lipomed

Litak® CLADRIBINE

Medical Information

LITAK® 10 Solution

For Subcutaneous or Intravenous Injection / Infusion

Cytotoxic Agent (Antimetabolite)

INGREDIENTS
1 vial with 5 mL solution contains per 1 mL:
Active ingredient: cladribine (2-CdA) 2 mg
Inactive ingredients: sodium chloride 9 mg, water q.s. ad solution, no preservatives

DESCRIPTION AND MECHANISM OF ACTION
LITAK 10 contains cladribine as active ingredient, a cytotoxic agent acting as antimetabolite. Cladribine is a purine nucleoside analog with the chemical name 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine. The substitution of chlorine for hydrogen at position 2 distinguishes cladribine from its natural counterpart 2′-deoxyadenosine which 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). 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.
Unlike other nucleoside analogs 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 tumors. The mechanism of action of 2-CDA is attributed to the incorporation of CdATP into DNA strands: the synthesis of new DNA in dividing cells is blocked and the DNA repair mechanism is inhibited resulting in an accumulation of DNA strand breaks and a decrease of NAD and ATP concentration even in resting cells. Furthermore CdATP inhibits ribonucleotide reductase, the enzyme responsible for the conversion of ribonucleotides into deoxyribonucleotides. Cell death occurs from energy depletion and apoptosis.

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

Distribution
The steady-state plasma concentration of cladribine amounts to about 7 ng/mL and is reached within 5 to 8 hours after the start of a 2-hour infusion. A maximum plasma drug concentration c_{max} of 48 ng/mL is measured on average 112 minutes after the infusion. After subcutaneous bolus injection a maximum plasma drug concentration c_{max} of 91 ng/mL is reached on average after 20 minutes only (dose: 0.14 mg/kg body weight (BW)/day). The clinical relevance of the different peak plasma concentrations after intravenous and subcutaneous administration was not examined. Intracellular concentration of cladribine exceeds plasma drug concentration by 128 to 375 times. The mean volume of distribution of cladribine is 9.2 L/kg BW. Plasma protein binding of cladribine accounts on average 25% with a wide interindividual variation (5–50%). Intrathecal concentrations of cladribine average 25% of plasma concentrations. Peak cerebrospinal fluid concentrations of 6 and 2 ng/mL, respectively, could be measured after intermittent 2-hour infusion or continuous intravenous infusion (dose: 0.12 mg/kg BW/day).

Metabolism
Intracellular cladribine is metabolized predominantly by deoxycytidine kinase to 2-chlorodeoxyadenosine-5′-monophosphate which 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-lifes $t_{1/2}$ of on average 35 minutes and 6.7 hours, respectively. The terminal plasma half-life amounted to 7–10 hours after continuous intravenous administration for 7 days (0.1 mg/kg BW/day) and was on average 19.5 hours after intermittent 2-hour intravenous infusion on 5 consecutive days (0.14 mg/kg BW/day). The bioexponential 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-lifes of initially 15 hours and subsequently more than 30 hours were measured in leukemic cells.
Cladribine is eliminated mainly by the kidneys. The renal excretion of unmetabolized cladribine occurs within 24 hours and accounts 15% and 18% of the total dose after 2-hour intravenous and subcutaneous administration, respectively. The fate of the remainder is unknown. The mean plasma clearance amounts to 849 mL/min after intravenous infusion and to 768 mL/min after subcutaneous bolus injection at a dose of 0.1 mg/kg BW/day.

Pharmacokinetics in Special Clinical Situations
There are no studies available using LITAK 10 Solution in patients with renal or hepatic impairment (see «Precautions»). The use of LITAK 10 Solution in children and patients older than 75 years has not been investigated yet.

INDICATIONS FOR USE
LITAK 10 Solution is indicated for the treatment of hairy cell leukemia. LITAK 10 Solution is further indicated as second-line treatment for patients with recurrent or refractory low-grade lymphoproliferative diseases, such as follicular or diffuse non-Hodgkin's lymphoma, chronic lymphocytic leukemia, or Waldenström's macroglobulinemia.

