ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LITAK 2 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 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.

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

Deviations from the posology indicated above are not advised.

Elderly
Experience with patients older than 65 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 (see section 4.4).

Renal and hepatic impairment
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 ≤ 50 ml/min) or with moderate to severe hepatic impairment (Child-Pugh score > 6) (see sections 4.3, 4.4 and 5.2).

Paediatric population
LITAK is contraindicated in patients less than 18 years of age (see section 4.3).

Method of administration
LITAK is supplied as a ready-to-use solution for injection. The recommended dose is directly withdrawn by a syringe and injected as a subcutaneous bolus injection without dilution. LITAK should be inspected visually for particulate matter and discoloration prior to administration. LITAK should warm up to room temperature prior to administration.

Self-administration by the patient
LITAK can be self-administered by the patient. Patients should be instructed and trained appropriately. Detailed instructions are contained in the Package Leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

Pregnancy and lactation.

Patients less than 18 years of age.

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).

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 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).

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.

Haematologic toxicity

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 impairment

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 sections 4.3 and 5.2). Careful treatment is required in patients with known or suspected renal or hepatic impairment. For all patients treated with LITAK, periodic assessment of renal and hepatic function is advised as clinically indicated.

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 (see section 4.2).

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.

Fertility

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 (see sections 4.6 and 5.3).

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 must not be used concomitantly with other myelosuppressive medicinal products. An influence of cladribine on the activity of other antineoplastic agents has not been observed *in vitro* (e.g. doxorubicin, vincristine, cytarabine, cyclophosphamide) and *in vivo*. 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'-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

Pregnancy
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 in pregnancy.

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 woman should be informed about the potential hazard to the foetus.

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

Fertility
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 5.3).

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 (see section 4.4).

4.7 Effects on ability to drive and use machines

LITAK has a major influence on the ability to drive and use machines. In case certain adverse reactions with a potential impact on performance occur (e.g. dizziness, very common, or drowsiness, which may occur due to anaemia, which is very common), patients should be advised not to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Very common adverse reactions observed during the three most relevant clinical trials with cladribine in 279 patients treated for various indications and in 62 patients with hairy cell leukaemia (HCL) were myelosuppression, especially severe neutropenia (41% (113/279), HCL 98% (61/62)), severe thrombocytopenia (21% (58/279), HCL 50% (31/62)) and severe anaemia (14% (21/150), HCL 55% (34/62)), as well as severe immunosuppression/lymphopenia (63% (176/279), HCL 95% (59/62)), infections (39% (110/279), HCL 58% (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 concomitantly administered medicinal products known to cause rash (antibiotics and/or allopurinol). Gastrointestinal adverse reactions 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. Cladribine is unlikely to cause alopecia; mild and transient alopecia for a few days was observed in 4/523 patients during the treatment, but could not clearly be associated with cladribine.

Tabulated list of adverse reactions

Adverse reactions that have been reported are listed in the table below by frequency category and system organ class. The frequencies are defined as follows: 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), very rare (<1/10,000), not known (cannot be estimated from the available data). For severity, please see text below the table.

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 * Rare: hypereosinophilia Very rare: amyloidosis
Immune system disorders	Very common: immunosuppression * Rare: graft-versus-host disease *
Metabolism and nutrition disorders	Very common: decreased appetite Uncommon: cachexia
Nervous system disorders	Very common: headache, dizziness Common: insomnia, anxiety Uncommon: somnolence, paraesthesia, lethargy, polyneuropathy, confusion, ataxia Rare: apoplexy, neurological disturbances in speech and swallowing Very rare: depression, epileptic seizure
Eye disorders	Uncommon: conjunctivitis Very rare: 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 Very rare: 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 Rare: hepatic failure Very rare: cholecystitis
Skin and subcutaneous tissue disorders	Very common: rash, localised exanthema, diaphoresis Common: pruritus, skin pain, erythema, urticaria Rare: Stevens-Johnson syndrome/Lyell syndrome
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 below.

