SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Leustat™ Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LEUSTAT (cladribine) Injection is a synthetic antineoplastic agent for continuous intravenous infusion. It is a clear, colourless, sterile, preservative-free, isotonic solution. LEUSTAT Injection is available in single-use vials containing 10 mg (1 mg/ml) of cladribine, a chlorinated purine nucleoside analogue. Each millilitre of LEUSTAT Injection contains 1 mg of the active ingredient, cladribine

Excipients with known effect

Each 10 ml vial of LEUSTAT contains 38.2 mg of sodium (total sodium content from sodium chloride and dibasic sodium phosphate).

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

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

A sterile buffered solution in vials containing 10ml (1mg/ml) of cladribine for dilution and subsequent continuos intravenous infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LEUSTAT™ injection is indicated for the primary or secondary treatment of patients with Hairy Cell Leukaemia (HCL).

LEUSTAT 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 Posology and method of administration

Usual Dose:

Adults and Elderly:

HCL: The recommended treatment for Hairy Cell Leukaemia is a single course of LEUSTAT™ given by continuous intravenous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day (3.6 mg/m2/day). Deviations from this dosage regimen are not advised. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs.

CLL: In patients with CLL, the recommended treatment consists of a continuous intravenous infusion of LEUSTAT 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). The patient's response to therapy should be determined every two cycles of treatment. It is recommended that LEUSTAT Injection be administered in responding patients for 2 cycles after maximum response has occurred, up to a maximum of 6 cycles. Therapy should be discontinued after 2 cycles in non-responding patients. Response for this treatment decision is defined as a lymphocyte reduction of 50% or more, i.e. if lymphocyte count decreases by 50% or more, administer 2 more cycles and re-evaluate response for decision whether to continue with 2 more cycles up to a maximum of 6 cycles.

Children:

Safety and efficacy in children have not been established.

Specific risk factors predisposing to increased toxicity from LEUSTAT™ 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 aetiology. Patients should be monitored closely for haematologic and renal and hepatic toxicity.

Preparation and Administration of Intravenous Solutions:

LEUSTAT™ Injection must be diluted with the designated diluent prior to administration. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of a solution of LEUSTAT™. For full details concerning preparation of an infusion solution, see 6.6 Instructions for Use/Handling.

4.3 Contraindications

LEUSTAT Injection is contra-indicated in patients hypersensitive to cladribine or other components of this product.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

LEUSTAT Injection is a potent antineoplastic agent with potentially significant toxic side effects. It should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

CLL: The weight of evidence suggests that a patient whose disease has progressed while treated with fludaribine is unlikely to respond to treatment with LEUSTAT 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) have been reported (see section 4.8: Undesirable Effects).

Patients with active infection should be treated for the underlying condition prior to receiving therapy with LEUSTAT Injection. Patients who are or who become Coombs' positive should be monitored carefully for potential haemolysis.

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

This medicinal product contains 38.2 mg of sodium per vial, equivalent to 1.91% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration in patients with a sodium free regimen.

Elderly patients should be treated by individual assessment, and careful monitoring of blood counts and renal and hepatic function. The risk requires assessment on a case-by-case basis.

Patients with high tumour burden or who are considered at risk for the development of hyperuricaemia as a result of tumour breakdown should receive appropriate prophylactic treatment. Allopurinol and adequate hydration should be considered for patients with initially high WBC, to alleviate potential tumour lysis syndrome side effects of therapy.

4.4.1 Progressive multifocal leukoencephalopathy (PML)

Cases of PML, including fatal cases, have been reported with cladribine. PML was reported 6 months to several years after treatment with cladribine. An association with prolonged lymphopenia has been reported in several of these cases. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms.

Suggested evaluation for PML includes neurology consultation, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established. Patients with suspected PML should not receive further treatment with cladribine.

