AUSTRALIAN PRODUCT INFORMATION

LITAK®

(cladribine) solution for injection

1 NAME OF THE MEDICINE

Cladribine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL of the preservative-free, isotonic solution contains 10 mg of cladribine as the active ingredient, 45 mg of sodium chloride and water for injections to make the solution up to 5 mL. The product may also contain sodium hydroxide or hydrochloric acid to adjust the pH. The pH range of the solution is 6.5 - 7.5.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

LITAK is available in single-use vials containing 10 mg of cladribine in 5 mL of solution, ready-to-use for subcutaneous injection without dilution or can be diluted for intravenous infusion.

The solution for injection is presented as a clear, colourless, odourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LITAK is indicated for the treatment of hairy cell leukaemia and the second line treatment of lymphoplasmacytic lymphoma (Waldenström's Macroglobulinaemia), i.e. after failure of alkylating agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Therapy with LITAK should be initiated by a qualified physician with experience in cancer chemotherapy.

LITAK contains no antimicrobial agent. Product is for single use in one patient only. Opened vials should be used immediately to assure sterility. Discard any residue.

LITAK is supplied as ready-to-use solution for subcutaneous bolus injection or can be diluted for intravenous infusion. Aseptic technique and proper environment precautions must be observed while handling LITAK solution and preparing infusions.

For subcutaneous bolus injection

The recommended dose is directly withdrawn by a syringe and injected without dilution. Allow LITAK to warm up to room temperature prior to administration.

For intravenous infusion

The fresh infusion should be prepared daily. The recommended dose is diluted in 500 mL of 0.9% sodium chloride. The ready-to-use solution should be used immediately; if storage is necessary refrigerate between 2°C and 8°C for not more than 8 hours prior to administration.

Hairy cell leukaemia

Subcutaneous bolus injection

The recommended treatment of hairy cell leukaemia is a single course of LITAK given by subcutaneous bolus injection at a dose of 0.14 mg/kg body weight/day for 5 consecutive days.

Intravenous infusion

The recommended treatment of hairy cell leukaemia is a single course of LITAK given by 0.10 mg/kg body weight/day for 7 consecutive days.

Under certain haematological conditions (recovery of severe myelosuppression) a small proportion of patients may require a second cycle and occasionally a third cycle of LITAK in order to achieve a stable and prolonged response.

Lymphoplasmacytic lymphoma

Subcutaneous bolus injection

The recommended treatment of lymphoplasmacytic lymphoma is 0.10 mg/kg body weight/day of LITAK for 5 consecutive days at monthly intervals given by subcutaneous bolus injection. Experience at dosages exceeding 3 cycles is limited.

Deviations from the dosage regimens indicated above are not advised (see Section 4.9 OVERDOSE). The physician should consider delaying or discontinuing LITAK if severe toxicity occurs until serious complications resolve. In case of infections, antibiotic treatment should be initiated as required.

Instruction for Handling and Disposal

Procedures for proper handling and disposal of antineoplastic drugs should be considered. Cytotoxic drugs should be handled with caution. Avoid contact by pregnant women and keep out of the reach of children.

The use of disposable gloves and protective garments is recommended when handling and administering LITAK. If LITAK contacts the skin or mucous membranes, rinse the involved surface immediately with copious amounts of water.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. A precipitate may occur during the storage of LITAK at low temperatures. Precipitates can be resolubilised by exposure to room temperature and by shaking vigorously. Do not heat or microwave.

4.3 CONTRAINDICATIONS

LITAK is contraindicated in patients with a history of hypersensitivity to cladribine or any of its excipients.

LITAK is also contraindicated:

- During pregnancy and lactation.
- In patients less than 18 years of age.
- In patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) or moderate to severe hepatic impairment (Child-Pugh score > 6) (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- In concomitant use of other myelosuppressive medicinal products.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cladribine is an antineoplastic and immunosuppressive substance that can induce considerable toxic adverse effects, like myelo- and immunosuppression, long-lasting lymphocytopenia, and opportunistic infections. Patients undergoing treatment with cladribine should be closely monitored for signs of haematologic and non-haematologic toxicities.