Description of selected adverse reactions

Non-haematological adverse reactions

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.

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 neutrophil 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 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.

Infections

Severe long-term lymphocytopenias have been reported rarely 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 dose 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 have been reported. All patients were successfully treated with 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 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.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Frequently observed symptoms of overdose 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. Acute, irreversible neuro- and nephrotoxicity 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 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 for at least four weeks.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Purine analogues, ATC code: L01BB04

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

Mechanism of action
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 cladribine

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.

Clinical efficacy
In the clinical trial using LITAK subcutaneously, 63 patients with hairy cell leukaemia (33 newly diagnosed patients and 30 patients with relapsed or progressive disease) were treated. The overall response rate was 97% with long-lasting remission, with 73% of patients staying in complete remission after four years follow-up time.

5.2 Pharmacokinetic properties

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

Distribution
After subcutaneous bolus injection of a 0.14 mg/kg cladribine dose, a C_{max} of 91 ng/ml is reached on average after 20 minutes only. 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).

Intracellular concentration of cladribine exceeds its plasma 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%).

Biotransformation
The prodrug cladribine is metabolised intracellularly, 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 α- and β-half-lives of on average 35 minutes and 6.7 hours, respectively. 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.

Special populations
Renal and hepatic impairment
There are no studies available using cladribine in patients with renal or hepatic impairment (see also section 4.2 and section 4.4). 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 (see section 4.3).

Paediatric use
The use of LITAK in children has not been investigated (see section 4.2).

Elderly
Experience with patients older than 65 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 (≥ 0.3 mg/kg/day), bone marrow, skin, mucous membranes, nervous system and testes (≥ 0.6 mg/kg/day) and kidneys (≥ 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 dose, 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 µM.

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 sections 4.4 and 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
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 in a refrigerator (2°C-8°C).

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. Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

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. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
D-79576 Weil/Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/275/001
EU/1/04/275/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14/04/2004
Date of last renewal: 27/03/2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Lipomed GmbH
Hegenheimer Strasse 2
D-79576 Weil/Rhein
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER 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)

Each ml solution contains 2 mg cladribine.
10 mg/5 ml

3. LIST OF EXCIPIENTS

Contains sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic. Special handling precautions (see package leaflet)

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store 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 unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
D-79576 Weil/Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/275/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER 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)

Each ml solution contains 2 mg cladribine.
10 mg/5 ml

3. LIST OF EXCIPIENTS

Contains sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic. Special handling precautions (see package leaflet)

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store 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 unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
D-79576 Weil/Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/275/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg/5 ml

6. OTHER

Cytotoxic

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

LITAK 2 mg/ml solution for injection
cladribine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LITAK is and what it is used for

LITAK contains the active substance cladribine. Cladribine is a cytostatic agent. It affects the growth of malignant (cancerous) white blood cells which play a role in hairy cell leukaemia. LITAK is used to treat this disease.

2. What you need to know before you use LITAK

Do not use LITAK
- if you are allergic to cladribine or any of the other ingredients of LITAK (listed in section 6)
- if you are pregnant or breast-feeding
- if you are less than 18 years of age
- if you have moderate to severe kidney or liver impairment
- if you are using other medicines which affect the production of blood cells in the bone marrow (myelosuppression).

Warnings and precautions
Talk to your doctor or pharmacist before using LITAK.

At any time during or after your treatment, **tell your doctor or nurse immediately** if you: experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy **(PML)**.

If you had these symptoms prior to treatment with cladribine, **tell your doctor** about any change in these symptoms.

Tell your doctor if you have or have had:
- liver or kidney problems
- **infections**
  - if you suffer from an infection, this will be treated before you start using LITAK.
  - if you notice any signs of infections (such as flu-like symptoms or fever) during or after treatment with LITAK, inform your doctor immediately.
- fever

Before and during treatment with LITAK, you will have regular blood tests to check whether it is safe for you to continue with your treatment. Your doctor may decide that you should receive blood transfusions to improve your level of blood cells. In addition, the proper function of your liver and your kidneys will be checked.

