NEW ZEALAND DATA SHEET

1. LEUSTATIN® 1 mg/mL solution for infusion

LEUSTATIN® 1 mg/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LEUSTATIN 1 mg/mL solution for infusion is available in single-use vials containing 10 mg (1 mg/mL) of cladribine in 10 mL of solution, for dilution and subsequent infusion.

The solution also contains 9 mg/mL (0.15 mEq) of sodium chloride.

Phosphoric acid and/or dibasic sodium phosphate may also have been added to adjust the pH to 6.3 ± 0.6.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

LEUSTATIN Injection is a clear, colourless, sterile, preservative-free, buffered isotonic solution, supplied in a single-use, flint glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LEUSTATIN is indicated in the treatment of patients with hairy cell leukaemia (HCL).

LEUSTATIN injection is also indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent-containing regimen.

4.2 Dosage and method of administration

HCL: The recommended treatment for hairy cell leukaemia is a single course given by continuous intravenous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day (3.6 mg/m^2/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 leukaemia, it is unlikely that they will benefit from additional courses. (However, limited experience indicates that additional courses may be beneficial in patients who relapse after an initial response to LEUSTATIN Injection).

CLL: In patients with CLL, the recommended treatment consists of a continuous infusion of LEUSTATIN injection for 2 hours on days 1 to 5 of a 28 day cycle at a dose of 0.12 mg/Kg/day (4.8 mg/m^2/day). It is recommended that LEUSTATIN injection be administered in responding patients up to a maximum of 6 monthly cycles, and that non-responding patients receive no more than two cycles of treatment.

Preparation and Administration of Intravenous Solutions:

LEUSTATIN injection must be diluted with the designated diluent prior to administration. Since this agent does not contain any anti-microbial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of LEUSTATIN injection solutions.

Should the medicine accidentally be given extravenously, local tissue damage is unlikely. If extravasation occurs, the administration should be stopped immediately and restarted in another vein. Other recommended local measures include elevating the arm and applying an ice pack to reduce swelling.

HCL:

To prepare a single daily dose:

LEUSTATIN injection should be passed through a sterile 0.22µm disposable hydrophilic syringe filter prior to introduction into the infusion bag, prior to each daily infusion.

Add the calculated dose (0.09 mg/kg or 0.09 mL/kg) of LEUSTATIN injection through the sterile filter 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 injection are chemically and physically stable for at least 24 hours at room temperature under normal room fluorescent light in most commonly available PVC infusion containers. Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised.

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 minimise the risk of microbial contamination, both LEUSTATIN Injection and the diluent should be passed through a sterile 0.22 µm disposable hydrophilic syringe filter as each solution is being introduced into the infusion reservoir. First add the calculated dose of LEUSTATIN Injection (7 days x 0,09 mg/kg or mL/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 averaging 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 the SIMS Deltec MEDICATION CASSETTE™ Reservoir.

CLL:

Preparation of a Single Daily Dose: LEUSTATIN injection should be passed through a sterile 0.22µm disposable hydrophilic syringe filter prior to introduction into the infusion bag, prior to each daily infusion. Add the calculated dose (0.12 mg/Kg or 0.12 mg/mL of LEUSTATIN Injection through the sterile filter to an infusion bag containing 100 mL or 500 mL of 0,9% Sodium Chloride, USP, infuse continuously over 2 hours. Repeat daily for a total of 5 consecutive days, the use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine.

4.3 Contraindications

LEUSTATIN is contraindicated in those patients who are hypersensitive to this agent or any of its components.

LEUSTATIN is contraindicated during pregnancy and lactation and for 6 months after the last cladribine dose.

4.4 Special warnings and precautions for use

WARNINGS

Progressive Multifocal Leukoencephalopathy (PML)

Cases of Progressive Multifocal Leukoencephalopathy (PML) including fatal ones have been reported following the use of LEUSTATIN. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded (see Section 4.8).