Particular caution is advised and risks/benefits should be carefully evaluated if administration of cladribine is considered in patients with increased infection risk, manifested bone marrow failure or infiltration, myelosuppressive pre-treatments, as well as in patients with suspected or manifested renal and hepatic insufficiency. Patients with active infection should be treated for the underlying condition prior to receiving therapy with LITAK. Patients who are or who become Coombs' positive should be monitored closely for occurrence of haemolysis.

If severe toxicity occurs, the physician should consider delaying or discontinuing the therapy with the medicinal product until serious complications resolve. In case of infections, antibiotic treatment should be initiated as required.

There have been reports of graft-versus-host disease in patients treated with cladribine who have received transfusions of non-irradiated cellular blood components/products. Fatal cases have been reported. See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

It is recommended that patients receiving cladribine should receive irradiated cellular blood components/products to prevent transfusion-related graft-versus-host disease (Ta-GVHD).

Acute, irreversible neuro- and nephrotoxicity have only been observed at high doses of cladribine (≥4 times the recommended dose).

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.

Secondary Malignancies

Like other nucleoside analogues, treatment with cladribine is associated with myelosuppression and profound and prolonged immunosuppression. Treatment with these agents is associated with the occurrence of second malignancies. Secondary malignancies are expected to occur in patients with hairy cell leukaemia. Their frequency varies widely, ranging from 2% to 21%. The peak risk is at 2 years after diagnosis with a median between 40 and 66 months. The cumulative frequencies of second malignancy are 5%, 10-12% and 13-14% following 5, 10 and 15 years respectively after diagnosis of hairy cell leukaemia. Following cladribine, the incidence of second malignancies ranges from 0% to 9.5% after a median observation period of 2.8 to 8.5 years. The frequency of second malignancy following treatment with LITAK was 3.4% in all 232 hairy cell leukaemia patients treated, during a 10-year period. The highest incidence of second malignancy with LITAK was 6.5% after a median follow- up of 8.4 years. Therefore, patients treated with cladribine should be regularly monitored.

Haematology

Haematological toxicity may be more pronounced with subcutaneous compared to intravenous administration (see Section 4.8 ADVERSE EFFECTS). During the first month following treatment, myelosuppression is most notable and red blood cell or platelet transfusions may be required. Patients with a manifestation of bone marrow depression should be treated with caution since further suppression of bone marrow function should be anticipated. Therapeutic risks and benefits should be carefully evaluated in patients with active or suspected infections. The risk of severe myelotoxicity and long-lasting immunosuppression is increased in patients with a disease-related bone marrow infiltration or a previous myelosuppressive treatment. A dose reduction and a regular monitoring of the patient is required in such cases.

Increased haematological toxicity (myelosuppression, infections) has been observed in patients receiving repeated cycles of LITAK. Therefore, it is recommended that the dosage regimen of LITAK should not exceed 0.5 mg/kg body weight per cycle in patients receiving multiple treatment courses. A discontinuation of the therapy may be necessary depending on the severity and intensity of the complications. Pancytopenia is normally reversible, and the intensity of bone marrow aplasia is dose dependent. An increased incidence of opportunistic infections is expected during and 6 months following therapy with LITAK. Careful and regular monitoring of peripheral blood counts is essential during and 2 to 4 months following treatment with LITAK to detect potential side effects and consequent complications (anaemia, neutropenia, thrombocytopenia, infections, haemolysis or bleedings), and to survey haematologic recovery. Fever of unknown origin frequently occurs in patients treated for hairy cell leukaemia but rarely in patients with other neoplasias and is manifested predominantly during the first 4 weeks of therapy. The origin of febrile events should be investigated by appropriate laboratory and radiologic tests. Less than a third of febrile events are associated with a documented infection. In case of fever related to infections or agranulocytosis an antibiotic treatment is indicated.

Impaired Bone Marrow

Patients with known or suspected renal insufficiency as well as patients with a manifestation of bone marrow impairment related to multiple pre-treatments, tumour infiltration or due to any other aetiology should be treated carefully and monitored regularly for haematologic and non-haematologic toxicity.