If you want to father a child, please tell your doctor before treatment with LITAK is started. You should not father a child during treatment and up to 6 months after treatment with LITAK. Your doctor may advise you about the possibility to store deep-frozen sperm (cryoconservation).

Other medicines and LITAK
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, tell your doctor if you are using any medicines containing:
- corticosteroids, commonly used to treat inflammation
- antiviral agents, used to treat viral infections

You must not use LITAK with other medicines that affect the production of blood cells in the bone marrow (myelosuppression).

Pregnancy and breast-feeding
Your must not use LITAK if you are pregnant. You must take adequate contraceptive precautions during therapy and for at least six months after your last LITAK dose. If pregnancy occurs during your treatment, you must immediately inform your doctor.

You must not breast-feed while you are treated with LITAK and for at least six months after your last LITAK dose.

Driving and using machines
LITAK has a major effect on the ability to drive and use machines. If you feel drowsy, which may occur due to a low number of red blood cells caused by LITAK treatment, or dizzy, you should not drive or use machines.

3. How to use LITAK

Always use LITAK as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will calculate your dose according to your body weight and explain the treatment schedule in detail. The recommended daily dose is 0.14 mg per kg body weight for five consecutive days (single treatment course).

LITAK has to be injected under your skin (subcutaneous injection), at about the same time each day. If you are injecting LITAK yourself, first you must receive adequate training by your doctor or nurse. You will find detailed instructions for injection at the end of this leaflet.

You may also receive an additional medicine containing the active substance allopurinol in order to reduce excess of uric acid.

If you use more LITAK than you should
In case you inject an incorrect dose, tell your doctor immediately.

If you forget to use LITAK
Do not inject a double dose to make up for a forgotten dose. In case you miss an injection of a dose, tell your doctor immediately.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, LITAK can cause side effects, although not everybody gets them.

Tell your doctor immediately if you have any of the following during or after treatment with LITAK:
- any signs of infections (such as flu-like symptoms)
- fever

Repeated occurrence of malignant (cancerous) disease cannot be excluded. This means that the risk that you develop a malignant disease in the future is slightly higher than for healthy people. This slightly increased risk can be due to hairy cell leukaemia or to therapies used to treat the disease including LITAK.

The following side effects may occur:

Very common side effects (may affect more than 1 in 10 people)
- Infections.
- Fever.
- Low numbers of certain white blood cells (neutrophils and lymphocytes) and platelets in blood tests.
- Low number of red blood cells, which may result in anaemia, with symptoms such as tiredness and drowsiness.
- Reduced function of your body's immune system.
- Headache, dizziness.
- Abnormal breath sounds, abnormal chest sounds, cough.
- Feeling sick, vomiting, constipation and diarrhoea.
- Skin eruption (rash), swelling, redness as well as soreness around the site of injection, sweating. Skin reactions are mostly mild to moderate and usually resolve within a few days.
- Tiredness, chills, decreased appetite.
- Weakness.

Common side effects (may affect up to 1 in 10 people)
- Repeated occurrence of malignant (cancerous) disease.
- Low number of platelets, which can cause unusual bleeding (for example nose or skin bleeds).
- Sleeplessness, anxiety.
- Increased heart rate, abnormal heart sound, low blood pressure, decreased blood supply to the heart muscle.
- Shortness of breath, swelling in lung tissue due to infection, inflammation of mouth and tongue.
- Abdominal pain and presence of excessive amount of gas in the stomach or bowels, mostly mild increases in liver laboratory values (bilirubin, transaminases) which will return to normal values once treatment is over.
- Itching, itching skin eruption (urticaria), redness of the skin and skin pain.
- Swelling in tissues (oedema), not feeling well, pain (muscle pain, joint pain, and bone pain).

Uncommon side effects (may affect up to 1 in 100 people)
- Anaemia caused by destruction of red blood cells.
- Sleepiness, numbness and tingling of the skin, feebleness, inactivity, disorder of peripheral nerves, confusion, impaired ability to coordinate movements.
- Eye inflammation.
- Sore throat.
- Inflammation of a vein.
- Severe weight loss.