Bone Marrow Suppression

Suppression of bone marrow function, including neutropenia, anaemia, and thrombocytopenia, should be anticipated. This is usually reversible and appears to be dose dependent, although prolonged lymphopenia up to 5 years following treatment has been reported. In clinical trials, during the first two weeks after treatment initiation mean platelet count, absolute neutrophil count (ANC), and haemoglobin concentration declined and

then subsequently increased with normalisation of mean counts by Day 15, Week 5 and Week 8, respectively. The myelosuppressive effects of LEUSTATIN were most notable during the first month following treatment. Careful haematologic monitoring, especially during the first 4 to 8 weeks after treatment with LEUSTATIN injection is recommended. Proceed carefully in patients with severe bone marrow impairment of any aetiology since further suppression of bone marrow function should be anticipated (see Sections 4.4 - Laboratory Tests and 4.8).

Due to the prolonged immunosuppression associated with the use of nucleoside analogues like LEUSTATIN, secondary malignancies are a potential risk. Primary haematological malignancies are also a risk factor for secondary malignancies.

HCL

During the first two weeks after treatment initiation, mean platelet count, ANC, and haemoglobin concentration declined and subsequently increased with normalisation of mean counts by Day 15, Week 5 and Week 8, respectively. The myelosuppressive effects of LEUSTATIN were most notable during the first month following treatment. 44% of patients received transfusions with RBCs and 14% received transfusions with platelets during Month 1. Careful haematological monitoring, especially during the first 4 to 8 weeks after treatment with LEUSTATIN injection, is recommended. (see Section 4.4).

CLL

During the first two cycles of LEUSTATIN Injection therapy, haemoglobin concentration, platelet count and absolute neutrophil count declined to a nadir usually observed in cycle 2. There appeared to be no cumulative toxicity upon administration of further cycles of therapy. Careful haematological monitoring is recommended throughout administration of LEUSTATIN injection treatment.

Serious Skin Reactions

An increased incidence of serious skin reactions (Stevens-Johnson syndrome (SJS) (see Section 4.8), toxic epidermal necrolysis (TEN), erythema multiforme, acute generalized exanthematous pustulosis) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome has been observed in patients receiving LEUSTATIN when administered concomitantly with antimicrobials and other drugs known to be associated with severe skin reactions (e.g., trimethoprim-sulfamethoxazole, allopurinol). It is recommended that patients be informed about the signs of serious skin reactions, and that use of LEUSTATIN be discontinued at the first appearance of rash indicative of a serious skin reaction.

Neurotoxicity

Serious neurological toxicity (including irreversible paraparesis and quadraparesis) has been reported in patients who receive LEUSTATIN Injection by continuous infusion at high doses (4 to 9 times the recommended dose for hairy cell leukemia). Neurological toxicity appears to demonstrate a dose relationship; however, severe neurological toxicities have been rarely reported with the recommended dose. Physicians should consider delaying or discontinuing therapy if neurotoxicity occurs.

Fever/Infection

HCL

In clinical trials, fever was associated with the use of LEUSTATIN Injection in approximately 72% (89/124) of patients. Most febrile episodes occurred during the first month and were not associated with documented infection.

CLL

Pyrexia was reported in 22-24% of CLL patients during Cycle 1 of LEUSTATIN Injection therapy, and in less than 3% of patients during subsequent cycles. Forty of 123 patients (32.5%) reported at least one infection during Cycle 1 Infections that occurred in 5% or more were: respiratory infection/inflammation (8.9%), pneumonia (7.3%), bacterial infection (5.7%) and viral skin infections 5.7%). Approximately 70% of patients had at least one infection during the overall study period of 6 years, including treatment and follow-up.

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. Febrile events should be investigated with appropriate clinical diagnostic tests. Practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections. Since fever may be accompanied by increased fluid toss, patients should be kept well hydrated (see Section 4.8).

Fever (T > 37.8°C) 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) including 62 patients (32%) with severe neutropenia (i.e. ANC > 600).

Rare cases of tumour lysis syndrome have been reported in patients treated with cladribine with other hematologic malignancies having a high tumour burden.