4.4.2 Bone Marrow Suppression:

Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Severe bone marrow suppression, including neutropenia, anaemia and thrombocytopenia, has been commonly observed in patients treated with LEUSTAT, especially at high doses. At initiation of treatment, most patients in the clinical studies had haematological impairment as a manifestation of active Hairy Cell Leukaemia or Chronic Lymphocytic Leukaemia. Following treatment with LEUSTAT, further haematological impairment occurred before recovery of peripheral blood counts began. Proceed carefully in patients with severe bone marrow impairment of any aetiology since further suppression of bone marrow function should be anticipated (See: 4.4.5 Laboratory Tests and 4.8 Undesirable Effects).

Due to the prolonged immunosuppression associated with the use of nucleoside analogues like LEUSTAT, 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, 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 LEUSTAT were most notable during the first month following treatment. Forty three percent (43%) of patients received transfusions with RBCs and 13% received transfusions with platelets during month 1. Careful haematological monitoring, especially during the first 4 to 8 weeks after treatment with LEUSTAT is recommended. (See 4.8, Undesirable Effects).

CLL: During the first 2 cycles of therapy with LEUSTAT Injection, 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 LEUSTAT Injection.

4.4.3 Neurotoxicity:

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

4.4.4 Fever/Infection:

HCL: Fever (temperature greater than or equal to 37.8°C) was associated with the use of LEUSTAT in approximately 72% (89/124) of patients. Most febrile episodes occurred during the first month. Although seventy percent (70%) of patients were treated empirically with parenteral antibiotics, less than a third of febrile events were associated with documented infection.

CLL: Pyrexia was reported in 22-24% of CLL patients during Cycle 1 of therapy with LEUSTAT Injection, 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 empirical antibiotics should be initiated as clinically indicated. Given the known myelosuppressive effects of

LEUSTAT, 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 loss, patients should be kept well hydrated (See 4.8, Undesirable effects).

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

4.4.6 Effect on Renal and Hepatic Function:

Acute renal insufficiency has developed in some patients receiving high doses of LEUSTAT. In addition, there are inadequate data on dosing of patients with renal or hepatic insufficiency. Until more information is available, caution is advised when administering the drug to patients with known or suspected renal or hepatic insufficiency. 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: 4.8 Undesirable Effects and 4.9 Overdose)

LEUSTAT Injection must be diluted in a designated intravenous solution prior to administration (See 6.6, Instructions for Use/Handling for full details concerning preparation of an infusion solution).

4.4.7 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 15, the mean absolute neutrophil count reached 1500 x 10^6/l by week 5, and the mean hemoglobin reached 12 g/dl by week 8.]

In HCL patients, bone marrow aspiration and biopsy should be performed to confirm response to treatment with LEUSTAT after peripheral counts have normalised. Febrile events should be investigated with appropriate laboratory and radiological studies.

4.4.8 Carcinogenesis/Mutagenesis:

No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine. [In mammalian cells in culture, cladribine causes an imbalance of intracellular deoxyribonucleotide triphosphate pools. This imbalance results in the inhibition of DNA synthesis and DNA repair synthesis, yielding DNA strand breaks and subsequently cell death. Inhibition of thymidine incorporation into human lymphoblastic cells was 90% at concentrations of 0.3mM. Cladribine was also incorporated into the DNA of these cells.] 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. Cladribine was not mutagenic to bacteria and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures.

4.4.9 Impairment of Fertility:

When administered intravenously to Cynomolgus monkeys, LEUSTAT (cladribine) has been shown to cause suppression of rapidly generating cells, including testicular cells. Men being treated with LEUSTAT Injection should be advised not to father a child up to 6 months after the last LEUSTAT dose (see section 4.6 Fertility, Pregnancy and Lactation).

4.4.10 Extravasation:

Should the drug 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.

4.4.11 Paediatric Use:

Safety and efficacy in children have not been established.

In a Phase I study of 1-21 year old patients with leukaemia, LEUSTAT Injection 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 recommended dose for hairy cell leukaemia). The dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose, 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised if LEUSTAT Injection is administered following or in conjunction with other drugs known to cause myelosuppression. Following administration of LEUSTAT Injection, caution should be exercised before administering other immunosuppressive or myelosuppressive therapy. (See 4.4.1 and 4.8.1.2 Bone Marrow Suppression).

