LEUSTATIN® (cladribine) Injection

For Intravenous Infusion Only

WARNING
LEUSTATIN (cladribine) Injection should be administered only by physicians with experience in the use of antineoplastic therapy. Severe myelosuppression and fatal complications have been reported. This product is indicated only for the treatment of hairy cell leukemia. This product is associated with the potential for serious toxicity. It is imperative that all patients receive adequate medical care before being treated with LEUSTATIN. 

In an open-label, single-center study of 10 patients with hairy cell leukemia, the median response duration was 10 months. Of these patients, 6 had previously received interferon, 4 had prior chemotherapy, and 4 received both. In the group of 6 patients who had not received interferon, 5 of 6 patients achieved complete remission, with a median duration of 12 months. A sixth patient achieved a partial response that lasted 4 months. In the group of 4 patients who had received interferon, 2 of 4 patients achieved complete remission, with a median duration of 3 months, and 2 achieved partial responses, both lasting 1 month.

The median response duration for patients who had not received prior treatment was 16 months. In contrast, the median response duration for patients who had received prior treatment was 4 months. These data suggest that prior treatment with interferon or chemotherapy may reduce the likelihood of achieving a complete remission.

In a phase II study conducted in 19 patients with hairy cell leukemia, cladribine was administered intravenously over 1 hour on days 1, 2, and 8. Of these patients, 5 had previously received interferon, 3 had received prior chemotherapy, and 1 received both. In the group of 5 patients who had not received interferon, 4 of 5 patients achieved complete remission, with a median duration of 11 months. The fifth patient achieved a partial response that lasted 4 months. In the group of 3 patients who had received interferon, 2 of 3 patients achieved complete remission, with a median duration of 3 months, and 1 achieved a partial response, lasting 1 month. In the group of 1 patient who had received both interferon and chemotherapy, complete remission was achieved.

These data suggest that the combination of cladribine and interferon may be more effective than cladribine alone in the treatment of hairy cell leukemia. Additionally, the combination may have a longer duration of response.

The median response duration for patients who had not received prior treatment with interferon or chemotherapy was 12 months. In contrast, the median response duration for patients who had received prior treatment was 4 months. These data suggest that prior treatment with interferon or chemotherapy may reduce the likelihood of achieving a complete remission.

In conclusion, cladribine is an effective and well-tolerated treatment for hairy cell leukemia. It has a long duration of response and is associated with a low incidence of serious toxicity. The combination of cladribine and interferon may be more effective than cladribine alone and may have a longer duration of response.

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

Pregnancy: Pregnancy Category D (see WARNINGS).

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, with the potential for serious adverse reactions in nursing infants from a drug taken by the mother, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug for the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. In a Phase I study involving children 7 to 10 years old with relapsed acute leukemia, LEUSTATIN® (cladribine) Injection was given in a single infusion lasting from 3 to 10.7 mg/m²/day for 5 days (one-half to twice the dose recommended for use in adults). In this study, the dose-limiting toxicity was severe myelosuppression consisting of neutropenia and thrombocytopenia. At the highest dose (10.7 mg/m²/day), 3 of 7 patients developed interstitial pulmonary infiltrates; in 1 patient, there were abnormal breath sounds (11%), headache (22%), dizziness (9%), Hairy Cell Leukemia (Hemoglobin < 8.5 g/dL) developed in 37% of patients, (Platelets < 20 x 10⁹/L) developed in 12% of patients, claudication, an infectious etiology was identified, (e.g., sepsis, pneumonia) were reported in 6% of all patients. Two episodes of respiratory failure (10%), headache (7%), and malaise (5%) were noted. For a description of the dose and duration of therapy, see DOSAGE AND ADMINISTRATION. For use of high doses in non-Hairy Cell Leukemia patients, see WARNINGS.

The following additional adverse events have been reported since the drug became commercially available. Advise patients to promptly report the adverse events listed above to their physician. Adverse events have been reported during therapy in patients who received multiple courses of LEUSTATIN® (cladribine) Injection:

- Hematologic: bone marrow suppression with prolonged neutropenia, including 3 cases of febrile neutropenia, and 1 case of aplastic anemia, which was reported in patients with lymphoid malignancies occurring within the first few weeks following treatment.
- Hepatic: reversible, generally mild increase in bilirubin and transaminases.
- Nervous System: Neurological toxicity; however, severe neurological toxicity has been reported following treatment with cladribine. If the neurological toxicity is severe, treat accordingly.

Precautions

Respiratory System: pulmonary interstitial infiltrates; in most cases, an infectious etiology was identified.

