LITAK® 10

Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

Litak 10

Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LITAK 10 contains 10 mg (2 mg/mL) of cladribine in 5 ml of clear, colourless, sterile, preservative-free, isotonic solution.

Each milliliter of solution contains 2 mg of cladribine (2-CdA).

For the full list of excipients, see section 6.1.

9 mg (0.15 mEq) of sodium chloride as an inactive ingredient.

3. PHARMACEUTICAL FORM

S.C. Injection and I.V. Infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

- Hairy cell leukaemia
- Chronic lymphocytic leukaemia
- Second line treatment for low grade Non-Hodgkin's lymphoma

4.2 Posology and method of administration:

Hairy cell leukaemia:

Subcutaneous: The recommended treatment for hairy cell leukaemia is a single course of LITAK 10 given by subcutaneous bolus injection at a dose of 0.14 mg/kg BW/day (5.6 mg/m^2/day) for 5 consecutive days.

Intravenous: The recommended treatment for hairy cell leukaemia is a single course of LITAK 10 given by continuous intravenous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day (3.6 mg/m^2/day).

Deviations from this dosage regimen are not advised. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs.

Chronic lymphocytic leukaemia and Non-Hodgkin's lymphoma:

Subcutaneous: The recommended dose is 0.1 mg/kg BW/day on 5 consecutive days (4.0 mg/m^2/day) given at monthly intervals. Experience with treatment for more than 3 cycles is limited.

Intravenous: In patients with Chronic lymphocytic leukaemia, the recommended treatment consists of a continuous intravenous infusion of LITAK 10 for 2 hours on days 1 to 5 of a 28 day cycle at a dose of 0.10 mg/kg/day (4.0 mg/m^2/day). The patient's response to therapy should be determined every two cycles of treatment. It is recommended that LITAK 10 is administered in responding patients for 2 cycles after maximum response has occurred, up to a maximum of 6 cycles. Therapy should be discontinued after 2 cycles in non-responding patients. Response for this treatment decision is defined as a lymphocyte reduction of 50% or more, e.g. if lymphocyte count decreases by 50% or more, administer 2 more cycles and re-evaluate response for decision whether to continue with 2 more cycles up to a maximum of 6 cycles.

Children

Safety and efficacy in children have not been established.

Specific risk factors predisposing to increased toxicity from LITAK 10 have not been defined. In view of the known toxicities of agents of this class, it would be prudent to proceed carefully in patients with known or suspected renal insufficiency or severe bone marrow impairment of any aetiology. Patients should be monitored closely for haematological as well as renal and hepatic toxicity.

Preparation and administration of intravenous solutions

LITAK 10 must be diluted with the designated diluent prior to administration. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of a solution of LITAK 10. For full details concerning preparation of an infusion solution (see Instructions for use/handling).

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients.
- Pregnancy and breastfeeding.

4.4. Special warnings and precautions for use

Myelotoxicity

Cladribine is myelotoxic. Careful and regular monitoring of peripheral blood counts is essential during therapy and during two to four months following treatment to detect, at an early stage, potential hematological side effects (anemia, neutropenia, thrombocytopenia) as well as infections, hemolysis or bleedings at an early stage, and to monitor hematological recovery.

Patients with a manifestation of bone marrow depression should be treated with caution. Therapeutic risks and benefits should be carefully evaluated in patients with active infection or increased infection risk. Repeated cycles of LITAK 10 should be given with caution since a cumulative increase of myelosuppression is expected.

Depending on the severity of the myelotoxicity a discontinuation of therapy may be indicated. Since patients with an active hairy cell leukemia 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 hematopoietic growth factors neither improves the recovery of neutrophil counts nor decreases the incidence of fever.

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.

Opportunistic infections usually occur during the first weeks after therapy start. An anti-infective prophylaxis may be beneficial for patients immunocompromised prior to therapy with cladribine or for patients with a pre-existing agranulocytosis.

Fever of unknown origin frequently occurs in patients treated for hairy cell leukemia but rarely in patients with other neoplasias and is observed predominantly during the first four weeks of therapy. The origin of febrile events should be investigated by appropriate laboratory and radiologic tests. In case of fever related to infections or agranulocytosis an antibiotic treatment is indicated.