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

Due to the similar intracellular metabolism, cross-resistance with other nucleoside analogues, such as fludarabine or 2'-deoxycoformycin may occur. Therefore, simultaneous administration of nucleoside analogues with cladribine is not advisable

Since interactions with medicinal products undergoing intracellular phosphorylation, such as antiviral agents, or with inhibitors of adenosine uptake (e.g. didanosine, tenofovir, adefovir) may be expected, their concomitant use with cladribine is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

LEUSTAT Injection is teratogenic in mice and rabbits. A significant increase in foetal 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 foetal malformations were observed when mice received 3.0 mg/kg/day (9 mg/m^2). Foetal death and malformations were observed in rabbits that received 3.0 mg/kg/day (33.0 mg/m^2). No adverse foetal 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.

Breastfeeding

Limited data from cases have shown that LEUSTAT is excreted in breast milk. The amount has not yet been well established. Given the potential for serious adverse reactions in infants, Lactation is contraindicated during treatment with LEUSTAT and for 6 months after the last dose of LEUSTAT.

Fertility

Men being treated with LEUSTAT Injection should be advised not to father a child up to 6 months after the last LEUSTAT dose (see section 4.4). Family planning should be discussed with patients as appropriate.

4.7 Effects on ability to drive and use machines

Given the patients underlying medical condition and the safety profile of LEUSTAT ™ caution should be exercised when a patient is performing activities requiring substantial physical well-being (See 4.8, Undesirable Effects).

4.8 Undesirable effects

4.8.1 Hairy Cell Leukaemia (HCL):

The safety of LEUSTAT was evaluated in 576 LEUSTAT-treated patients with hairy cell leukaemia (HCL) (studies K90-091 and L91-048, n=576). These subjects received at least 1 injection of LEUSTATand provided safety data. Based on pooled safety data from the HCL clinical trials, the most commonly reported (i.e., ≥10% incidence) adverse drug reactions (ADRs) were: pyrexia (33%), fatigue (31%), nausea (22%), rash (16%), headache (14%), and administration site reaction (11%).

Including the above-mentioned ADRs, Table A displays ADRs that have been reported with the use of LEUSTAT in HCL-treated patients from clinical trial experiences or from the consolidated (not indication specific) listing of post-marketing experiences.

The displayed frequency categories use the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

Table A: Adverse Drug Reactions from HCL Clinical Trials and Post-marketing	
Infection and Infestation	
Common:	Septic shock[a]
Uncommon:	Opportunistic infections[a]

Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Secondary malignancies[a1], Primary haematological malignancies[a1]
Blood and Lymphatic System Disorders	
Common:	Haemolytic anaemia[a,b], Anaemia, Febrile neutropenia
Uncommon:	Bone marrow suppression with prolonged pancytopenia[a], Aplastic anaemia[a], Hypereosinophilia[a], Myelodysplastic syndrome[a]
Immune System Disorders	
Common:	Hypersensitivity[a]
Metabolism and Nutrition Disorders	
Uncommon:	Tumour lysis syndrome[a]
Psychiatric Disorders	
Common:	Confusion[a,c], Anxiety, Insomnia
Nervous System Disorders	
Very common:	Headache
Common:	Dizziness
Uncommon:	Depressed level of consciousness[a], Neurological toxicity[a,d]
Eye Disorders	
Common:	Conjunctivitis[a]
Cardiac Disorders	
Common:	Tachycardia, Myocardial ischaemia
Rare:	Heart failure, Arrhythmia
Respiratory, Thoracic and Mediastinal Disorders	
Common:	Pulmonary interstitial infiltrates[a,e], Breath sounds abnormal, Cough, Dyspnoea[f], Rales
Gastrointestinal Disorders	
Very common:	Nausea
Common:	Abdominal pain[g], Constipation, Diarrhoea, Flatulence, Vomiting
Hepatobiliary Disorders	
Uncommon:	Increases in bilirubin[a], Increases in transaminases[a]
Skin and Subcutaneous Tissue Disorders	
Very common:	Rash[h]
Common:	Urticaria[a], Ecchymosis, Hyperhidrosis, Petechiae, Pruritus
Uncommon:	Stevens-Johnson syndrome[a]
Musculoskeletal and Connective Tissue Disorders	
Common:	Arthralgia, Myalgia, Pain[i]
Renal and Urinary Disorders	
Common:	Renal failure[a,j]
General Disorders and Administration Site Conditions	

