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 The recommended dose is directly withdrawn by a syringe and injected as a subcutaneous bolus injection without dilution.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	Very common: decreased appetite

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

4.9 Overdose

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

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

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 19745/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

29/01/2025