

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

LITAK 2 mg/ml solution for injection

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

1 ml of solution for injection contains 2 mg of cladribine (2-CdA). Each vial of LITAK contains 10 mg of cladribine in 5 ml of solution for injection.

For excipients, see 6.1.

## **3. PHARMACEUTICAL FORM**

Solution for injection.

Clear, colourless solution.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

LITAK is indicated for the treatment of hairy cell leukaemia.

### **4.2 Posology and method of administration**

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

LITAK is supplied as a ready-to-use solution for 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 The recommended dose is directly withdrawn by a syringe and injected without dilution.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.

The recommended treatment for 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.

Deviations from the dosage regimen indicated above are not advised (see Section 4.9 Overdose).

Experience with patients older than 75 years is limited. 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.

There are no data on the use of LITAK in patients with renal or hepatic impairment. LITAK is contraindicated in patients with moderate to severe renal impairment (creatinine clearance  $\leq 50$  ml/min) or with moderate to severe hepatic impairment (Child-Pugh score  $\geq 4$ ) (see Section 4.3 Contraindications, Section 4.4 Special warnings and special precautions for use and Section 5.2 Pharmacokinetic properties).

### ***Paediatric use***

LITAK is contraindicated in patients less than 16 years of age.

### **4.3 Contraindications**

Hypersensitivity to the active substance or any of the excipients.

During pregnancy and lactation.

In patients less than 16 years of age.

In patients with moderate to severe renal impairment (creatinine clearance  $\leq 50$  ml/min) or with moderate to severe hepatic impairment (Child-Pugh score  $\geq 4$ ) (see also Section 4.4 Special warnings and special precautions for use).

Concomitant use of other myelosuppressive medicinal products.

#### **4.4 Special warnings and special precautions for use**

Cladribine is an antineoplastic and immunosuppressive substance that can induce considerable toxic adverse reactions, such as 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 cladribine. Although anti-infective prophylaxis is not generally recommended, it may be beneficial for patients immunocompromised prior to therapy with cladribine or for patients with a pre-existing agranulocytosis.

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.

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

##### ***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 time of 8.4 years. Therefore, patients treated with cladribine should be regularly monitored.

##### ***Haematology***

During the first month following treatment, myelosuppression is most notable and red blood cell or platelet transfusions may be required. Patients with symptoms 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. Dose reduction and regular monitoring of the patient is required in such cases. Pancytopenia is normally reversible and the intensity of bone marrow aplasia is dose-dependent. An increased incidence of opportunistic infections is expected during, and for 6 months following, therapy with cladribine. Careful and regular monitoring of peripheral blood counts is essential during, and for 2 to 4 months following, treatment with cladribine to detect potential adverse reactions 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 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.

#### ***Renal and hepatic function***

There are no data on the use of LITAK in patients with renal or hepatic impairment. Clinical experience is very limited and safety of LITAK in these patients is not well established (see Section 5.2 Pharmacokinetic properties).

Careful treatment is required in elderly patients and in patients with known or suspected renal or hepatic dysfunction. For all patients treated with LITAK, periodic assessment of renal and hepatic function is advised as clinically indicated.

#### ***Prevention of tumour lysis syndrome***

In patients with a high tumour burden, prophylactic allopurinol therapy to control serum levels of uric acid, together with adequate or increased hydration, should be commenced 24 hours before the start 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.

#### ***Impairment of fertility***

Men being treated with cladribine are 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 (see Section 5.3 Preclinical safety data).

### **4.5 Interaction with other medicinal products and other forms of interaction**

Due to a potential increase of haematological toxicity and bone marrow suppression, cladribine should not be used concomitantly with other myelosuppressive medicinal products. Cross-reactions with other antineoplastic agents *in vitro* (e.g. doxorubicin, vincristine, cytarabine, cyclophosphamide) and *in vivo* have not been observed. However, an *in vitro* study revealed cross-resistance between cladribine and nitrogen mustard (chlormethine); for cytarabine, one author has described an *in vivo* cross-reaction without loss of activity. Due to the similar intracellular metabolism, cross-resistance with other nucleoside analogues, such as fludarabine or 2'-deoxycytosine 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 drugs 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 Pregnancy and lactation**

Cladribine causes serious birth defects when administered during pregnancy. Animal studies and *in vitro* studies with human cell lines demonstrated the teratogenicity and mutagenicity of cladribine. Cladribine is contraindicated during pregnancy. Women of childbearing potential have to use effective contraception during treatment with cladribine. In case of pregnancy during therapy with cladribine, the woman should be informed about the potential hazard to the foetus.