Effect on Renal and Hepatic Function

Acute renal insufficiency has developed in some patients receiving high doses of LEUSTATIN injection. As there are inadequate data on dosing of patients with renal or hepatic insufficiency, caution is advised when administering the drug to such patients. As with other potent chemotherapeutic agents, monitoring of renal and hepatic function should be performed as clinically indicated, especially in patients with underlying kidney or liver dysfunction. Physicians should consider delaying or discontinuing therapy if renal toxicity occurs (see Sections 4.8 and 4.9).

In a Phase I investigational study using LEUSTATIN, high doses (4 to 9 times the recommended dose for hairy cell leukaemia) as part of a bone marrow transplant conditioning regimen which included high dose cyclophosphamide and total body irradiation, acute nephrotoxicity and delayed onset neurotoxicity were observed. 31 poor-risk patients with drug-resistant acute leukaemia in relapse (29 cases) or non-Hodgkin's lymphoma (2 cases) received LEUSTATIN for 7 to 14 days prior to bone marrow transplantation. During infusion, 8 patients experienced gastrointestinal symptoms.

While the bone marrow was initially cleared of all haematopoietic elements, including tumour cells, leukaemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with LEUSTATIN, 6 patients (19%) developed manifestations of renal dysfunction (e.g. 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. 11 patients (35%) experienced delayed onset neurological toxicity. In the majority, this was characterised by progressive irreversible motor weakness (paraparesis/quadraparesis), 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. Severe neurological toxicity has also been noted with high doses of another agent in this class.

In patients with hairy cell leukaemia treated with the recommended treatment regimen (0.09 mg/kg/day for 7 consecutive days), there have been no reports of similar nephro- or neurological toxicities. Mild neurological toxicities, specifically paraesthesias and dizziness, have been reported rarely.

Of the 196 hairy cell leukaemia patients entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious aetiology, including 3 with pneumonia, and 2 occurred in the first month following LEUSTATIN therapy. Of the 8 deaths, 6 occurred in previously treated patients who were refractory to alpha interferon.

PRECAUTIONS

General

LEUSTATIN 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 haematological and non-haematological toxicity. Periodic assessment of peripheral blood counts, particularly during the first 4 to 8 weeks post-treatment, is recommended to detect the development of anaemia, neutropenia and thrombocytopenia and for early detection of any potential sequelae (e.g. infection or bleeding).

The weight of evidence suggests that a patient with CLL whose disease has progressed while treated with fludarabine is unlikely to respond to treatment with LEUSTATIN Injection and therefore use in such a patient is not recommended.

Serious (e.g. respiratory infection, pneumonia and viral skin infections), including fatal infections (e.g. sepsis) were reported. (see Section 4.8)

Patients with active infections should be treated for these underlying conditions prior to receiving LEUSTATIN Injection therapy. Patients who are or become Coombs' positive should be monitored carefully for potential haemolysis.

Allopurinol and adequate hydration should be considered for patients with initially high WBC, to alleviate potential tumour lysis syndrome side effects of therapy.

Patients should be monitored closely for infections. Those presenting with herpes infections should be treated with acyclovir.

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 Sections 4.4 and 4.8).

Fever was a frequently observed side effect during the first month on study. 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 Sections 4.4 and 4.8).

The kidney has not been established as the organ of excretion for LEUSTATIN. There are inadequate data on dosing of patients with renal or hepatic insufficiency. Development of acute renal insufficiency in some patients receiving high doses of LEUSTATIN has been described. Until more information is available, caution is advised when administering the medicine to patients with known or suspected renal or hepatic insufficiency (see Section 4.4).

Rare cases of tumour lysis syndrome have been reported in patients with haematological malignancies having a high tumour burden.

LEUSTATIN injection must be diluted in designated intravenous solutions prior to administration (see Section 4.2).