It is recommended that patients requiring transfusions should receive irradiated cellular blood components/products to prevent transfusion-related graft-versus-host disease.

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

Secondary malignancies are expected to occur in patients with hairy cell leukemia. Their frequency varies widely between 2% and 21%. Following treatment with cladribine, the incidence of second malignancies ranges from 0% to 9.5% after a median observation period of 2.8 to 8.5 years. Therefore, patients treated with cladribine should be regularly monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Due to a potential increase of bone marrow suppression, cladribine should not be used concomitantly with other myelosuppressive medicinal products.

Due to the similar intracellular metabolism, cross-resistance with other nucleoside analogs, such as fludarabine, may occur. Therefore, simultaneous administration of nucleoside analogs 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 Fertility, pregnancy and lactation

Pregnancy

There is clear evidence for risks for the human fetus.

Investigations in animals and *in vitro* studies with human cell lines demonstrated the teratogenicity and mutagenicity of cladribine. There are no controlled studies in humans available. LITAK 10 is absolutely contraindicated during the entire period of pregnancy. Female patients in reproductive age should be advised to use contraceptive precautions during the treatment with cladribine if such a treatment is necessary. In case of pregnancy during chemotherapy, the woman should be apprised of the potential hazard to the fetus.

Breastfeeding

It is not known whether LITAK 10 is excreted in human milk. Because of the risk of possible serious adverse reactions in nursing infants, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

There are no studies on the influence of LITAK 10 on the ability to drive and use machines. But LITAK 10 may strongly impair the patient's performance. In such a case, driving a vehicle or operating machines should be avoided.

4.8 Undesirable effects

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

The very common undesirable effects following administration of LITAK 10, observed in the three most important clinical trials including 279 patients with different indications as well as 62 patients suffering from hairy cell leukemia, are listed thereafter. The incidences refer to patients treated for hairy cell leukemia. In these patients the incidence of adverse drug reactions is much higher than for the other indications, which can be partly explained as consequence of the underlying disease:

bone marrow suppression, particularly severe neutropenia (98%), severe thrombocytopenia (50%) and severe anemia (55%) as well as severe immunosuppression/lymphopenia (95%), infections (58%), and fever (up to 64%). The majority of skin rashes (2-31%) occur in patients using concomitant medication known to induce cutaneous reactions (antibiotics and/or allopurinol). Gastrointestinal adverse drug reactions such as nausea (5-28%), vomiting (1-13%) and diarrhea (3-12%) as well as fatigue (2-48%), headache (1-23%) and loss of appetite (1-22%) have also been reported as side effects of a therapy with cladribine. Tumor lysis syndrome as well as transfusion-related graft-versus-host-disease have been reported in very rare cases.

Infections and infestations

Very common: Infections (27%-58%)

Opportunistic infections with pneumocystis carinii, toxoplasma gondii, listeria, candida, herpes viruses, cytomegalovirus and atypical mycobacteria may occur. 40% of the patients who were treated with LITAK 10 at a dose of 0.7 mg/kg 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 per cycle. 43% of patients with hairy cell leukemia experienced infectious complications at standard dosage regimen. One third of these infections had to be considered as severe (e.g. septicemia, pneumonia).
Unknown: progressive multifocal leukoencephalopathy.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Common: secondary malignancies

Blood and lymphatic system disorders

Very common: pancytopenia/myelosuppression (41%), severe thrombocytopenia (21-50%), severe anemia (14-55%), severe neutropenia (37-98%)

Common: petechiae, hemorrhages, epistaxis

Rare: hypereosinophilia (with erythematous skin rash, pruritus and facial edema)

Immune system disorders

Very common: immunosuppression (63%)

Uncommon: hemolytic anemia

Very rare: graft-versus-host disease

Metabolism and nutrition disorders

Very common: loss of appetite (22%)