DOSAGE AND ADMINISTRATION
LITAK 10 Solution can be administered as subcutaneous bolus injection or intravenous infusion.

Usual Doses
Hairy cell leukemia
Subcutaneous Bolus Injection
The recommended dose for hairy cell leukemia is a single cycle at 0.14 mg/kg BW/day given on 5 consecutive days.

Continuous 24-hour Intravenous Infusion
The recommended dose for hairy cell leukemia is a single cycle at 0.1 mg/kg BW/day given on 7 consecutive days.

Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Waldenström's macroglobulinemia
The recommended dose for recurrent or refractory low-grade lymphoma is the subcutaneous bolus injection of 0.1 mg/kg BW/day on 5 consecutive days, recycled every month. Experience at dosages exceeding 3 cycles is limited.

Special Dosage Recommendations
Deviations from the dosage regimens indicated above are not advised (see «OVERDOSAGE»). LITAK 10 Solution should be discontinued or delayed in case of severe toxicity. In case of infections antibiotic treatment should be initiated as required.

Patients with Renal or Hepatic Failure
Patients with known or suspected renal failure as well as patients with a manifestation of bone marrow depression related to multiple pretreatments or tumor infiltration should be treated carefully. No data are available concerning the treatment of patients with hepatic insufficiency.

Pediatric Use
Safety and effectiveness of LITAK 10 Solution in children has not been established.

HANDLING AND DISPOSAL
Instructions for proper handling and disposal of antineoplastic drugs should be considered according to the guidelines for the handling with and disposal of cytotoxic drugs. LITAK 10 Solution should not be handled by pregnant women and kept out of the reach of children. Cautious handling with LITAK 10 Solution and with the prepared infusion is required. The use of disposable gloves, protective glasses and garments are recommended to avoid the direct contact with the drug. If LITAK 10 Solution contacts the eyes, skin, or mucous membranes, the involved surface is to be rinsed immediately with copious amounts of water.
Aseptic conditions must be observed while handling with LITAK 10 Solution and preparing the infusion. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Cladribine may precipitate if stored at low temperature. Precipitated substance can be resolubilized by exposure to room temperature and by vigorous shaking of the vial. The drug is sensitive to temperature. Therefore, do not heat or microwave.

Subcutaneous Administration
The recommended dose is directly withdrawn by a syringe and injected without dilution. Allow LITAK 10 Solution to warm up to room temperature prior to administration.

Intravenous Administration
Prepare daily a fresh infusion. Dilute the calculated daily dose of LITAK 10 Solution in 500 mL of 0.9% sodium chloride (e.g. Baxter 0.9% NaCl Infusion in Viaflex® disposable PVC container). The ready-to-use solution may be stored refrigerated between +2° C and +8° C for no more than 8 hours prior to administration.

RESTRICTIONS ON USE
Cladribine is an antineoplastic and immunosuppressive substance that can induce considerable toxic side effects (especially myelosuppression and infections). LITAK 10 Solution should only be administered under the supervision of qualified physicians with experience in cancer chemotherapy.

Contraindications
LITAK 10 Solution is contraindicated in case of hypersensitivity to the drug, pregnancy, and nursing.

Precautions
Patients undergoing treatment with cladribine should be closely monitored for signs of hematologic and non-hematologic toxicities.

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.