Very common:	Administration site reaction[k], Fatigue, Pyrexia
Common:	Asthenia, Chills, Decreased Appetite, Malaise, Muscular weakness, Oedema peripheral
Injury, Poisoning and Procedural Complications	
Common:	Contusion

[a] Events reported as ADRs during the post-marketing experience.
[b] Haemolytic anaemia includes autoimmune haemolytic anaemia
[c] Confusion includes disorientation
[d] Neurological toxicity includes peripheral sensory neuropathy, motor neuropathy (paralysis), polyneuropathy, and paraparesis
[e] Pulmonary interstitial infiltrates includes lung infiltration, interstitial lung disease, pneumonitis and pulmonary fibrosis
[f] Dyspnoea includes dyspnoea, dyspnoea exertional, and wheezing
[g] Abdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain (lower and upper)
[h] Rash includes erythema, rash, and rash (macular, macula-papular, papular, pruritic, pustular, and erythematous)
[i] Pain includes pain, back pain, chest pain, arthritis pain, bone pain, and pain in extremity
[j] Renal failure includes renal failure acute and renal impairment
[k] Administration site reaction includes administration site reaction, catheter site (cellulitis, erythema, haemorrhage, and pain), and infusion site reaction (erythema, oedema, and pain)
[l] Due to the prolonged immunosuppression associated with the use of nucleoside analogues like LEUSTAT, secondary malignancies are a potential risk. Primary haematological malignancies are also a risk factor for secondary malignancies.

The following safety data are based on a subset of 124 patients with HCL that were enrolled in the pivotal study (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.

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 LEUSTAT 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 red blood cells (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 after 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 LEUSTAT Injection toxicity.

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 of study. During the first month, 12% of patients experienced severe fever (ie greater than or equal to 40°C). Of the 124 patients treated, 11 were noted to have a documented infection in the month prior to treatment. In the month following treatment, 31% of patients had a documented infection: 13.7% of patients had bacterial infection, 6.5% had viral and 6.5% had fungal infections. Seventy percent (70%) of these patients were treated empirically with antibiotics. During the first month, serious, including fatal, infections (eg septicaemia, pneumonia) were reported in 7% of all patients; the remainder were mild or moderate. During the second month, the overall rate of documented infection was 8%; 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 LEUSTAT 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.

4.8.2 Chronic Lymphocytic Leukaemia (CLL):

The safety of LEUSTAT was evaluated in 266 LEUSTAT-treated patients with B-cell chronic lymphocytic leukaemia (CLL) noted in the CLL clinical trial dataset (studies L91-999 and L091-048, n=266). These subjects received at least 1 injection of LEUSTAT and provided safety data. Based on pooled safety data from the CLL clinical trials, the most commonly reported (i.e., ≥10% incidence) ADRs were: pyrexia (28%), fatigue (22%), administration site reaction (21%), and headache (11%).

Including the above-mentioned ADRs, Table B displays ADRs that have been reported with the use of LEUSTAT in CLL-treated patients from clinical trial experiences or from the consolidated (not indication specific) listing of post-marketing experiences.

The displayed frequency categories use the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100).