Prevention of Tumour Lysis Syndrome

Prophylactic allopurinol therapy to control the serum levels of uric acid, adequate hydration, and close monitoring of renal function are recommended in patients with a high tumour burden. The allopurinol prophylaxis usually starts at the first day of chemotherapy. A daily oral dose of 100 mg of allopurinol is recommended for a period of 2 weeks. In case of an accumulation of the serum uric acid above the normal range, the dose of allopurinol may be increased to 300 mg/day.

Use in Hepatic Impairment

Inadequate data is available on dosing of patients with hepatic insufficiency. There is no experience in patients with hepatic impairment.

Use in Renal Impairment

Inadequate data is available on dosing of patients with renal insufficiency.

For all patients treated with LITAK, periodic assessment of renal and hepatic function is advised as clinically indicated.

Use in the Elderly

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

Paediatric Use

The safety and efficacy of LITAK in children have not been established.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with other medicinal products are not known.

Due to a potential increase of haematological toxicity and bone marrow suppression, LITAK should not be used concomitantly with other myelosuppressive drugs. Cross reactions with other antineoplastic agents *in vitro* (e.g. doxorubicin, vincristine, cytarabine) and *in vivo* have not been observed.

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.

Corticosteroids have been shown to enhance the risk for severe infections when used in combination with cladribine and should not be given concomitantly with cladribine.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The effects of cladribine on fertility have not been studied in animals. However, a toxicity study conducted with Cynomolgus monkeys has shown that cladribine suppresses maturation of rapidly generating cells, including testicular cells. The effect of cladribine on human fertility is unknown. Antineoplastic agents, such as cladribine, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on human gametogenesis.

Men being treated with cladribine should be advised not to father a child up to 6 months after treatment and to seek advice of cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with cladribine.

Use in Pregnancy

Pregnancy Category: Category D

Cladribine may cause serious birth defects when administered during pregnancy. Animal studies have demonstrated the teratogenicity of cladribine. LITAK is contraindicated in pregnancy (see Section 4.3 CONTRAINDICATIONS). Women of childbearing potential must use effective contraception during treatment with cladribine and for 6 months after the last cladribine dose. In case of pregnancy during therapy with cladribine, the women should be informed about the potential hazard to the fetus.

Use in Lactation

It is unknown whether cladribine is excreted in human milk. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

LITAK may strongly impair the patient's performance. In case of drowsiness, driving a vehicle or operating machines should be avoided.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Very common side effects observed during the three most relevant clinical trials with LITAK in 279 patients treated for various indications and in 62 patients with hairy cell leukaemia (HCL) are:

Table 1: Common Side Effects

Side Effect	No. of patients affected	Total no. of patients	% affected
Myelosuppression (severe)			
Neutropenia	113	279	41%
	61 (HCL)	62 (HCL)	98% (HCL)
Thrombocytopenia	58	279	21%
	31 (HCL)	62 (HCL)	50% (HCL)
Anaemia	21	150	14%
	34 (HCL)	62 (HCL)	55% (HCL)
Immunosuppression/Lymphopenia	176	279	63%
	59 (HCL)	62 (HCL)	95% (HCL)
Infections (all grades)	110	279	39%
	36 (HCL)	62 (HCL)	58% (HCL)
Fever (all grades)			Up to 64%

Haematological toxicity may be more pronounced with subcutaneous compared to intravenous administration (see Table 2).

Table 2: Comparison of Haematological Toxicity of HCL Patients in Study PS 1 (i.v.) and SAKK Study 32/93 (s.c.)

	Worst haematological toxicity by WHO Grade III and IV (% of patients)	
	Study PS 1 (i.v.) n=21*	**SAKK Study 32/93 (s.c.)** n=62
Anaemia	not analysed	48.4%
Neutropenia	85.7%	98.4%
Lymphocytopenia	76.2%	95.2%
Thrombocytopenia	19.0%	50.0%

* one of the 22 HCL patients of study PS 1 was not evaluable for haematotoxicity since no blood values from day 14 were available.

Culture-negative fever following treatment with LITAK occurs in 10 - 40% of patients with hairy cell leukaemia and is rarely observed in patients with other neoplastic disorders. Skin rashes (2 - 31%) are mainly described in patients with other concomitant medications known to cause rash (antibiotics and/or allopurinol). Gastrointestinal side effects like nausea (5 - 28%), vomiting (1 - 13%), and diarrhoea (3 - 12%) as well as fatigue (2 - 48%), headache (1 - 23%), and decreased appetite (1 - 22%) have been reported during treatment with LITAK. There are only isolated reports of alopecia, mucositis or conjunctivitis.