Hematology
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 or suspected infections. The risk of severe myelotoxicity and long-lasting immunosuppression is increased in patients with a diseaserelated bone marrow infiltration or a previous myelosuppressive treatment. A dose reduction and a regular monitoring of the patient is required in such cases. Increased hematological toxicity (myelosuppression, infections) has been observed in patients receiving repeated cycles of LITAK 10 Solution. Therefore, it is recommended that the dosage regimen of LITAK 10 Solution should not exceed 0.5 mg/kg BW per cycle in patients receiving multiple treatment courses. A discontinuation of the therapy may be necessary depending on the severity and intensity of the complications. Pancytopenia is normally reversible and the intensity of bone marrow aplasia is dose-dependent. Opportunistic infections usually occur during the first weeks after therapy start.
Careful and regular monitoring of peripheral blood counts is essential during 2 to 4 months following treatment with LITAK 10 Solution to detect potential side effects and consequent complications (anemia, neutropenia, thrombocytopenia, infections, hemolysis or bleedings), and to survey hematologic recovery.
Fever of unknown origin frequently occurs in patients treated for hairy cell leukemia but rarely in patients with other neoplasias and is manifested predominantly during the first 4 weeks of therapy. The origin of febrile events should be investigated by appropriate laboratory and radiologic tests. In case of fever re-lated to infections or agranulocytosis an antibiotic treatment is indicated.

Renal and Hepatic Function
Careful treatment is required in patients with known or suspected renal or hepatic impairments. Periodic assessment of renal and hepatic function is advised as clinically indicated.

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

Driving and Operating Machineries
LITAK 10 Solution may strongly impair the patient's performance. In case of drowsiness, driving a vehicle or operating machineries should be avoided.

Pregnancy / Nursing
Pregnancy Category D: There is clear evidence for fetal harm. Investigations in animals and in vitro studies with human cell lines demonstrated the teratogenicity and mutagenesis of cladribine. Although there are no controlled studies in humans available, it has to be considered that other cytostatic drugs inhibiting DNA and RNA synthesis (e.g. methotrexate and aminopterin) have been reported as embryotoxic in humans. Therefore a treatment with cladribine is absolutely contraindicated during the entire period of pregnancy. Patients in reproductive age should be advised to use contraceptive precautions. In case of pregnancy during chemotherapy with LITAK 10 Solution, the woman should be apprised of the potential hazard to the fetus.
It is not known whether LITAK 10 Solution is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, discontinuation of nursing is advised.

ADVERSE REACTIONS
Hematological Toxicity
The most frequent side effects are myelosuppression, especially anemia, thrombocytopenia and neutropenia, as well as immunosuppression, infections and fever.
Since patients with an active hairy cell leukemia mostly present with low blood counts, especially low granulocyte counts, more than 90% of the cases have transient severe neutropenias ($< 1.0 \times 10^9$/L). The use of hematopoietic growth factors neither improves the recovery of neutrophil counts nor decreases the incidence of fever. Severe thrombocytopenias ($< 50 \times 10^9$/L) are observed in about 20% to 30% of all patients. Lymphocytopenia lasting for several months and immunosuppression with an increased risk for infections are expected. The recovery of cytotoxic T-lymphocytes and natural killer cells occurs within 3 to 12 months. A complete recovery of T-helper cells and B-lymphocytes is delayed for up to 2 years.
The majority of drug-related deaths are due to infectious complications. Further rare cases with fatal outcome, reported in association with cladribine chemotherapy, were second malignancy, cerebroand 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.
Cladribine induces a remarkable and prolonged reduction of CD4+ and CD8+ T-lymphocytes. At present there exists no experience on possible long-term consequences of this immunosuppression.
Serious long-term lymphocytopenias are reported occasionally which, however, could not be associated with late infectious complications. The most common severe complications with partially fatal outcome are opportunistic infections (e.g. pneumocystis carinii, toxoplasmosa gondii, listeria, candida, herpes viruses, cytomegalovirus and atypical mycobacteria). Forty percent of the patients who were treated with LITAK 10 at a dose of 0.7 mg/kg BW 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 BW per cycle. Forty-three percent of patients with hairy cell leukemia experienced infectious complications at standard dosage regimen. One third of these infections had to be considered as serious (e.g. septicemia, pneumonia). An increased risk of infection is expected when cladribine is administered as continuous infusion by peripherally inserted central catheters. At least 10 cases with acute autoimmune hemolytic anemia are known. All patients have been successfully treated by corticosteroids.