It is unknown whether cladribine is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, cladribine is contraindicated during lactation. Therefore, nursing is contraindicated during or following treatment with cladribine.

### **4.7 Effects on ability to drive and use machines**

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

#### **4.8 Undesirable effects**

Very common adverse reactions 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) were myelosuppression, especially severe neutropenia (41% (113/279), 98% (HCL, 61/62)), severe thrombocytopenia (21% (58/279), 50% (HCL, 31/62)) and severe anaemia (14% (21/150), 55% (HCL, 34/62)), as well as severe immunosuppression/lymphopenia (63% (176/279), 95% (HCL, 59/62)), infections (39% (110/279), 58% (HCL, 36/62)) and fever (up to 64%).

Culture-negative fever following treatment with cladribine 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 adverse events 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 cladribine. LITAK is unlikely to cause alopecia; mild and transient alopecia for a few days was observed in 4/523 patients during the treatment with LITAK, but could not clearly be associated with cladribine.

Adverse reactions that have been reported including information on frequency are listed in the table below. The frequencies are defined as follows: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000) including isolated reports. For severity, please see text below the table.

Infections and infestations	Very common: infections * (e.g. pneumonia *, septicaemia *)
Neoplasms benign, malignant and unspecified	Common: second malignancies *
Vascular disorders	Very common: pancytopenia/myelosuppression *, purpura Common: petechiae, haemorrhages *
Immune system disorders	Very common: immunosuppression * Uncommon: haemolytic anaemia * Very rare: graft-versus-host disease *, tumour lysis syndrome *
Metabolism and nutrition disorders	Very common: decreased appetite
Nervous system disorders	Very common: headache, dizziness Common: insomnia, anxiety Uncommon: somnolence, paraesthesia, weakness, lethargy, polyneuropathy, confusion, ataxia Very rare: depression, epileptic seizure
Eye disorders	Uncommon: conjunctivitis Very rare: blepharitis
Cardiac disorders	Common: tachycardia, heart murmur, hypotension, epistaxis, myocardial ischemia *
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 Very rare: lung embolism
Gastrointestinal disorders	Very common: nausea, vomiting, constipation, diarrhoea Common: gastrointestinal pain, flatulence
Hepato-biliary disorders	Common: reversible, mostly mild increases in bilirubin and transaminases Very rare: cholecystitis
Skin and subcutaneous tissue disorders	Very common: rash, localised exanthema, diaphoresis Common: pruritus, skin pain, erythema, urticaria Uncommon: phlebitis
Musculoskeletal and connective tissue disorders	Common: myalgia, arthralgia, arthritis, bone pain
General disorders and administration site conditions	Very common: injection site reactions, fever, fatigue, chills, asthenia Common: oedema, malaise, pain Uncommon: cachexia Very rare: amyloidosis

\* see descriptive section below.

Non-haematological adverse reactions are generally mild to moderate in severity. Treatment of nausea with antiemetics is usually not necessary. Adverse reactions related to skin and subcutaneous tissue are mostly mild or moderate and transient, usually resolving within a cycle interval of 30 days.

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 ( $< 1.0 \times 10^9/l$ ). The use of haematopoietic growth factors neither improves the recovery of neutrophil counts nor decreases the incidence of fever. Severe thrombocytopenias ( $< 50 \times 10^9/l$ ) are observed in about 20% to 30% of all patients. Lymphocytopenia lasting for several months and immunosuppression with an increased risk of 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-lymphocytes is delayed for up to 2 years.

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

Severe long-term lymphocytopenias are reported occasionally which, however, could not be associated with late infectious complications. The most common severe complications with partially fatal outcome are opportunistic infections (e.g. pneumocystis carinii, toxoplasmosis 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.

Serious adverse events 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.

The majority of deaths related to the medicinal product 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.