Non-haematological adverse effects

Most non-haematological adverse reactions are mild to moderate in severity. Treatment with antiemetics is usually not necessary.

Blood counts

Since patients with an active hairy cell leukaemia mostly present with low blood counts, especially low neutrophil counts, more than 90% of the cases have transient severe neutropenias (<1.0 x 10^9/L). The use of haematopoietic growth factors neither improves the recovery of neutrophiI counts nor decreases the incidence of fever. Severe thrombocytopenias (<50 x 10^9/L) are observed in about 20% to 30% of all patients.

Lymphocytopenia lasting for several months and immunosuppression with an increased risk for infections are expected. The recovery of cytotoxic T-lymphocytes and natural killer cells occurs within 3 to 12 months. A complete recovery of T-helper cells and B- Iymphocytes is delayed for up to 2 years.

Cladribine induces a remarkable and prolonged reduction of CD4+ and CD8+ T- lymphocytes. At present there exists no experience on possible long-term consequences of this immunosuppression.

Infections

Serious long-term lymphocytopenias are reported occasionally which, however, could not be associated with late infectious complications. Very common severe complications, in some cases with fatal outcome, are opportunistic infections (e.g. Pneumocystis carinii, Toxoplasma gondii, listeria, candida, herpes viruses, cytomegalovirus and atypical mycobacteria). Forty percent of the patients who were treated with LITAK at a dose of 0.7 mg/kg body weight per cycle suffered from infections. These were on average more severe than the infections manifested in 27% of all patients receiving a reduced dose of 0.5 mg/kg body weight per cycle. Forty-three percent of patients with hairy cell leukaemia experienced infectious complications at standard dosage regimen. One third of these infections have to be considered as severe (e.g. septicaemia, pneumonia). At least 10 cases with acute autoimmune haemolytic anaemia are known. All patients have been successfully treated by corticosteroids.

Rare serious adverse reactions

Serious adverse reactions like ileus, severe hepatic failure, renal failure, cardiac failure, atrial fibrillation, cardiac decompensation, apoplexy, neurological disturbances in speech and swallowing, tumour lysis syndrome with acute renal failure, transfusion- related graft-versus-host disease, Stevens-Johnson syndrome/Lyell syndrome (toxic epidermal necrolysis), haemolytic anaemia, hypereosinophilia (with erythematous skin rash, pruritus, and facial oedema) are rare.

Fatal Outcome

The majority of drug-related deaths are due to infectious complications. Further rare cases with fatal outcome, reported in association with LITAK chemotherapy, were second malignancy, cerebro- and cardiovascular infarctions, graft-versus-host disease caused by multiple transfusions of non-irradiated blood, as well as tumour lysis syndrome with hyperuricaemia, metabolic acidosis, and acute renal failure.

Adverse reactions that have been reported including information on frequency

(very common >= 1/10, common > = 1/100 and < 1/10, uncommon >= 1/1000 and < 1/100, rare > = 1/10000 and < 1/1000, very rare < 1/10000 are listed below):

Table 3: Adverse Reactions

Infections and infestations	*Very common:* infections* (e.g. pneumonia*, septicaemia*)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Common:* second malignancies*
	Rare: tumour lysis syndrome*
Blood and lymphatic system disorders	*Very common:* pancytopenia/myelosuppression*, neutropenia, thrombocytopenia, anemia, lymphopenia