Psychiatric disorders

Common: anxiety

Uncommon: confusion

Very rare: depression

Nervous system disorders

Very common: headache (23%), dizziness

Common: insomnia

Uncommon: somnolence, paresthesia, weakness, lethargy, polyneuropathy, ataxia

Very rare: epileptic seizure, neurological disturbances in speech and swallowing

Eye disorders
Uncommon: conjunctivitis
Very rare: blepharitis

Cardiac disorders
Common: tachycardia, heart murmur, hypotension, myocardial ischemia
Rare: heart failure, atrial fibrillation, cardiac decompensation, apoplexy

Vascular disorders:
Uncommon: phlebitis
Very rare: pulmonary embolism

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 etiology
Uncommon: pharyngitis

Gastrointestinal disorders
Very common: nausea (28%), vomiting (13%), constipation, diarrhea (12%)
Common: gastrointestinal pain, flatulence, mucositis
Very rare: ileus

Hepato-biliary disorders
Common: reversible, mostly mild increases of bilirubin and transaminase levels
Very rare: cholecystitis, hepatic failure

Skin and subcutaneous tissue disorders
Very common: rash (31%), localized exanthema, diaphoresis
Common: pruritus, skin pain, erythema, urticaria
Very rare: Stevens-Johnson syndrome / Lyell syndrome (toxic-epidermal necrolysis)

Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia, arthritis, bone pain

Renal and urinary disorders
Rare: Renal failure

General disorders and administration site conditions
Very common: injection site reactions, fever (up to 64%), fatigue (48%), chills, asthenia
Common: edema, malaise, pain
Uncommon: cachexia
Very rare: amyloidosis, tumor lysis syndrome

The majority of deaths related to the medicinal product are due to infectious complications. Further rare cases with fatal outcome, reported in association with chemotherapy with LITAK 10, were secondary malignancies, cerebro- and cardiovascular infarctions, graft-versus-host disease caused by multiple transfusions of non-irradiated blood, as well as tumor lysis syndrome with hyperuricemia, metabolic acidosis, and acute renal failure.

Reporting 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

4.9 Overdose

Signs and symptoms
Common symptoms after overdose are nausea, vomiting, diarrhea, severe bone marrow depression (including anemia, thrombocytopenia, leukopenia and agranulocytosis), acute renal insufficiency as well as irreversible neurotoxicity (paraparesis/quadriparesis), Guillain-Barré syndrome and Brown-Séquard syndrome. The neurotoxic and nephrotoxic complications have been described in individual patients treated at a dose which was 4 times higher than recommended.

Treatment
No specific antidote exists. Immediate discontinuation of therapy and initiation of appropriate supportive measures (blood transfusions, dialysis, hemofiltration, antiinfectious therapy, etc.) are the indicated treatment of overdose of LITAK 10. Patients who have been exposed to overdose should be closely monitored for at least four weeks and blood values should be checked regularly.

5. PHARMACOLOGICAL PROPERTIES

ATC Code: L01BB04

Mechanism of action
LITAK 10 contains cladribine as active substance, a cytotoxic agent acting as an antimetabolite. Cladribine is a purine nucleoside analog with the chemical name 2-chloro-2'-deoxy-β-D-adenosine (2-CdA). The 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.
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).
The mechanism of action of cladribine is attributed to the incorporation of CdATP into DNA strands: the synthesis of new DNA in dividing cells is blocked and the DNA repair mechanism is inhibited resulting in an accumulation of DNA strand breaks and a decrease of NAD and ATP concentration even in resting cells. Furthermore, CdATP inhibits ribonucleotide reductase, the enzyme responsible for the conversion of ribonucleotides into deoxyribonucleotides. Cell death occurs from energy depletion and apoptosis.

5.1 Pharmacodynamic properties

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 hematopoietic cells. The cytotoxicity of cladribine is dose-dependent. Non-hematologic tissues seem to be unaffected, explaining the low incidence of non-hematologic toxicity of the cytostatic drug. No cytotoxic effect of cladribine could be observed in cell lines of solid tumors. Unlike other nucleoside analogs cladribine is toxic in rapidly proliferating cells as well as in resting cells.

Clinical efficacy
No specific data.

5.2 Pharmacokinetic properties

Absorption
After subcutaneous injection, t_{max} is 20 minutes and bioavailability is 100%.