#### **4.9 Overdose**

Common symptoms of 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), Guillan-Barré syndrome, and Brown-Séquard syndrome. 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 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 cladribine. Patients who have been exposed to overdosage of cladribine should be monitored haematologically for at least four weeks.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmaco-therapeutic group: Purine analogue (cytostatic medicinal product)

ATC code: L01BB04

LITAK contains cladribine as active substance, 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 in cells after parenteral administration, and is phosphorylated intracellularly to the active nucleotide 2-chlorodeoxyadenosine-5'-triphosphate (CdATP) 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-haematologic tissues seem to be unaffected, explaining the low incidence of non-haematopoietic toxicity of the cytostatic medicinal product.

Unlike other nucleoside analogues cladribine is toxic in rapidly proliferating cells as well as in resting cells. No cytotoxic effect of cladribine could be observed in cell lines of solid tumours. 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 (nicotinamide adenine dinucleotide) 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.

## 5.2 Pharmacokinetic properties

### *Clinical pharmacokinetics*

#### *Absorption*

Cladribine shows complete bioavailability after parenteral administration; the mean area under the concentration versus time curve (AUC) in plasma is comparable after continuous or intermittent 2-hour intravenous infusion and after subcutaneous injection.

#### *Distribution*

The steady-state plasma concentration of cladribine amounts to about 7 ng/ml and is reached within 5 to 8 hours after the start of a 2-hour infusion. A maximum plasma concentration  $C_{\max}$  of 48 ng/ml is measured on average 112 minutes after the infusion. After subcutaneous bolus injection a maximum plasma concentration  $C_{\max}$  of 91 ng/ml is reached on average after 20 minutes only (dose: 0.14 mg/kg body weight/day). In another 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). The clinical relevance of the different peak plasma concentrations after intravenous and subcutaneous administration of cladribine has not been examined.

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 is 25% on average with a wide interindividual variation (5 - 50%). Intrathecal concentrations of cladribine average 18 - 25% of the plasma concentrations in studies with intravenous administration. 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). In one single patient administered LITAK by subcutaneous bolus, intrathecal concentration after 2 hours reached 8.75% of the plasma concentration, but further experience is needed.

#### *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.

#### *Elimination*

Pharmacokinetic studies in humans showed that the plasma concentration curve of cladribine fits a 2- or 3-compartment model with  $\alpha$ - and  $\beta$ -half-lives of on average 35 minutes and 6.7 hours, respectively. The terminal plasma half-life  $t_{1/2}$  amounted to 7 - 10 hours after continuous intravenous administration for 7 days (0.10 mg/kg body weight/day) and was on average 19.5 hours after

intermittent 2-hour intravenous infusion on 5 consecutive days (0.14 mg/kg body weight/day). The biexponential decline of the serum concentration of cladribine after subcutaneous bolus injection is comparable to elimination parameters after 2-hour intravenous infusion with an initial and terminal half-life of approximately 2 hours and 11 hours, respectively. 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 for 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 populations***

There are no studies available using cladribine in patients with renal or hepatic impairment (see also Section 4.2 Posology and method of administration and Section 4.4 Special warnings and special precautions for use). Clinical experience is very limited and safety of LITAK in these patients is not well established. LITAK is contraindicated in patients with moderate to severe renal impairment or with moderate to severe hepatic impairment.

The use of LITAK in children has not been investigated. Experience with patients older than 75 years is limited. Elderly patients should be treated by individual assessment and careful monitoring of the blood counts and of the renal and hepatic function.

### **5.3 Preclinical safety data**

Cladribine is moderately acutely toxic to mice, with an  $LD_{50}$  of 150 mg/kg by intraperitoneal administration.

In 7- to 14-day continuous intravenous infusion studies in Cynomolgus monkeys, the target organs were the immune system ( $\geq 0.3$  mg/kg/day), bone marrow, skin, mucous membranes, nervous system and testes ( $\geq 0.6$  mg/kg/day) and kidneys ( $\geq 1$  mg/kg/day). Unless fatal, indications were that most or all of these effects would be slowly reversible upon cessation of exposure.