	Uncommon: haemolytic anaemia, amyloidosis[†]
	Rare: hypereosinophilia
Immune system disorders	*Very common:* immunosuppression[*]
	Uncommon: graft-versus-host disease[*†]
Metabolism and nutrition	*Very common:* decreased appetite
disorders	*Uncommon:* cachexia
Nervous system disorders	*Very common:* headache, dizziness
	Common: insomnia, anxiety
	Uncommon: somnolence, paraesthesia, lethargy, polyneuropathy, confusion, ataxia, weakness, depression[†], epileptic seizure[†]
	Rare: apoplexy, neurological disturbances in speech and swallowing
Eye disorders	*Uncommon:* conjunctivitis, blepharitis[†]
Cardiac disorders	*Common:* tachycardia, heart murmur, hypotension, epistaxis, myocardial ischemia[*]
	Rare: Cardiac failure, atrial fibrillation, cardiac decompensation
Vascular disorders	*Very common:* purpura
	Common: petechiae, haemorrhages[*]
	Uncommon: phlebitis
Respiratory, thoracic and mediastinal disorders	*Very common:* abnormal breath sounds, abnormal chest sounds, cough
	Common: shortness of breath, pulmonary interstitial infiltrates mostly due to infectious aetiology, mucositis
	Uncommon: pharyngitis, lung embolism[†]
Gastrointestinal disorders	*Very common:* nausea, vomiting, constipation, diarrhoea
	Common: gastrointestinal pain, flatulence
	Rare: ileus
Hepato-biliary disorders	*Common:* reversible, mostly mild increases in bilirubin and transaminases
	Uncommon: cholecystitis[†]
	Rare: hepatic failure

Skin and subcutaneous tissue disorders	*Very common:* rash, localised exanthema, diaphoresis *Common:* pruritus, skin pain, erythema, urticaria *Rare:* Stevens-Johnson syndrome/Lyell syndrome (toxic epidermal necrolysis)
Musculoskeletal and connective tissue disorders	*Common:* myalgia, arthralgia, arthritis, bone pain
Renal and urinary disorders	*Rare:* renal failure
General disorders and administration site conditions	*Very common:* injection site reactions, fever, fatigue, chills, asthenia *Common:* oedema, malaise, pain

* see descriptive section above.

† single cases

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Common symptoms after overdosage are 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-Barré syndrome, and Brown-Séquard syndrome. The neurological complications have been described in individual patients treated at a dose, which was ≥4 times higher than the recommended regimen for hairy cell leukaemia.

No specific antidotal therapy 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 overdosage of LITAK. Patients who have been exposed to overdosage of LITAK should be monitored haematologically for at least four weeks.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

LITAK (cladribine) is a synthetic antineoplastic agent for subcutaneous injection and intravenous infusion.

LITAK contains cladribine as active ingredient, a purine nucleoside analogue acting as an antimetabolite. The single substitution of chlorine for hydrogen at position 2 distinguishes cladribine from its natural counterpart 2'-deoxyadenosine and renders the molecule resistant to deamination by adenosine deaminase.

Cellular resistance and sensitivity

Cladribine is a prodrug, which is taken up rapidly into cells after parenteral administration and is phosphorylated intracellularly to the active nucleotide 2- chlorodeoxyadenosine-5’-triphosphate (CdATP),

initially by deoxycytidine kinase (dCK). An accumulation of active CdATP is observed predominantly in cells with a high dCK activity and a low deoxynucleotidase activity, particularly in lymphocytes and in other haematopoietic cells. The cytotoxicity of cladribine is dose dependent. Non-haematological tissues seem to be less affected, explaining the low incidence of non-haematopoietic toxicity of the cytostatic drug.

Unlike other nucleoside analogues cladribine is toxic in rapidly proliferating cells as well as in resting cells. The mechanism of action of cladribine is attributed to the incorporation of CdATP into DNA strands: The synthesis of new DNA in dividing cells is blocked and the DNA repair mechanism is inhibited resulting in an accumulation of DNA strand breaks and a decrease of NAD and ATP concentration even in resting cells. Furthermore, CdATP inhibits ribonucleotide reductase, the enzyme responsible for the conversion of ribonucleotides into deoxyribonucleotides. Cell death occurs from energy depletion and apoptosis.

Clinical Trials

Hairy cell leukaemia

Cladribine is particularly effective for the treatment of hairy cell leukaemia (HCL) capable of inducing long-term responses in the majority of patients after one cycle of a 7-day infusion only. The subcutaneous bolus injection for 5 days is clinically equivalent to continuous intravenous infusion for 7 days. The antimetabolite has been established as first line chemotherapy for this rare disorder.