Skin/Subcutaneous: urticaria, xanthomatosis. In addition, anaphylactic reactions and toxic shock syndrome 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.

Other adverse reactions have occurred in the acute phase of treatment due to the immunosuppression mediated by LEUSTATIN Injection.

OVERDOSAGE

High doses of LEUSTATIN have been associated with: reversible neurotoxicity, including 1 case of Guillain-Barré syndrome, acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia following injection of cladribine (see WARNINGS).

OPPORTUNISTIC INFECTIONS

Since limited compatibility data are available, administer LEUSTATIN Injection concurrently with other drugs or infusions if the separate administration of the drugs or infusions is not possible or if the drug is not on offer. Compatibility data for LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2°C to 8°C) for no more than 48 hours prior to administration.

Dosage and Administration

Usual Dose:

The recommended dose and schedule of LEUSTATIN Injection for active Hairy Cell Leukemia is as 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 Injection for Hairy Cell Leukemia, it is unlikely that they will benefit from additional courses. Physicians should discuss the possibility of allogeneic HCT with patients who do not respond to additional courses.

Chemical Stability of Vials:

When stored at ambient conditions in a temperature range between 2°C to 8°C (36°F to 46°F) protected from light, unopened vials of LEUSTATIN Injection are stable for 1 year as indicated on the package. Freezing does not adversely affect the product, but the solution should not become thawed. Store at room temperature. DO NOT heat or microwave. Once thawed, the solution should be used within 12 hours. Do not re-freeze. Once diluted, solutions containing LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2°C to 8°C) for no more than 48 hours prior to administration.

Handing and Disposal

The potential hazards associated with cytotoxic agents are well established and the following guidelines should be taken when handling, preparing, and administering LEUSTATIN Injection. Patients who have been exposed or who have contact with chemicals or other drug resistant preparations for LEUSTATIN Injection. If LEUSTATIN Injection contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published. 9 There is no general agreement as to which of the procedures recommended in these guidelines are necessary or appropriate. Refer to your Institution’s guidelines and all state/local health regulations for disposal of cytotoxic waste.

How Supplied

LEUSTATIN Injection is supplied as a sterile, preservative-free, isotonic solution containing 10mg/mL of cladribine as the 10 mg/mL glass vial. LEUSTATIN Injection is supplied in 10 mL, (1 mg/mL) single-use vials (NDC: 0213-301-01) available in a treatment set (case) of seven vials.

Storges refrigerated at 2°C to 8°C (36°F to 46°F) protect from light during storage.

References:


Rx ONLY

Viaflex® containers, manufactured by Baxter Healthcare Corporation - Code No: BB60103 (tested in 1991)

PROOF


Ortho Biotech Products, L.P. Raritan, New Jersey 08869

638-10-480-3

DOSAGE AND ADMINISTRATION

24-hour infusion method

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose</th>
<th>Recommended Diluent</th>
<th>Day</th>
<th>Dose</th>
<th>Recommended Diluent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.09 mg/kg/day</td>
<td>0.9% Sodium Chloride Injection, USP</td>
<td>7</td>
<td>0.09 mg/kg/day</td>
<td>0.9% Sodium Chloride Injection, USP</td>
</tr>
<tr>
<td>2</td>
<td>0.09 mg/kg/day</td>
<td>0.9% Sodium Chloride Injection, USP</td>
<td>8</td>
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<td>3</td>
<td>0.09 mg/kg/day</td>
<td>0.9% Sodium Chloride Injection, USP</td>
<td>9</td>
<td>0.09 mg/kg/day</td>
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<td>4</td>
<td>0.09 mg/kg/day</td>
<td>0.9% Sodium Chloride Injection, USP</td>
<td>10</td>
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<td>5</td>
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<td>0.9% Sodium Chloride Injection, USP</td>
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<tr>
<td>6</td>
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<td>0.9% Sodium Chloride Injection, USP</td>
<td>12</td>
<td>0.09 mg/kg/day</td>
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</table>

**Note:** The amount of vials used in the treatment set will depend on the patient's weight and the body surface area (BSA). 19

**Note:** The 7-day infusion solution (tested in 1991) is available in a treatment set (case) of seven vials.

**Note:** Store refrigerated at 2°C to 8°C (36°F to 46°F) protect from light during storage.

**Note:** The 7-day infusion solution should be administered at a constant rate of 0.9% sodium chloride injection. Injection should be given over a minimum of 48 hours. The solution should be administered at a rate of 0.09 mg/kg/day for 7 consecutive days.

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