Laboratory Tests

During and following treatment, the patient's haematological profile should be monitored regularly to determine the degree of haematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the mean platelet count reached 100 x 10^9/L by Day 12, the mean absolute neutrophil count reached 1500 x 10^6/L by Week 5 and the mean haemoglobin reached 12 g/dL by Week 8. After peripheral counts have normalised, bone marrow aspiration and biopsy should be performed to confirm response to treatment with LEUSTATIN. Febrile events should be investigated with appropriate laboratory and radiological studies. Periodic assessment of renal function and hepatic function should be performed as clinically indicated.

Paediatric population

Safety and effectiveness in children has not been established. In a Phase I study involving patients 1 to 21 years old with relapsed acute leukaemia, 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 leukaemia). 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 Section 4.4).

4.5 Interactions with other medicines and other forms of interaction

There are no known medicine interactions with LEUSTATIN. Caution should be exercised if LEUSTATIN is administered following or in conjunction with other agents known to cause myelosuppression. Caution is also necessary when using LEUSTATIN in combination with other agents which interfere with DNA synthesis as these interactions have not been examined and could be potentially significant. (see Section 4.4 for further information). 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 injection.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D

LEUSTATIN is contraindicated in pregnancy. Women of childbearing potential must use effective contraception during treatment with LEUSTATIN and for 6 months after the last LEUSTATIN dose. If LEUSTATIN Injection

is used during pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be appraised of the potential hazard to the foetus.

LEUSTATIN Injection is teratogenic in mice and rabbits. [A significant increase in fetal variations was observed in mice receiving 1.5 mg/kg/day (4.5 mg/m^2, a dose approximately equivalent to the recommended dose in humans of 3.6 mg/m^2). 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 adverse 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).]

There are no adequate and well controlled studies in pregnant women.

Breast-feeding

Limited data from case reports have shown that cladribine is excreted in human milk. The quantity is not yet well established. Because of the potential for serious adverse reactions in nursing infants, lactation is contraindicated during treatment with cladribine and for 6 months after the last cladribine dose.

Fertility

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 Injection should be advised not to father a child up to 6 months after the last LEUSTATIN dose.

4.7 Effects on ability to drive and use machines

Given the patient's underlying medical condition, caution should be exercised when a patient is performing activities requiring substantial physical well-being while using LEUSTATIN injection.

4.8 Undesirable effects

a. Summary of the safety profile

Bone Marrow Suppression:

HCL (data based on a subset of 124 patients enrolled in K90-091):

Myelosuppression was frequently observed during the first month after starting treatment with LEUSTATIN Injection. Neutropenia (ANC less than 500 x 10^6/L)) was noted in 69 % of patients, [compared with 25 % in whom it was present initially]. Severe anaemia (haemoglobin less than 8.5 g/dL) occurred in 41% of patients, [compared with 12% initially] and thrombocytopenia (platelets less than 20 x 10^9/L) occurred in 15% of patients [compared to 5 % in whom it was noted initially]. [Forty three percent (43%) of patients received transfusions with RBCs and 13% received transfusions with platelets during month 1].

Treatment with cladribine is associated with prolonged depression of CD4 lymphocyte counts and transient suppression of CD8 lymphocyte counts. [In a follow-up of 78 of the 124 patients enrolled in the clinical trials, prior to treatment the 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 the mean CD4 count remained below 500/µl, Although CD8 counts decreased initially, increasing counts were observed by 9 months.] The clinical significance of the prolonged CD4 lymphopenia is unclear.

Prolonged bone marrow hypocellularity (< 35%) was observed. [It is not known whether the hypocellularity is the result of disease related marrow fibrosis or LEUSTATIN injection toxicity.

CLL (data based on a subset of 124 patients enrolled in L91-999):

Patients with CLL treated with LEUSTATIN injection were more severely myelosuppressed prior to therapy than HCL patients: increased myelosuppression was observed during Cycle 1 and Cycle 2 of therapy, reaching a nadir during Cycle 2.

The percentage of patients having a haemoglobin level below 8.5 g/dL was 16.9% at baseline, 37.9% in Cycle 1, and 46.1% in Cycle 2. The percentage of patients with platelet counts below 20 x 10(9)/L was 4.0% at baseline, 20.2% during Cycle 1, and 22.5% during Cycle 2.