Cladribine is teratogenic in mice (at doses of 1.5 – 3.0 mg/kg/day, given on gestation days 6 – 15). Effects on sternal ossification were seen at 1.5 and 3.0 mg/kg/day. Increased resorptions, reduced live litter sizes, reduced foetal weights and increased foetal malformations of the head, trunk and appendages were seen at 3.0 mg/kg/day. In rabbits, cladribine is teratogenic at doses of 3.0 mg/kg/day (given on gestation days 7 – 19). At this dosage, severe limb anomalies were seen as well as a significant decrease in the mean foetal weight. Reduced ossification was observed at 1.0 mg/kg/day.

#### ***Carcinogenesis/mutagenesis***

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 cladribine to humans.

Cladribine is a cytotoxic medicinal product, which is mutagenic to cultured mammalian cells. 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 at concentrations of 5 nM to 20  $\mu$ M.

#### ***Impairment of 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 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 (see Section 4.4 Special warnings and special precautions for use).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium chloride  
Sodium hydroxide  
Hydrochloric acid  
Water for injections

### **6.2 Incompatibilities**

LITAK must not be mixed with other medicinal products.

### **6.3 Shelf-life**

4 years.

From a microbiological point of view, unless the opening precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

### **6.4 Special precautions for storage**

Store at 2°C - 8°C (in a refrigerator).

Do not freeze.

### **6.5 Nature and contents of container**

10 ml type I glass vial with rubber stopper (bromobutyl) and flip-off aluminium cap.

Packs contain 1 or 5 vials each with 5 ml of solution.

### **6.6 Instructions for use, handling and disposal**

Procedures for proper handling and disposal of antineoplastic medicinal products should be used. Cytotoxic medicinal products should be handled with caution. Avoid contact by pregnant women.

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 area immediately with copious amounts of water.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

The vials are for single use only. Remaining contents should be disposed of appropriately.

## **7. MARKETING AUTHORISATION HOLDER**

Lipomed GmbH  
Schönaugasse 11  
D-79713 Bad Säckingen

Germany

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

**ANNEX II**

- A. MANUFACTURING AUTHORISATION HOLDER  
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Lipomed GmbH  
Schönaugasse 11  
D-79713 Bad Säckingen  
Germany

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

• **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**OUTER CARTON (1-VIAL PACK)**

**1. NAME OF THE MEDICINAL PRODUCT**

LITAK 2 mg/ml solution for injection  
cladribine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

5 ml solution for injection contain cladribine 10 mg (2 mg/ml)

**3. LIST OF EXCIPIENTS**

Contains sodium chloride, sodium hydroxide, hydrochloric acid and water for injections

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 vial containing 5 ml solution for injection

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use

Read the package leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Handle with caution (see package leaflet)

For single use only

**8. EXPIRY DATE**

Exp. date

**9. SPECIAL STORAGE CONDITIONS**

Store at 2°C – 8°C (in a refrigerator)

Do not freeze

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any portion of the contents remaining after use should be disposed of appropriately

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Lipomed GmbH  
Schönaugasse 11  
D-79713 Bad Säckingen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/275/001

**13. MANUFACTURER'S BATCH NUMBER**

Batch no.

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

Use as directed by medical practitioner

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**OUTER CARTON (5-VIAL PACK)**

**1. NAME OF THE MEDICINAL PRODUCT**

LITAK 2 mg/ml solution for injection  
cladribine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

5 ml solution for injection contain cladribine 10 mg (2 mg/ml)

**3. LIST OF EXCIPIENTS**

Contains sodium chloride, sodium hydroxide, hydrochloric acid and water for injections

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 vials each containing 5 ml solution for injection

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use

Read the package leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Handle with caution (see package leaflet)

For single use only

**8. EXPIRY DATE**

Exp. date

**9. SPECIAL STORAGE CONDITIONS**

Store at 2°C – 8°C (in a refrigerator)

Do not freeze

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any portion of the contents remaining after use should be disposed of appropriately

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Lipomed GmbH  
Schönaugasse 11  
D-79713 Bad Säckingen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/275/002

**13. MANUFACTURER'S BATCH NUMBER**

Batch no.