Rare side effects (may affect up to 1 in 1.000 people)
- Reduced liver function.
- Reduced kidney function.
- Complications caused by cancer treatment due to break-down of cancer cells.
- Rejection response to blood transfusions.
- Increased number of certain white blood cells (eosinophils).
- Stroke.
- Disturbances in speech and swallowing.
- Heart failure.
- Abnormal heart rhythm.
- Inability of the heart to maintain adequate blood circulation.
- Obstruction of the bowels.
- Serious allergic skin reaction (Stevens-Johnson syndrome or Lyell syndrome).

Very rare side effects (may affect up to 1 in 10.000 people)
- Depression, epileptic attack.
- Swelling of the eyelid.
- Blood clot in the lung.
- Inflammation of the gallbladder.
- Reduced function of organs due to high amounts of a specific substance produced by the body (a glycoprotein).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LITAK

Keep out of the sight and reach of children.

Store in a refrigerator (2°C-8°C). Do not freeze.

Do not use LITAK after the expiry date which is stated on the vial label and the outer carton after EXP. The expiry date refers to the last day of that month.

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.

Do not use LITAK if you notice that the vial is damaged or that the solution is not clear or contains any particles.

Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What LITAK contains
- The active substance is cladribine. Each ml solution contains 2 mg cladribine. Each vial contains 10 mg cladribine in 5 ml solution.
- The other ingredients are sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

What LITAK looks like and contents of the pack
LITAK is available in glass vials containing 5 ml of clear, colourless solution for injection.
Pack size of 1 or 5 vials. Not all pack-sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Lipomed GmbH
Hegenheimer Strasse 2
D-79576 Weil/Rhein
Germany

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

INSTRUCTIONS FOR INJECTION

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. Your doctor will tell you how much LITAK you need and how often and when you have to inject yourself. LITAK should be injected into the tissue just under the skin (subcutaneous injection). If you have any question with regard to giving the injection, please ask your doctor or nurse for help.

LITAK is a cytotoxic and should therefore be handled with caution. When LITAK is not self-administered by the patient, 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. Pregnant women must avoid contact with LITAK.

What do I need for the injection?

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).

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

- one sterile syringe (e.g. 10 ml LUER syringe),
- one sterile injection needle (e.g. 0.5 x 19 mm, 25 G x ¾’’),
- 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).

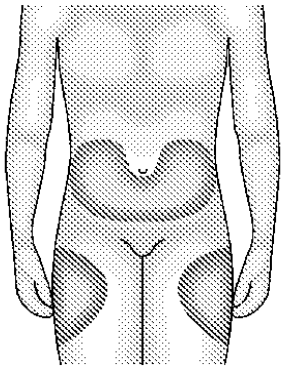
4. Pull the needle out of the vial.

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.

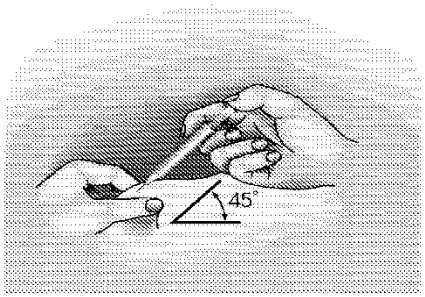
7. Inject straight away.

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°, 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.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATIONS

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSURs for cladribine (apart from products with multiple sclerosis indication), the scientific conclusions of PRAC are as follows:

In view of available data on excretion of cladribine in human breastmilk from the literature, the PRAC considers that excretion of cladribine in human milk is at least a reasonable possibility. The PRAC concluded that the product information of products containing cladribine (apart from products with multiple sclerosis indication) should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the Marketing Authorisations

On the basis of the scientific conclusions for cladribine (apart from products with multiple sclerosis indication) the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing cladribine (apart from products with multiple sclerosis indication) is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisations should be varied.