Table B: Adverse Drug Reactions from CCL Clinical Trials and Post-marketing	
Infection and Infestation	
Common:	Septic shock[a], Bacteraemia, Cellulitis, Localised infection, Pneumonia
Uncommon:	Opportunistic infections[a] Herpes infections (Herpesretinitis, Herpes zoster) have been

	observed months and up to years after therapy with Leustat[a].
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Secondary malignancies[a,k], Primary haematological malignancies[a,k]
Blood and Lymphatic System Disorders	
Common:	Haemolytic anaemia[a,b], Anaemia, Thrombocytopenia (with bleeding or petechiae)
Uncommon:	Bone marrow suppression with prolonged pancytopenia[a], Aplastic anaemia[a], Hypereosinophilia[a], Myelodysplastic syndrome[a]
Immune System Disorders	
Common:	Hypersensitivity[a]
Metabolism and Nutrition Disorders	
Uncommon:	Tumour lysis syndrome[a]
Psychiatric Disorders	
Common:	Confusion[a,c]
Nervous System Disorders	
Very common:	Headache
Uncommon:	Depressed level of consciousness[a], Neurological toxicity[a,d]
Eye Disorders	
Common:	Conjunctivitis[a]
Vascular Disorders	
Common:	Phlebitis
Respiratory, Thoracic and Mediastinal Disorders	
Common:	Pulmonary interstitial infiltrates[a,e], Breath sounds abnormal, Cough, Dyspnoea[f], Rales
Gastrointestinal Disorders	
Common:	Diarrhoea, Nausea, Vomiting
Hepatobiliary Disorders	
Uncommon:	Increases in bilirubin[a], Increases in transaminases[a]
Skin and Subcutaneous Tissue Disorders	
Common:	Urticaria[a], Hyperhidrosis, Purpura, Rash[g]
Uncommon:	Stevens-Johnson syndrome[a]
Musculoskeletal and Connective Tissue Disorders	
Common:	Pain[h]
Renal and Urinary Disorders	
Common:	Renal failure[a,i]
General Disorders and Administration Site Conditions	
Very common:	Administration site reaction[j], Fatigue, Pyrexia
Common:	Asthenia, Crepitations, Localised oedema, Muscular weakness, Oedema, Oedema peripheral

[a] Events reported as ADRs during the post-marketing experience.

[b] Haemolytic anaemia includes autoimmune haemolytic anaemia
[c] Confusion includes disorientation
[d] Neurological toxicity includes peripheral sensory neuropathy, motor neuropathy (paralysis), polyneuropathy, and paraparesis
[e] Pulmonary interstitial infiltrates includes lung infiltration, interstitial lung disease, pneumonitis and pulmonary fibrosis
[f] Dyspnoea includes dyspnoea and dyspnoea exertional
[g] Rash includes rash (macula-papular, pruritic, and pustular) and erythema
[h] Pain includes pain, arthralgia, back pain, bone pain, musculoskeletal pain, and pain in extremity
[i] Renal failure includes renal failure acute and renal impairment
[j] Administration site reaction includes administration site reaction, catheter site (erythema and infection), and infusion site (cellulitis, erythema, irritation, oedema, pain, infection, and phlebitis)
[k] Due to the prolonged immunosuppression associated with the use of nucleoside analogues like LEUSTAT, secondary malignancies are a potential risk. Primary haematological malignancies are also a risk factor for secondary malignancies.

Bone Marrow Suppression:

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

Patients with CLL treated with LEUSTAT 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:

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 during 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 9, 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 therapy with LEUSTAT Injection. Of these, 32.6% had been administered concomitant immunosuppressive therapy (prednisone).

4.8.3 Effects of high doses:

In a Phase 1 study with 31 patients in which LEUSTAT Injection was administered at high doses (4 to 9 times that recommended for hairy cell leukaemia) for 7-14 days in conjunction with cyclophosphamide and total body irradiation as preparation for bone marrow transplantation, acute

nephrotoxicity, delayed onset neurotoxicity, severe bone marrow suppression with neutropenia, anaemia, and thrombocytopenia and gastro-intestinal symptoms were reported.

