursing mother.

**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, cladribine was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m<sup>2</sup>/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<sup>2</sup>/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 cladribine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than 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  $100 \times 10^9/L$  by Day 12, the mean absolute neutrophil count reached  $1500 \times 10^9/L$  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 Cladribine for Injection. 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 cladribine therapy. Of the 8 deaths, 6 occurred in previously treated patients who were refractory to  $\alpha$ -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.*

**Effects of High Doses:** In a Phase I investigational study using cladribine 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 cladribine for 7 to 14 days prior to bone marrow transplantation. During cladribine infusion, 8 patients experienced gastrointestinal symptoms. While the bone marrow was initially cleared of all hematopoietic elements, including tumor cells, leukemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with cladribine, 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/quadruparesis) of the upper and/or lower extremities, first noted 35 to 84 days after starting high-dose therapy with cladribine. 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 neurologic toxicity has been reported rarely following treatment with standard cladribine dosing regimens. (See **WARNINGS AND PRECAUTIONS, Neurologic and Renal.**)

**Myelosuppression:** Myelosuppression was frequently observed during the first month after starting treatment. Neutropenia ( $ANC < 500 \times 10^9/L$ ) 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  $< 20 \times 10^9/L$ ) 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, 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 cladribine 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/ $\mu$ L. The mean CD4 count nadir, which occurred 4 to 6 months following treatment, was 272/ $\mu$ L. Fifteen months after treatment, mean CD4 counts remained below 500/ $\mu$ L. 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%). Those 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.,  $\geq 40^\circ C$  or  $104^\circ F$ ). 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 cladribine, 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  $\geq 5\%$  of patients are listed in the following table.

<b>Table 1: Adverse Reactions Reported by ≥ 5% of Patients During the First 2 Weeks Following Treatment Initiation</b> (regardless of relationship to drug)	
<b>Body Systems</b>	<b>Adverse Events</b>
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%).

#### Postmarket Adverse Drug Reactions

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

**Hematologic:** Bone marrow suppression with prolonged pancytopenia, including some reports of aplastic anemia; 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 (0.03%).

**Hepatic:** Reversible, generally mild increases in bilirubin and transaminases.

**Nervous system:** Neurological toxicity; however, severe neurotoxicity has been reported rarely following treatment with standard cladribine dosing regimens.

**Respiratory system:** Pulmonary interstitial infiltrates; in most cases, an infectious etiology was identified.

**Skin/subcutaneous:** Urticaria, hypereosinophilia. 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. 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 cladribine. Caution should be exercised if Cladribine for Injection is administered before, after or in conjunction with other drugs known to cause immunosuppression or myelosuppression. (See **WARNINGS AND PRECAUTIONS**.)

### 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 cladribine 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 Cladribine for Injection 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 Cladribine for Injection 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 occur. (See **WARNINGS AND PRECAUTIONS**.)

Specific risk factors predisposing to increased toxicity from cladribine 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 cladribine. 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 Cladribine for Injection to patients with known or suspected renal or hepatic insufficiency. (See **WARNINGS AND PRECAUTIONS**.)

## Administration

### Reconstitution

**Parenteral Products:** Cladribine for Injection 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 Cladribine for Injection solutions.**

**Preparation of a Single Daily Dose:** Add the calculated dose (0.09 mg/kg or 0.09 mL/kg) of Cladribine for Injection 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 Cladribine for Injection are chemically and physically stable for at least 24 hours at room temperature under normal room fluorescent light in Baxter Viaflex™ PVC infusion containers.

<b>Table 2: 24-Hour Infusion Method</b>		
<b>Dose of Cladribine for Injection</b>	<b>Recommended Diluent</b>	<b>Quantity of Diluent</b>
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 Cladribine for Injection and the diluent should be passed through a sterile 0.22 μ disposable hydrophilic syringe filter as each solution is being introduced into the infusion reservoir. First add the calculated dose of Cladribine for Injection (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 Deltac Inc. MEDICATION CASSETTES®.