Non-hematological Toxicity
Culture-negative fever following treatment with LITAK 10 Solution occurs on average in 40% of patients with hairy cell leukemia and is rarely observed in patients with other neoplastic disorders. Skin rashes are mainly described in patients with other concomitant medications known to cause rash (antibiotics and/or allopurinol). Occasionally mild gastrointestinal side effects like nausea, vomiting, and diarrhea are reported during treatment with LITAK 10 Solution. Treatment with antiemetics is usually not necessary. LITAK 10 Solution causes no alopecia and only in single cases mucositis or conjunctivitis.

Further frequently observed adverse reactions, which are usually mild and occur predominantly within the first two weeks after therapy start:
General reactions: fever (43–71%), fatigue (48%), chills (13%), asthenia (11%), diaphoresis (11%), lethargy, malaise
Gastrointestinal: decreased appetite (22%), constipation (14%), abdominal pain
Hemic/lymphatic: purpura (12%), petechiae, epistaxis, hemorrhages
Neurologic: headache (23%), dizziness (12%), somnolence, resthesia, depression
Cardiovascular: edema, tachycardia, myocardial ischemia
Respiratory: abnormal breath and chest sounds (13%), cough (12%), shortness of breath
Dermatologic: localized exanthema (31%), injection site reactions (e.g. redness, swelling, pain) (15%), erythema, pruritus, phlebitis after continuous intravenous infusion
Musculoskeletal: myalgia, arthralgia, bone pain
Rare serious complications like ileus, cardiac failure, atrial fibrillation, cardiac decompensation, apoplexia, neurological disturbances in speech and swallowing, tumor lysis syndrome with acute renal failure, transfusion-related graft-versus-host disease, Stevens-Johnson syndrome/Lyell syndrome (toxicepidermal necrolysis), hypereosinophilia (with erythematous skin rash, pruritus and facial edema) are noticed.

INTERACTIONS
Interactions with other drugs are not known. Due to a potential increase of hematological toxicity and bone marrow suppression, LITAK 10 Solution should not be administered with other concomitant myelosuppressive drugs. Cross reactions with other antineoplastic agents in vitro (e.g. doxorubicin, vincristin, cytarabine) and in vivo have not been observed.

OVERDOSAGE
Common symptoms after overdosage are nausea, vomiting, diarrhea, severe bone marrow depression (including anemia, thrombocytopenia, leukopenia and agranulocytosis), acute renal insufficiency as well as irreversible neurologic toxicity (paraparesis / quadriparesis), Guillan-Barré syndrome and Brown-Séquard syndrome. The neurological complications have been described in individual patients treated at a dose, which was 4 times higher than recommended.
No specific antidotal therapy exists. Immediate discontinuation of therapy and initiation of appropriate supportive measures (blood transfusions, dialysis, hemofiltration, antiinfectious therapy, etc.) are the indicated treatment of overdosage of LITAK 10 Solution. Patients who have been exposed to overdosage should be monitored hematologically for at least four weeks.

FURTHER INFORMATIONS
LITAK 10 Solution should be kept out of the reach of children.

Incompatibilities
The use of dextrose 5% as diluent is not recommended due to an expected degradation of cladribine. No data about incompatibilities with other parenteral diluents, additives, infusion systems, and cytostatic drugs are available. LITAK 10 Solution should not be diluted with other applicable drugs or additives for i.v. use. If the same infusion tube is used for consequent administration of several different drugs, the tubes should be rinsed by a compatible diluent prior and after application of cladribine.

Chemical Stability
LITAK 10 Solution should be stored refrigerated between +2° C and +8° C and should be used before the date of expiration indicated as «EXP» on the package. Vials are for single use only and do not contain any antimicrobial preservatives. Opened vials should be used immediately to assure sterility. Once diluted, infusions should be administered promptly or may be stored refrigerated between +2° C and +8° C for no more than 8 hours prior to administration. Sterility has to be maintained while preparing and storing the infusion.

HOW SUPPLIED
Vials of 10 mg / 5 mL: 1 and 5 (on prescription only)

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