SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

LITAK ® 10 (solution for injection)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each 5 ml vial contains 10 mg of cladribine.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Colourless, odourless, clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

First line treatment: Hairy cell leukaemia.

4.2 Posology and method of administration

Posology

Subcutaneous injection:

The recommended treatment for hairy cell leukaemia is a single course of LITAK given by subcutaneous bolus injection at a dose of 0,14 mg/kg body weight/day for 5 consecutive days.

Intravenous infusion:

Prepare daily a fresh solution. Dilute the calculated daily dose of LITAK in 500 ml of 0,9 % sodium chloride solution. The ready to use solution may be stored refrigerated between 2 °C and 8 °C for not more than 8 hours prior to administration. The recommended treatment for hairy cell leukaemia is a

single course of LITAK given by continuous intravenous infusion at a dose of 0,10 mg/kg body weight/day for 7 consecutive days.

Special populations

Elderly population:

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*).

Impaired bone marrow, renal and hepatic impairment:

Patients with known or suspected renal insufficiency as well as patients with a manifestation of bone marrow impairment related to multiple pre-treatments, tumour infiltration or due to any other aetiology should be treated carefully and monitored regularly for haematologic and non-haematologic toxicity. There is no experience in patients with hepatic impairment.

Paediatric population

Safety and efficacy of LITAK in children have not been established.

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- The recommended dose is directly withdrawn by a syringe and injected as a subcutaneous bolus injection without dilution.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.

4.3 Contraindications

- Patients hypersensitive to cladribine or any of the ingredients.
- Pregnancy and lactation.
- Children (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 section 4.4)*.
- Concomitant use of other myelosuppressive medicines.

4.4 Special warnings and precautions for use

Cladribine is an antineoplastic and immunosuppressive substance that can induce considerable toxic adverse effects, like myelo- and immunosuppression, long-lasting lymphocytopenia, and opportunistic infections.

Patients undergoing treatment with LITAK 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 LITAK 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 LITAK. Although anti-infective prophylaxis is not generally recommended, it may be beneficial for patients immunocompromised prior to therapy with LITAK or for patients with a pre-existing agranulocytosis.

If severe toxicity occurs, the doctor should consider delaying or discontinuing the therapy with the medicine until serious complications resolve. In case of infections, antibiotic treatment should be initiated as required.

It is recommended that patients receiving LITAK 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, as contained in LITAK. PML was reported 6 months to several years after treatment with cladribine, as contained in LITAK. An association with prolonged lymphopenia has been reported in several of these cases. Doctors 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, as contained in LITAK.

Secondary malignancies

Treatment with cladribine is associated with myelosuppression and profound and prolonged immunosuppression. Secondary malignancies are expected to occur in patients with hairy cell leukaemia. Their frequency varies widely, ranging from 2 % to 21 %. The peak risk is at 2 years after diagnosis with a median between 40 and 66 months. The cumulative frequencies of second malignancy are 5 %, 10 - 12 % and 13 - 14 % following 5, 10 and 15 years respectively after diagnosis of hairy cell leukaemia. Following cladribine, the incidence of second malignancies ranges from 0 % to 9,5 % after a median observation period of 2,8 to 8,5 years. The frequency of second malignancy following treatment with LITAK was 3,4 % in all 232 hairy cell leukaemia patients treated during a 10-year period. The highest incidence of second malignancy with LITAK was 6,5 % after a median follow up of time of 8,4 years. Therefore, patients treated with LITAK 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 a manifestation 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. A dose reduction and a regular monitoring of the patient is required in such cases. Increased haematological toxicity (myelosuppression, infections) has been observed in patients receiving repeated cycles of LITAK. Therefore, it is recommended that the dosage regimen of LITAK should not exceed 0,5 mg/kg body weight 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. An increased incidence of opportunistic infections is expected during and 6 months following therapy with LITAK. Careful and regular monitoring of peripheral blood counts is essential during and 2 to 4 months following treatment with LITAK to detect potential side effects 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 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. 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.

Patients with active infection should be treated for the underlying condition prior to receiving therapy with LITAK. Patients who are or who become Coombs‘ positive should be monitored closely for occurrence of haemolysis.

Acute, irreversible neuro- and nephrotoxicity have only been observed at high doses of cladribine (≥ 4 times the recommended dose)**.**

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

Elderly

Elderly patients should be treated by individual assessment and careful monitoring of the blood counts and of the renal and hepatic function.

Prevention of tumour 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 tumour burden. The allopurinol prophylaxis usually starts at the first day 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.

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 LITAK to humans.

Cladribine is a cytotoxic agent, 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:

Men being treated with LITAK 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).*

4.5 Interaction with other medicines and other forms of interaction

Interactions with other medicinal products are not known.

- Due to a potential increase of haematological toxicity and bone marrow suppression, LITAK should not be used concomitantly with other myelosuppressive medicines. Cross reactions with other antineoplastic medicines *in vitro* (e.g. doxorubicin, vincristin, cytarabine, cyclophosphamide) and *in vivo* have not been observed. However, an *in vitro* study revealed cross-resistance between cladribine and nitrogen mustard (chlormethine).
- 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

Women of childbearing potential/ Contraception in males and females

Women of childbearing potential must use effective contraception during treatment with LITAK and for 6 months after the last LITAK dose. In case of pregnancy during therapy with LITAK, the woman should be informed about the potential hazard to the foetus.