Absolute neutrophil count was below 500 x 10^6/L in 18,5 % of patients at baseline, 56.5% in Cycle 1, 61.8% in Cycle 2, 59.3% in Cycle 3 and 55.9% in Cycle 4. There appeared to be no cumulative toxicity upon administration of multiple cycles of therapy. Marked blood chemistry abnormalities noted during the study were

pre-existing, or were isolated abnormalities, which resolved, or were associated with death due to the underlying disease.

Fever/Infection:

HCL (data based on a subset of 124 patients enrolled in K90-091):

Fever was a frequently observed adverse event during the first month on study. [During the first month, 12% of patients experienced severe fever (i.e. greater than or equal to 40°C).] [Of the 124 patients studied, 11 were noted to have a documented infection in the month prior to treatment.] 31% of febrile patients had a documented infection: [13.7% of patients had bacterial infections, 6.5% had viral and 6.5% had fungal infections, Seventy percent (70%) of these patients were treated empirically with antibiotics].

Serious, including fatal, infections (septicaemia, pneumonia) were reported in 7% of all patients, [During the second month, the overall rate of documented infection was 8%; these infections were mild to moderate and no sever 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 Injection therapy].

[Of the 124 hairy cell leukaemia patients entered in the two trials, there were 6 deaths following treatment; one death was due to infection, two to underlying cardiac disease, and two to persistent hairy cell leukaemia with infectious complications. One patient died of progressive disease after receiving additional treatment with another chemotherapeutic agent].

CLL (data based on a subset of 124 patients enrolled in L91-999):

During Cycle 1, 23.6% of patients experienced pyrexia, and 32.5% experienced at least one documented infection. Infections that occurred in 5% or more of the patients in Cycle 1 were: respiratory infection/inflammation (8.9%), pneumonia (7.3%), bacterial infection 5.6%, and viral skin infections (5.7%). In Cycles 2 through 6, 71.3% of the patients had at least one infection. Infections that occurred in 10% or more of patients were: pneumonia (28.7%), bacterial infection (21.8%), viral skin infection (20.8%), upper respiratory infection (12.9%), other intestinal infection/inflammation (12.9%), oral candidiasis (11.9%), urinary tract infection (11.9%), and other skin infections (11.9%), Overall, 72.4% of the patients had at least one infection during LEUSTATIN injection therapy. Of these, 32.6% had been administered concomitant immunosuppressive therapy (prednisone).

Post-marketing Experience

The following additional adverse reactions have been reported since the drug became commercially available. Frequencies presented between brackets are derived from clinical trial data. These adverse reactions have been reported primarily in patients who received multiple courses of LEUSTATIN injection:

Infections and infestations:
Septic shock (common). Opportunistic infections (uncommon) have occurred in the acute phase of treatment; Progressive multifocal leukoencephalopathy (not known)

Blood and lymphatic system disorders:
Bone marrow suppression with prolonged pancytopenia (uncommon), including some reports of aplastic anaemia (uncommon); haemolytic anaemia (including autoimmune haemolytic anaemia) (common), which was reported in patients with lymphoid malignancies, occurring within the first few weeks following treatment; hypereosinophilia (uncommon). Rare cases of myelodysplastic syndrome (common) have been reported.

Immune system disorders:
Hypersensitivity (common)

Metabolism and nutrition disorders:
Tumour lysis syndrome (uncommon).

Psychiatric disorders:
Confusion (including disorientation) (common).

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

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

Eye disorders:
Conjunctivitis (common).

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

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

Skin and tissue disorders:
Urticaria (common), Steven-Johnson syndrome (uncommon).

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

b. Tabulated list of adverse reactions

Clinical Trials Experience

HCL:

Adverse drug reactions reported by ≥ 1% of LEUSTATIN-treated patients with HCL noted in the HCL clinical dataset (studies K90-091 and L91-048, n=576) are shown in **Table 1**.