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

Use as directed by medical practitioner

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

LITAK 2 mg/ml solution for injection  
cladribine

Subcutaneous use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use

**3. EXPIRY DATE**

Exp. date

**4. BATCH NUMBER**

Batch no.

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 ml

**B. PACKAGE LEAFLET**

## PACKAGE LEAFLET

**Read all of this leaflet carefully before you start using this medicine.**

Keep this leaflet. You may need to read it again.

If you have further questions, please ask your doctor or your pharmacist.

This medicine has been prescribed for you personally and you should not pass it on to others. Even if their symptoms are the same as yours, it may harm them.

### **In this leaflet**

1. What LITAK is and what it is used for
2. Before you use LITAK
3. How to use LITAK
4. Possible side effects
5. Storing LITAK
6. Information on how to inject LITAK

### **LITAK 2 mg/ml solution for injection cladribine**

The active substance is cladribine. Each vial contains 10 mg of cladribine in 5 ml of solution (2 mg per ml solution).

The other ingredients are sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

### **Marketing authorisation holder**

Lipomed GmbH  
Schönaugasse 11  
D-79713 Bad Säckingen  
Germany

### **Manufacturer**

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Germany

## **1. WHAT LITAK IS AND WHAT IT IS USED FOR**

LITAK is a solution for injection. Pack sizes with 1 vial or 5 vials of 5 ml of solution are available. The solution is clear and colourless.

LITAK has been prescribed by your doctor for the treatment of hairy cell leukaemia, a malignant disease of white blood cells.

## **2. BEFORE YOU USE LITAK**

### **Do not use LITAK**

- if you are hypersensitive (allergic) to cladribine or to any of the other ingredients in LITAK,

- if you are pregnant or breast-feeding,
- if you are less than 16 years of age,
- if you have moderate to severe kidney or liver dysfunction,
- if you take other medicines, which inhibit the production of blood cells in bone marrow.

***Please tell your doctor***

if you are suffering or have suffered from:

- infections,
- fever,
- liver disease,
- kidney disease.

**You should know before taking LITAK that**

- your treatment with LITAK has been prescribed by a qualified doctor experienced in cancer chemotherapy. If you suffer from an infection, this will be treated before treatment with LITAK. If you notice any signs of fever or infections (such as flu-like symptoms) during or after treatment with LITAK, be sure to inform your doctor immediately. Before you start treatment with LITAK and during treatment, you will have regular blood tests to check whether it is safe for you to continue with your treatment. In addition, the proper function of your liver and your kidneys will be checked. Your doctor may decide that you should receive blood transfusions or that you should receive an additional medicine containing the active substance allopurinol in order to reduce excess of uric acid. If you want to father a child, please tell your doctor before treatment with LITAK is started. You should not father a child up to 6 months after treatment with LITAK. Your doctor may advise you about the possibility to store deep-frozen sperm.

**Pregnancy**

LITAK must not be used if you are pregnant or if you are planning to become pregnant since it may cause harm to the unborn baby. You must take adequate contraceptive precautions during therapy and for at least three months after LITAK is no longer administered to you. If pregnancy occurs during your treatment, you must immediately inform your doctor.

**Breast-feeding**

You must not breast-feed while you are treated with LITAK.

**Driving and using machines**

LITAK has a major effect on the ability to drive and use machines since it may make you feel drowsy or dizzy. If you feel drowsy or dizzy, you should not drive a vehicle or operate machines.

**Using other medicines**

Take special care with LITAK if you are using any other medicines that affect the production of blood cells (e.g. other anti-cancer medicines or steroids).

Please tell your doctor:

- if you are using any other medicines which have been prescribed by a doctor for any other condition (e.g. antiviral medicines),
- if you are using any other medicines that you have bought for yourself without a prescription.

### 3. HOW TO USE LITAK

LITAK will be injected under your skin (subcutaneous use). LITAK should be injected at about the same time each day. The correct dosage will be calculated by your doctor and the treatment schedule will be explained to you in detail. The dosage depends on your body weight. The recommended dosage is a single course of LITAK at a dose of 0.14 mg per kg body weight per day for five consecutive days.

LITAK is supplied as ready-to-use solution for subcutaneous injection. The recommended dose is directly withdrawn by a syringe and injected without dilution. Allow LITAK to warm up to room temperature before administration.