<b>Table 3: 7-Day Infusion Method</b>		
<b>Dose of Cladribine for Injection</b>	<b>Recommended Diluent</b>	<b>Quantity of Diluent</b>
7 (days) x 0.09 mg/kg	Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol)	q.s. to 100 mL
<b>N.B. – Use sterile 0.22 μ filter when preparing infusion solution</b>		

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

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of Cladribine for Injection 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 Cladribine for Injection 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 Cladribine for Injection 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 Cladribine for Injection, 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

Cladribine for Injection (also commonly known as 2-chloro-2'-deoxy- $\beta$ -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- $\beta$ -D-adenosine (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- $\beta$ -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 cladribine (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 cladribine at 0.14 mg/kg (8 patients with hematologic malignancies), the mean end-of-infusion plasma cladribine concentration was  $48 \pm 19$  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  $978 \pm 422$  mL/hr/kg and  $4.52 \pm 2.82$  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 cladribine for 5 consecutive days. Cladribine was administered as a 2-hour i.v. 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 i.v. administration with  $\alpha$  and  $\beta$  half-lives ranging from 0.24 to 2.33 hours (mean  $\pm$  SD =  $0.70 \pm 0.60$  hours) and 4.5 to 21.8 hours (mean  $\pm$  SD =  $9.9 \pm 4.6$  hours), respectively. The mean  $\pm$  SD  $C_{max}$ , clearance, and apparent volume of distribution of cladribine when the 2-hour infusion was administered as the initial dose were  $213 \pm 193$  nmol/L ( $n = 3$ ),  $29.5 \pm 8.3$  L/h/m<sup>2</sup> ( $n = 6$ ), and  $67.6 \pm 28.9$  L/m<sup>2</sup> ( $n = 6$ ), respectively. In another study, twelve patients with lymphoproliferative diseases were treated with cladribine at a dose of 0.14 mg/kg for 5 consecutive days. Cladribine was administered as a 2-hour i.v. infusion on Days 1, 3, 4 and 5 and as a 24-hour i.v. infusion on Day 2. Cladribine declined bi-exponentially after the first i.v. dose with  $\alpha$  and  $\beta$  half-lives ranging from 19 to 58 minutes (mean  $\pm$  SD =  $35 \pm 12$  minutes) and 2.8 to 12.1 hours (mean  $\pm$  SD =  $6.7 \pm 2.5$  hours), respectively. The mean  $\pm$  SD  $C_{max}$  and apparent volume of distribution of cladribine after the first i.v. dose was  $198 \pm 87$  nmol/L and  $9.2 \pm 5.4$  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 i.v. 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 - 8.1 mg/m<sup>2</sup>/day of cladribine. Other investigators reported an 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<sup>2</sup>/day of cladribine in patients with solid tumours and during 5-day 2-hour intravenous infusion of 6 - 12 mg/m<sup>2</sup>/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 and 8°C (36 to 46°F) protected from light, unopened vials of Cladribine for Injection 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 Cladribine for Injection is stable until expiry if refrigerated. **Do not** refreeze. Once diluted, solutions containing Cladribine for Injection should be administered promptly or stored in the refrigerator (2 to 8°C) for no more than 8 hours prior to administration.

Store refrigerated between 2 and 8°C (36 to 46°F).

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 Cladribine for Injection. The use of disposable gloves and protective garments is recommended. If Cladribine for Injection 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.

Cladribine for Injection 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 Cladribine for Injection solutions.**

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Composition:

#### Cladribine for Injection 1 mg/mL

Each mL of solution contains: 1 mg of the active ingredient, cladribine and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. May contain phosphoric acid and/or dibasic sodium phosphate for pH adjustment.

### Availability of Dosage Forms:

Cladribine for Injection is available in the following form and package size:

C104010 **Cladribine for Injection 1 mg/mL:** Each mL of solution contains: cladribine, 1 mg. Each vial of Cladribine for Injection contains 10 mL of solution and is available in 20 mL clear flint glass vials for single-use, packaged individually in cartons.

Vial stoppers do not contain any natural rubber latex.

<sup>†</sup>Viaflex containers, manufactured by Baxter Healthcare Corporation

<sup>\*</sup>MEDICATION CASSETTES<sup>®</sup> (available in Canada through SIMS Canada Ltd)

## PHARMACEUTICAL PARTNERS OF CANADA INC.

Richmond Hill, ON L4B 3P6

☎ 1-877-821-7724