4.8.4 Nephrotoxicity:

Six patients (19%) developed manifestations of acute renal dysfunction/insufficiency (eg acidosis, anuria, elevated serum creatinine, etc) within 7 to 13 days after starting treatment with LEUSTAT, 5 of the affected patients required dialysis. Renal insufficiency was reversible in 2 of these patients. Evidence of tubular damage was noted at autopsy in 2 (of 4) patients whose renal function had not recovered at the time of death. Several of these patients had also been treated with other medications having known nephrotoxic potential.

4.8.5 Neurotoxicity:

Eleven patients (35%) experienced delayed onset neurological toxicity. In the majority, this was characterised by progressive irreversible motor weakness, of the upper and/or lower extremities (paraparesis/quadraparesis), noted 35 to 84 days after starting high dose therapy.

Non-invasive neurological testing was consistent with demyelinating disease.

4.8.6 Safety experience following intravenous or subcutaneous administration in patients with multiple sclerosis:

While the use of cladribine cannot be recommended in indications other than hairy cell leukaemia or chronic lymphocytic leukaemia, nor can subcutaneous administration be recommended, data are available from the following investigations which were designed to evaluate the potential efficacy of the drug in the treatment of multiple sclerosis.

In two studies which employed the intravenous route, cladribine was infused in doses ranging from 0.087 to 0.1 mg/kg/day for seven days, with this regimen being repeated for a total of 4 to 6 months. Cumulative doses achieved thus ranged from 2.8 to 3.65 mg/kg. Additionally, in three studies which utilized the subcutaneous route, cladribine was administered in doses ranging from 0.07 to 0.14 mg/kg/day for 5 days, with this regimen being repeated for a total of 2 to 6 months. Cumulative total doses administered thus ranged from 0.7 to 2.1 mg/kg.

The safety profile established based on these trials reflects the drug's expected lymphocytotoxic and bone marrow-suppressing effects and is consistent with the safety profile attributable to the intravenous route of administration in the currently recommended indications of HCL and CLL.

In these trials, most of the frequently reported adverse events, including serious adverse events, were events typically associated with the underlying disease. Most occurred with comparable frequency in placebo- and cladribine-treated subjects. Inflammation and/or pain at the injection site were seen with subcutaneous injection of the study drug. Subjects treated with cladribine had a higher incidence of upper respiratory tract infection, purpura, hypertonia and muscle weakness than did subjects treated with placebo, with the between-group difference in the incidence of muscle weakness due primarily to results obtained by a single investigator. With the exception of a higher incidence of thrombocytopenia after re-treatment (8%) compared to initial treatment (4%), there were no notable differences in the adverse events profile associated with an initial cladribine treatment versus re-treatment among the 78 subjects who received more than one cladribine treatment course.

Less common, but clinically important adverse events, included those associated with myelosuppression and compromised immune function (pneumonia, aplastic anaemia, pancytopenia, thrombocytopenia, herpes simplex, and herpes zoster infections) and these occurred either exclusively or with increased incidence and severity in subjects who received a cumulative cladribine dose of 2.8 mg/kg or higher, particularly when the total dose was administered in an interval as short as four months.

4.8.7. Paediatric use:

Safety and effectiveness in children have not been established. [In a Phase I study of 1-21 year old patients with leukemia, LEUSTAT Injection was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m2/day for 5 days (one-half to twice the recommended dose for hairy cell leukemia). The dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose, 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted.]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

High doses of LEUSTAT have been associated with serious neurological toxicity (including irreversible paraparesis/quadraparesis), acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia, anaemia and thrombocytopenia (See 4.4, Special Warnings and Special Precautions for Use). There is no known specific antidote to overdosage. It is not known whether the drug can be removed from the circulation by dialysis or haemofiltration. Treatment of overdosage consists of discontinuation of LEUSTAT Injection, careful observation and appropriate supportive measures.