Do not use vials which are damaged, or if the solution is not clear or if it contains any particles.

LITAK should be handled with caution. Avoid contact by pregnant women. The use of disposable gloves and protective garments is recommended when handling and administering LITAK. If LITAK contacts the skin or eyes, rinse the involved surface immediately with copious amounts of water.

If you are injecting LITAK by yourself, you will be instructed how to prepare and to give the injection. Detailed instructions for subcutaneous injection are provided at the end of this leaflet.

LITAK should not be mixed with other medicines.

In case you inject an incorrect dose or you miss an injection of a dose, please report this immediately to your doctor.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, LITAK can have side effects. Side effects may occur during or following treatment. Your doctor will discuss the side effects of LITAK with you and will explain the risks and the benefits of your treatment.

Possible side effects may include:

(Frequencies are defined as follows: very common (more than 1 out of 10 persons), common (more than 1 out of 100 persons and less than 1 out of 10 persons), uncommon (more than 1 out of 1,000 persons and less than 1 out of 100 persons), rare (more than 1 out of 10,000 persons and less than 1 out of 1,000 persons), very rare (less than 1 out of 10,000 persons including isolated reports)

- ***Blood and immune system disorders:***

These are **very common** side effects of treatment with LITAK due to its inhibition of production of blood cells in bone marrow. A lower number of certain white blood cells (neutrophils, platelets and lymphocytes) may be found in your blood. Your blood may not contain enough red blood cells (anaemia). Your immune system may become impaired (immunosuppression). This could cause fever (high body temperature) as you may be more likely to develop infections.

**Common:** The lower number of platelets can cause unusual bleeding (for example nose or skin bleeds).

**Uncommon:** Prematurely induced destruction of red blood cells.

**Very rare:** Rejection response to blood transfusions and harmful effects due to the destruction of the tumour.

- ***Nervous system disorders:***  
**Very common:** Headache, dizziness, drowsiness.  
**Common:** Sleeplessness, anxiety.  
**Uncommon:** Sleepiness, numbness and tingling of the skin, weakness/feebleness, inactivity, disorder of peripheral nerves, confusion, impaired ability to coordinate movements.  
**Very rare:** Depression, epileptic attack.
- ***Eye problems:***  
**Uncommon:** Eye inflammation (conjunctivitis).  
**Very rare:** Swelling of the eyelid.
- ***Heart problems:***  
**Common:** Increased heart rate, heart murmur, low blood pressure, decreased blood supply to the heart muscle.
- ***Respiratory disorders:***  
**Very common:** Abnormal breath sounds, abnormal chest sounds, cough.  
**Common:** Shortness of breath, swelling (infiltrations) in lung tissue due to infection, inflammation of mouth and tongue.  
**Uncommon:** Sore throat.  
**Very rare:** Blood clot in the lung (lung embolism).
- ***Gastrointestinal and liver side effects:***  
**Very common:** Feeling and being sick, vomiting, constipation and diarrhoea.  
**Common:** Gastrointestinal pain and presence of excessive amount of gas in the stomach or bowels (flatulence), mostly mild increases in liver laboratory values (bilirubin, transaminases) which will return to normal values once treatment is over.  
**Rare:** Severely reduced liver function.  
**Very rare:** Inflammation of the gallbladder.
- ***Kidney disorders:***  
**Rare:** Reduced kidney function.
- ***Skin reactions:***  
**Very common:** Skin eruption (rash), swelling, redness as well as soreness around the site of injection, sweating.  
**Common:** Itching, itching skin eruption (urticaria) and skin pain.  
**Uncommon:** Inflammation of a vein.  
Skin reactions are mostly mild to moderate and usually resolve within a few days.
- ***General disorders:***  
**Very common:** Tiredness, chills, decreased appetite.  
**Common:** Swelling in tissues (oedema), not feeling well, pain (muscle pain, joint pain, and bone pain).  
**Uncommon:** Malnutrition.  
**Very rare:** Reduced function of organs due to high amounts of a specific substance produced by the body (a glycoprotein).
- Repeated occurrence of malignant disease cannot be excluded.

You may experience one or several of these symptoms; be sure to inform your doctor if you do.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

## 5. STORING LITAK

Keep out of the reach and sight of children.