In two non-randomised multicentre studies with LITAK solution the feasibility of the subcutaneous administration in comparison to the established and commonly used continuous intravenous application has been investigated. Twenty-three patients with evidence of active HCL disease were treated with one cycle of LITAK solution according to the standard regimen of 0.1 mg/kg/day as a continuous intravenous (i.v.) infusion for 7 days (control group). A second group of 62 HCL patients was treated with a single course of LITAK solution given by subcutaneous bolus injection for 5 consecutive days at a dose of 0.14 mg/kg/day. The total dose per treatment and cycle was 0.7 mg/kg in both groups. The patient characteristics were comparable in the two studies. Half of the patients have been pretreated with either chemotherapy and/or interferon-α at study entry, the other half had partly undergone splenectomy as the only prior treatment.

The overall response rate for patients with HCL was 96% and 97% in the control group (continuous i.v. administration) and the population receiving subcutaneous cladribine, respectively. Two patients of the control group with partial remission (PR) required a second cycle after 2 and 6 months, respectively in order to achieve a complete remission (CR). Two patients not achieving CR after the first cycle of s.c. 2-CdA, received a second or third cycle, respectively. The patient receiving a second s.c. bolus injection on 5 days achieved CR, whereas the patient treated with 2 additional continuous i.v. infusions of cladribine for 7 days remained in long-term PR.

After a median follow-up of 54 months, 5 patients of the control group had relapsed (22%). One patient of the control group died on day 28 due to infection. Twelve of the subcutaneously treated patients (19%) relapsed after a median follow-up time of 36 months.

LITAK solution is active in previously treated patients, although the overall CR rate decreases in pretreated versus non-pretreated patients (70% versus 76%).

Myelosuppression (neutropenia WHO grade >2) was comparable in both groups: 90% versus 98%, respectively. Opportunistic infections (WHO grade >1) were statistically not significantly different, i.e. 14% in patients treated with intravenously administered cladribine and 26% in patients receiving subcutaneous cladribine. Thrombocytopenia was more pronounced in patients receiving LITAK solution as a s.c. bolus injection (50% versus 19% of the control group). The significant variation of the platelet counts could be explained by the highly differing values at prestudy. It has to be considered that the incidence of haematological complications, such as myelosuppression, infections and thrombocytopenia, is influenced by the baseline pancytopenia, which is often regularly present in patients with hairy cell leukaemia. Furthermore, heamatological recovery is dependent on pretreatment levels of peripheral blood counts.

The overall response rates and percentage of remissions after long-term follow-up obtained in the non-randomised multicentre 2-cohort study using LITAK are comparable with the results described in the literature.

Lymphoplasmacytic Lymphoma (Waldenström's Macroglobulinaemia)

Twenty-five patients with lymphoplasmacytic lymphoma (LL) at Ann Arbor stage IV received 0.5 mg/kg/cycle of LITAK solution as subcutaneous bolus injections. All patients except one were pretreated (median number of prior treatments: 2), 6 patients were in relapse and 18 were refractory to the last chemotherapy. Altogether 67 cycles of 2-CdA were administered. The median number of cycles was 3 (range 1-6). Ten out of 25 patients (40%) responded to the therapy (95%-CI: 21-61%).

The IgM-counts are significantly decreased after 3 cycles as compared to the values measured before the therapy with 2-CdA (p=0.02).

The median time to treatment failure (TTF) was 4.4 months (range 0.5-33). The median follow-up time of all responding patients from therapy start to relapse or cut-off was 13.4 months (range 1-29). The median remission duration (RD) was 8 months (range 1- 29).

Severe neutropenia and thrombocytopenia (WHO grade >2) was observed in 30% and 10% of the cases and opportunistic infections occurred in 19% of the cycles. No long- lasting haematological toxicities were observed.

The overall response rates and remission duration obtained in the clinical trial using LITAK solution are comparable with results described in the literature.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Cladribine shows comparable bioavailability after subcutaneous or intravenous administration.

Distribution

In a study using a dose of 0.10 mg/kg body weight/day, the maximum plasma concentration C_{max} after continuous intravenous infusion was 5.1 ng/mL (t_{max}:12 hours) compared to 51 ng/mL after subcutaneous bolus injection (t_{max}:25 minutes).