Signs and symptoms of overdose may include nausea, vomiting, diarrhoea, severe bone marrow depression (including anaemia, thrombocytopenia, leukopenia, and agranulocytosis), acute renal insufficiency, as well as irreversible neurologic toxicity (paraparesis/quadriparesis), Guillain Barre and Brown Sequard syndromes. Acute, irreversible neuro- and nephrotoxicity have been described in individual patients treated at a dose which was $\geq$ 4 times higher than the recommended regimen for hairy cell leukaemia.

No specific antidote exists. Immediate discontinuation of therapy, careful observation, and initiation of appropriate supportive measures (blood transfusions, dialysis, haemofiltration, anti-infectious therapy, etc.) are the indicated treatment of

overdose of cladribine. Patients who have received an overdose of cladribine should be monitored haematologically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

LEUSTAT™ Injection (cladribine) is a synthetic antineoplastic agent.

Cellular Resistance and Sensitivity: The selective toxicity of cladribine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase, deoxynucleotidase and adenosine deaminase. 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. LEUSTAT™ 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

When LEUSTAT™ was given by continuous intravenous infusion over 7 days the mean steady-state serum concentration was estimated to be 5.7 ng/ml with an estimated systemic clearance of 663.5 ml/h/kg. Accumulation of LEUSTAT™ over the seven day treatment period was not noted.

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 9l/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.

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 tumours during a 5-day continuos intravenous infusion of 3.5 - 8.1 mg/m2/ day of LEUSTAT. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

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.

5.3 Preclinical safety data

Carcinogenesis/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. Cladribine is mutagenic in mammalian cells in culture. Cladribine was not mutagenic to bacteria and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures.

Other preclinical safety data has been included in specific sections of SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

9.0 mg (0.15 mEq) of sodium chloride as an inactive ingredient. Phosphoric acid and/or dibasic sodium phosphate to adjust the pH to a range of 5.5 to 8.0.

6.2 Incompatibilities

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

Solutions containing LEUSTAT 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 LEUSTAT. (See 4.2 or 6.6)

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

6.3 Shelf life

The shelf life for LEUSTAT Injection is 3 years.

When stored in refrigerated conditions between 2° to 8°C (36° to 46°F) protected from light, unopened vials of LEUSTAT 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 LEUSTAT Injection is stable until expiry if refrigerated. DO NOT REFREEZE.

Once diluted, solutions containing LEUSTAT 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.

6.4 Special precautions for storage

Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

6.5 Nature and contents of container

LEUSTAT Injection is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/ml) of cladribine (as 10 ml) in a single-use, Ph Eur Type I glass 10 ml vial.

6.6 Special precautions for disposal

Preparation and administration of intravenous solutions: LEUSTAT™ injection must be diluted with the designated diluent prior to administration. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of a solution of LEUSTAT™.

Parental 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 LEUSTAT™ 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*.

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

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering LEUSTAT™ Injection. The use of disposable gloves and protective garments is recommended. If LEUSTAT™ Injection contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water.

Preparation of a Single Daily Dose:

HCL: Add the calculated dose for a 24 hours period (0.09 mg/kg or 0.09 ml/kg or 3.6 mg/m2) of LEUSTAT™ injection to an infusion bag containing 100 ml to 500 ml of 0.9% sodium chloride injection. (Ph.Eur). Infuse continuously over 24 hours. Repeat daily for a total of 7 consecutive days.

CLL: Add the calculated dose for a 2 hours' period (0.12 mg/kg or 4.8 mg/m2) of LEUSTAT Injection to an infusion bag containing 100 ml to 500 ml of 0.9% sodium chloride injection (PhEur.). Infuse intravenously 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. Admixtures of LEUSTAT™ 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.

	DOSE OF LEUSTAT	RECOMMENDED DILUENT	QUANTITY OF DILUENT
HCL: 24-hour infusion method	0.09 mg/kg/day	0.9% sodium chloride injection, PhEur	100 ml to 500 ml
CLL: 2-hour infusion method	0.12 mg/kg/dag	0.9% sodium chloride injection, PhEur	100 ml to 500 ml

7 MARKETING AUTHORISATION HOLDER

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