Table 1: Adverse Drug Reactions in ≥ 1% of Patients Treated with LEUSTATIN in HCL Clinical Trials

System Organ Class Preferred Term	**LEUSTATIN (n=576)** **%**
Blood and Lymphatic System Disorder	
Anaemia	1
Febrile neutropenia	8
Psychiatric Disorders	
Anxiety	1
Insomnia	3
Nervous System Disorders	
Dizziness	6
Headache	14
Cardiac Disorders	
Tachycardia	2
Respiratory, Thoracic and Mediastinal Disorders	
Breath sounds abnormal	4
Cough	7
Dyspnoea*	5
Rales	1
Gastrointestinal Disorders	
Abdominal pain**	4
Constipation	4
Diarrhea	7
Flatulence	1
Nausea	22
Vomiting	9
Skin and Subcutaneous Tissue Disorders	
Ecchymosis	2
Hyperhidrosis	3
Petechiae	2
Pruritus	2
Rash***	16
Musculoskeletal, Connective Tissue, and Bone Disorders	
Arthralgia	3

System Organ Class Preferred Term	LEUSTATIN (n=576) %
Myalgia	6
Pain****	6
General Disorders and Administration Site Conditions	
Administration site reaction*****	11
Asthenia	6
Chills	2
Decreased appetite	8
Fatigue	31
Malaise	5
Muscular weakness	1
Oedema peripheral	2
Pyrexia	33
Injury, Poisoning and Procedural Complications	
Contusion	1

* Dyspnoea includes dyspnoea, dyspnoea exertional and wheezing

** Abdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain (lower and upper)

*** Rash includes erythema, rash, and rash macular, macula-papular, papular, pruritic, pustular and erythematous

**** Pain includes pain and back pain, chest pain, arthritis pain, bone pain, and pain in extremity

***** Administration site reactions includes administration site reaction, Catheter site cellulitis, erythema, haemorrhage, and pain, infusion site reaction, erythema, edema, and pain)

The following safety data are based on a subset of 124 patients with hairy cell leukaemia that were enrolled in the pivotal studies (K90-091). In the first month, severe neutropenia was noted in 70% of patients and infection in 31% of patients. Fever was noted in 72% of patients. Most non-haematologic adverse experiences were mild to moderate in severity.

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.

The majority of rashes were mild.

CLL:

Adverse reactions reported by ≥ 1% of LEUSTATIN-treated patients with CLL noted in the CLL clinical trial dataset (studies L91-999 and L091-048, n=266) are shown in **Table 2**.

Table 2: Adverse Drug Reactions in ≥ 1% of Patients Treated With LEUSTATIN in CLL Clinical Trials

System/Organ Class Preferred Term	LEUSTATIN (n=266) %
Infections and Infestations	
Bacteraemia	2
Cellulitis	2
Localised infection	1
Pneumonia	7
Blood and Lymphatic System Disorder	
Anaemia	1
Thrombocytopenia (with bleeding or petechiae)	6
Nervous System Disorders	
Headache	11
Vascular Disorders	
Phlebitis	5
Respiratory, Thoracic and Mediastinal Disorders	

System/Organ Class Preferred Term	LEUSTATIN (n=266) %
Breath sounds abnormal	4
Cough	8
Dyspnoea*	8
Rales	1
Gastrointestinal Disorders	
Diarrhea	5
Nausea	9
Vomiting	3
Skin and Subcutaneous Tissue Disorders	
Hyperhidrosis	6
Purpura	1
Rash**	7
Musculoskeletal, Connective Tissue, and Bone Disorders	
Pain***	6
General Disorders and Administration Site Conditions	
Administration site reaction****	21
Asthenia	5
Crepitations	1
Fatigue	22
Localised oedema	1
Muscular weakness	1
Oedema peripheral	6
Oedema	3
Pyrexia	28

* Dyspnoea includes dyspnoea and dyspnoea exertional

** Rash includes rash (macula-papular, pruritic, pustular) and erythema

*** Pain includes pain, arthralgia, back pain, bone pain, musculoskeletal pain and pain in extremity

**** Administration site reactions includes administration site reaction, catheter site (erythema and infection) and infusion site (cellulitis, erythema, irritation, oedema, pain, infection and phlebitis)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

High doses of LEUSTATIN have been associated with: irreversible neurological toxicity (paraparesis/quadraparesis), acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia, anaemia and thrombocytopenia. (see Section 4.4).