Store at 2°C to 8°C (in a refrigerator).

Do not freeze.

Do not use LITAK after the expiry date stated on the vial label and the outer carton.

## **6. INFORMATION ON HOW TO INJECT LITAK**

This section contains information on how to give an injection of LITAK. It is important that you do not try to give yourself the injection unless you have been instructed by your doctor or nurse. Syringes must be disposed in a puncture-proof container. If you have any question with regard to giving the injection, please ask your doctor or nurse for help.

### **How do I inject LITAK myself?**

You will need to give yourself an injection into the tissue just under the skin. This is known as subcutaneous injection. Your doctor will tell you how much LITAK you need and how often and when you have to inject yourself.

### **Equipment needed**

To give yourself a subcutaneous injection, you will need:

- one vial of LITAK (or two vials if you need to inject more than 5 ml),
- one sterile syringe (e.g. 10 ml LUER syringe),
- one sterile injection needle (e.g. 0.5 x 19 mm, 25 G x 3/4''),
- alcohol wipes,
- a puncture-proof container for safe disposal of the used syringe.

### **What should I do before I give myself a subcutaneous injection of LITAK?**

1. Before injection, allow LITAK to warm up to room temperature.
2. Wash your hands thoroughly.
3. Find a comfortable, well-lit place and put everything you need where you can reach it.

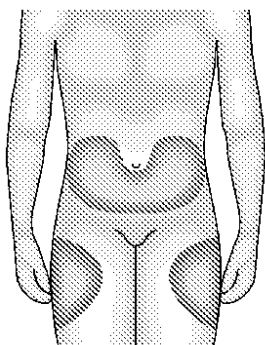
### **How do I prepare the injection?**

Before you inject LITAK, you must do the following:

1. Remove the red protective cap from the LITAK vial. Do not remove the rubber stopper of the vial. Clean the rubber top of the vial with an alcohol wipe. Remove the syringe from the wrapping without touching the tip of the syringe. Remove the injection needle from the wrapping and place it firmly on the tip of the syringe. Remove the needle guard without touching the needle.
2. Push the needle through the rubber stopper of the vial and turn the vial and the syringe upside down. Be sure that the tip of the needle is in the solution.

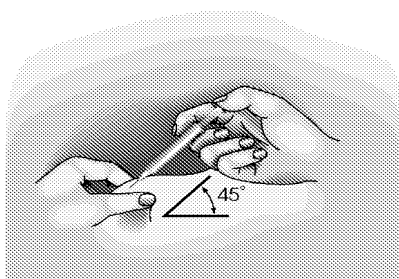
3. Draw the correct volume of LITAK into the syringe by pulling back the plunger (your doctor will inform you how many ml of LITAK you need to inject).
4. Pull the needle out of the vial.
5. Make sure there is no air left in the syringe: point the needle upwards and push the air out.
6. Check you have the right volume.
7. Inject straight away.

### **Where should I give my injection?**



The most suitable places to inject yourself are shown here: the top of your thighs and the abdomen, except for the area around the navel. If someone else is injecting you, they can also use the outer surface of the upper arms or the buttocks.

### **How do I give my injection?**



1. Disinfect your skin by using an alcohol wipe, wait for the area to dry and pinch the skin between your thumb and forefinger, without squeezing it.
2. Put the needle fully into the skin at an angle of about  $45^\circ$ , as shown in the picture.
3. Pull slightly on the plunger to check that no blood vessel has been punctured. If you see blood in the syringe, remove the needle and re-insert it in another place.
4. Inject the liquid slowly and evenly for approximately one minute, always keeping the skin pinched.
5. After injecting the liquid, remove the needle.
6. Put the used syringe in the puncture-proof container. Use a new syringe and injection needle for each injection. The vials are for single use only. Return any portion of the contents remaining after use to your doctor or pharmacist for proper disposal.

### **Disposing of used syringes**

Put used syringes into a puncture-proof container and keep it out of the reach and sight of children.

Dispose the puncture-proof container as instructed by your doctor, nurse or pharmacist.

Do not put used syringes into the normal household garbage bin.

**This leaflet was last approved on.....**