Distribution
The pharmacokinetics of cladribine fits a 2- or 3-compartment model. The mean volume of distribution of cladribine is 9.2 l/kg. Plasma protein binding of cladribine accounts for on average 25% with a wide interindividual variation (5-50%). Intrathecal concentrations of cladribine reach 18-25% of plasma concentrations. Intracellular concentration of cladribine exceeds plasma drug concentration by 128 to 375 times.

Metabolism
Intracellular cladribine is phosphorylated predominantly by deoxycytidine kinase to the active metabolite CdATP and is further hydrolyzed to inactive chloroadenin.

Elimination
The mean terminal plasma half-life amounts to 7-19 hours. Intracellular half-lives of cladribine nucleotides of initially 15 hours and subsequently more than 30 hours were measured in leukemic cells. Cladribine is eliminated mainly by the kidneys.

Pharmacokinetics in specific patient groups

Hepatic impairment
There are no studies available using LITAK 10 in patients with hepatic impairment.

Renal impairment
There are no studies available using LITAK 10 in patients with renal impairment.

Elderly patients
The use of LITAK 10 in patients older than 75 years has not been investigated yet.

Children and adolescents
The use of LITAK 10 in children and adolescents has not yet been investigated.

5.3 Preclinical safety data

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.

Mutagenicity
Cladribine 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 leukemic cells and cell lines at concentrations of 5 nM to 20 µM.

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

Toxicity to reproduction
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 fetal weights and increased fetal 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 fetal weight. Reduced ossification was observed at 1.0 mg/kg/day.
The effects of cladribine on fertility have not been studied in animals. However, a toxicity study conducted with Cynomolgus monkeys (Macaques) has shown that cladribine suppresses maturation of rapidly generating cells, including testicular cells.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride, Sodium Hydroxide or Hydrochloric Acid (for pH adjustment) and water for injections.

6.2 Incompatibilities
LITAK 10 must only be mixed with medicinal products described in Section 6.4 "Reconstitution & Dilution of the product" (0.9% sodium chloride solution). A degradation of the active substance is expected if glucose is used as diluent. If the same infusion tube is used for consequent administration of several different drugs, the tubes should be rinsed by a compatible diluent before and after application of LITAK 10.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

Shelf life after opening
The medicinal product does not contain any antimicrobial preservatives. Opened vials should be used immediately. If necessary, they can be stored in the refrigerator (+2 - +8 °C) for up to 24 hours if the solution is administered subcutaneously.

Subcutaneous administration:
The recommended dose is directly drawn into a syringe and injected subcutaneously without dilution. Allow LITAK 10 to warm up to room temperature prior to administration.

6.4. Reconstitution & Dilution of the product
Once diluted at a concentration of 0.03 mg/ml in sodium chloride 0.9%, the solution for infusion is physically and chemically stable for 30 days at a temperature of 4°C and 25°C.
For microbiological reasons, the solution should be used immediately after dilution.
The calculated daily dose of LITAK 10 is diluted in 500 ml of 0.9% sodium chloride solution and is administered intravenously for 24 hours. Prepare daily a fresh solution for infusion during the 7-day treatment course.

6.5 Special precautions for storage
Store in a refrigerator (2-8 °C), protected from light in its original package. Keep out of the reach of children.

6.6 Handling of cytotoxic medicinal products
Procedures for proper handling and disposal of antineoplastic medicinal products should be used while handling LITAK 10, preparing the solution for infusion and for disposal.

6.7 Nature and contents of container
Neutral, type I glass vial, with Omniflex and Omniflex Plus rubber stopper. Lithographed cardboard box, containing 1 vial and internal package leaflet.

7. MANUFACTURER
Lipomed AG, Fabrikmattenweg 4, CH-4144 Arlesheim, Switzerland

8. LICENSE HOLDER AND IMPORTER:
PHARMALOGIC LTD., P.O.B. 3838, Petah-Tikva 49130

9. REGISTRATION NO.: 119-99-30038-00

עלון לצרכן במתכונת עלון לרופא זה נערך בדצמבר 2020.

This Patient Insert Leaflet in the format of Physician Leaflet revised on December 2020.

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