Treatment

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, purine analogues, ATC code: L01BB04

Mechanism of action

LEUSTATIN is a synthetic antineoplastic agent. The selective toxicity of 2-chloro-2'-deoxy-ß-D-adenosine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase, deoxynucleotidase and adenosine deaminase. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, 2-chloro-2'-deoxy-ß-D-adenosine, a purine nucleoside analog, passively crosses the cell membrane. It is phosphorylated by deoxycytidine kinase to 2-chloro-2'-deoxy-ß-D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2'deoxy-ß-D-adenosine is resistant to deamination by adenosine deaminase and there is little deoxynucleotide deaminase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2'-deoxy-ß-D-adenosine triphosphate (2-CdATP.) It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2'-deoxy-ß-D-adenosine 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. LEUSTATIN 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.

5.2 Pharmacokinetic properties

Distribution

In one study of 17 patients with hairy cell leukaemia and normal renal function, the mean steady-state serum cladribine concentration was estimated to be approximately 5.7 ng/mL with a systemic clearance of approximately 663.5 mL/h/kg when LEUSTATIN Injection was given by continuous infusion at 0.09 mg/kg/day over 7 days.

Plasma concentrations are reported to decline multi-exponentially after intravenous infusions with terminal half-lives ranging from approximately 3-22 hours. In general, the apparent volume of distribution of cladribine is very large (mean approximately 9 L/kg), indicating an extensive distribution of cladribine in body tissues. The mean half-life of cladribine in leukaemic cells has been reported to be 23 hours.

Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 25% of those in plasma.

Cladribine is bound approximately 20% to plasma proteins.

Elimination

There is little information available on the metabolism or route of excretion of cladribine in man. An average of 18% of the administered dose has been reported to be excreted in urine of patients with solid tumors during a 5 day continuous intravenous infusion of 3.5-8.1 mg/m^2/day of LEUSTATIN. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

5.3 Preclinical safety data

Carcinogenicity

No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine.

Genotoxicity

As expected for compounds in this class, the actions of cladribine have been shown to yield DNA damage. In mammalian cells in culture, cladribine has been shown to cause an imbalance of intracellular

deoxyribonucleotide triphosphate pools. This imbalance results in the inhibition of DNA synthesis and DNA repair, yielding DNA strand breaks and subsequently cell death. Inhibition of thymidine incorporation into human lymphoblastic cells was 90% at concentrations of 0.3 µM. Cladribine was also incorporated into DNA of these cells. Cladribine was not mutagenic to bacteria and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride 9.0 mg (0.15 mEq)

Phosphoric acid and/or dibasic sodium phosphate to adjust the pH to a range of 5.5 to 8.0.

Water for injections

6.2 Incompatibilities

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised.

Solutions containing LEUSTATIN 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.

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 (See Section 4.2).

The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store refrigerated 2°C to 8°C. Protect from light during storage.

When stored in refrigerated conditions 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.

See Section 4.2.

6.5 Nature and contents of container

LEUSTATIN Injection is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/ml) of cladribine in 10 mL, in a single-use, flint glass vial.

6.6 Special precautions for disposal and other handling

Refer to section 4.2

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Clinect NZ Pty Limited

C/- Ebos Group Limited

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9. DATE OF FIRST APPROVAL

24 August 1995

10. DATE OF REVISION OF THE TEXT

12 August 2025

Summary Table of Changes

Section Changed	Summary of New Information
4.3	Addition of contraindication during pregnancy and lactation and for 6 months after the last dose.
4.6	Updated text regarding the use of cladribine during pregnancy and lactation.