Intracellular concentration of cladribine exceeds plasma drug concentration by 128 to 375 times. The mean volume of distribution of cladribine is 9.2 L/kg. Plasma protein binding of cladribine accounts on average 25% with a wide inter-individual variation (5 - 50%). Intrathecal concentrations of cladribine average 25% of plasma concentrations. Peak cerebrospinal fluid concentrations of 6 and 2 ng/mL, respectively, could be measured after intermittent 2-hour infusion or continuous intravenous infusion (dose: 0.12 mg/kg body weight/day).

Metabolism

Intracellular cladribine is metabolised predominantly by deoxycytidine kinase to 2-chlorodeoxyadenosine-5'-monophosphate that is further phosphorylated to the diphosphate by nucleoside monophosphate kinase and to the active metabolite 2-chlorodeoxyadenosine-5'-triphosphate (CdATP) by nucleoside diphosphate kinase.

Excretion

The terminal elimination half-life ($t_{1/2}$) of cladribine was approximately 10 hours after both intravenous infusion and subcutaneous bolus injection. The intracellular retention time of cladribine nucleotides *in vivo* is clearly prolonged as compared to the retention time in the plasma: Half-lives $t_{1/2}$ of initially 15 hours and subsequently more than 30 hours were measured in leukaemic cells.

Cladribine is eliminated mainly by the kidneys. The renal excretion of unmetabolised cladribine occurs within 24 hours and accounts 15% and 18% of the dose after 2-hour intravenous and subcutaneous administration, respectively. The fate of the remainder is unknown. The mean plasma clearance amounts to 794 mL/min after intravenous infusion and to 814 mL/min after subcutaneous bolus injection at a dose of 0.10 mg/kg body weight/day.

Pharmacokinetics in special clinical situations

There are no studies available using LITAK in patients with renal or hepatic impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The use of LITAK in children and patients older than 75 years has not been investigated.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cladribine is a cytotoxic drug, which has been shown to cause DNA damage. Cladribine is incorporated into DNA strands and inhibits DNA synthesis and repair. Exposure to cladribine induces DNA fragmentation and cell death in various normal and leukaemic cells and cell lines *in vitro*.

Carcinogenicity

Long-term studies in animals to evaluate the carcinogenic potential of cladribine have not been conducted. On the basis of available data, no evaluation can be made of the carcinogenic risk of LITAK to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LITAK solution contains sodium chloride, sodium hydroxide or hydrochloric acid (for pH adjustment) and water for injections.

6.2 INCOMPATIBILITIES

The use of glucose 5% as diluent is not recommended due to an expected degradation of cladribine. No data about incompatibilities with other parenteral diluents, additives, infusion systems, and cytostatic drugs are available. LITAK solution should not be diluted with other applicable drugs or additives for IV use. If the same infusion tube is used for consequent administration of several different drugs, the tubes should be rinsed by a compatible diluent prior to and after application of cladribine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Vials for single use only. Discard any residue.

6.5 NATURE AND CONTENTS OF CONTAINER

The solution is supplied in a 10 mL clear type I glass vial with a grey bromobutyl rubber stopper with a red flip-off aluminium polypropylene cap.

Pack sizes: 1 or 5 vials.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 104283 – LITAK cladribine 10 mg/5 mL injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

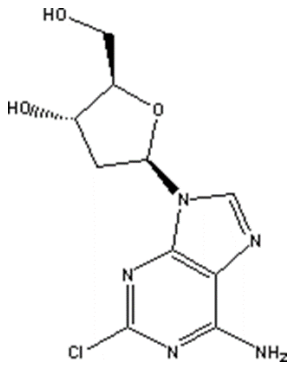
Procedures for proper handling and disposal of antineoplastic drugs should be considered. Cytotoxic drugs should be handled with caution. Avoid contact by pregnant women and keep out of the reach of children.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Cladribine is a chlorinated purine nucleoside analogue (cytostatic agent) with the chemical name 2-chloro-2'-deoxy-β-D-adenosine or 2-chloro-6-amino-9-(2-deoxy-β-D- erythropento-furanosyl)-purine.



Chemical Formula: $C_{10}H_{12}ClN_5O_3$

Molecular Weight: 285.7 g/mol

CAS Number

4291-63-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

01/07/2004

10 DATE OF REVISION

05/07/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Editorial updates
4.8	Update to frequency of tumour lysis syndrome in Table 3

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