Pregnancy

LITAK is contraindicated during pregnancy.

Cladribine as contained in LITAK 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.

Breastfeeding

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 LITAK and for 6 months after the last LITAK 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 (LITAK), which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on human gametogenesis.

Men being treated with LITAK 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 LITAK *(see section 4.4).*

4.7 Effects on ability to drive and use machines

LITAK may cause drowsiness or dizziness and have a major effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

a. Summary of the safety profile

Very common adverse reactions observed during the three most relevant clinical trials with LITAK in 279 patients treated for various indications and in 62 patients with hairy cell leukaemia (HCL) were myelosuppression, especially severe neutropenia (41 % (113/279), 98 % (HCL, 61/62)), severe thrombocytopenia (21 % (58/279), 50 % (HCL, 31/62) and severe anaemia (14 % (21/150), 55 % (HCL, 34/62), as well as severe immunosuppression/lymphopenia (63 % (176/279), 95 % (HCL, 59/62), infections (39 % (110/279), 58 % (HCL, 36/62) and fever (up to 64 %).

Culture-negative fever following treatment with cladribine occurs in 10 - 40 % of patients with hairy cell leukaemia and is rarely observed in patients with other neoplastic disorders. Skin rashes (2 – 31 %) are mainly described in patients with other concomitant medications known to cause rash (antibiotics and/or allopurinol). Gastrointestinal adverse events like nausea (5 – 28 %), vomiting (1 - 13%), and diarrhoea (3 – 12 %) as well as fatigue (2 – 48 %), headache (1 – 23 %), and decreased appetite (1 – 22 %) have been reported during treatment with cladribine. LITAK is unlikely to cause alopecia; mild and transient alopecia for a few days was observed in 4/523 patients during the treatment with LITAK, but could not clearly be associated with cladribine.

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

Tabulated list of adverse reactions

Body System	**Undesirable effect**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and Infestations:	Infections * (e.g. pneumonia *, septicaemia *)				
Neoplasms benign, malignant and unspecified (including cysts and polyps):		second malignancies *		tumour lysis syndrome *	
Blood and the lymphatic system disorders:	pancytopenia/ myelosuppression *, neutropenia, thrombocytopenia, anaemia, lymphopenia		haemolytic anaemia	hypereosinophilia	amyloidosis
Immune system disorders:	immunosuppression *			graft-versus-host disease *	
Metabolism and nutrition disorders:	decreased appetite		cachexia		

Nervous system disorders:	headache, dizziness	insomnia, anxiety	somnolence, paraesthesia, weakness, lethargy, polyneuropathy, confusion, ataxia	apoplexy, neurological disturbances in speech and swallowing.	depression, epileptic seizure
Eye disorders:			conjunctivitis	blepharitis	
Cardiac disorders:		tachycardia, heart murmur, hypotension, epistaxis, myocardial ischemia *		cardiac failure, atrial fibrillation, cardiac decompensation	
Vascular disorders:	purpura	petechiae, haemorrhages *	phlebitis		
Respiratory, thoracic and mediastinal disorders:	abnormal breath sounds, abnormal chest sounds, cough	shortness of breath, pulmonary interstitial infiltrates mostly due to infectious aetiology, mucositis	pharyngitis		lung embolism

Gastrointestinal disorders:	nausea, vomiting, constipation, diarrhoea	gastrointestinal pain, flatulence		ileus	
Hepato-biliary disorders:		reversible, mostly mild increases in bilirubin and transaminases		hepatic failure	cholecystitis
Skin and subcutaneous tissue disorders:	rash, localised exanthema, diaphoresis	pruritus, skin pain, erythema, urticaria		Stevens-Johnson syndrome/ Lyell syndrome	
Musculoskeletal, connective tissue and bone disorders:		myalgia, arthralgia, arthritis, bone pain			
Renal and urinary disorders:				renal failure	
General disorders and administrative site conditions:	injection site reactions, fever, fatigue, chills, asthenia	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 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 at a dose of 0,7 mg/kg body weight per cycle suffered from infections. These were on average more severe than the infections manifested in 27 % of all patients receiving a reduced dose of 0,5 mg/kg body weight per cycle. Forty-three percent of patients with hairy cell leukaemia experienced infectious complications at standard dosage regimen. One third of these infections have to be considered as severe (e.g. septicaemia, pneumonia). At least 10 cases with acute autoimmune haemolytic anaemia are known. All patients have been successfully treated by corticosteroids.

Rare serious adverse reactions

Serious adverse events like ileus, severe hepatic failure, renal failure, cardiac failure, atrial fibrillation, cardiac decompensation, apoplexy, neurological disturbances in speech and swallowing, tumour lysis syndrome with acute renal failure, transfusion-related graft-versus-host disease, Stevens-Johnson syndrome / Lyell syndrome (toxic epidermal necrolysis), haemolytic anaemia, hypereosinophilia (with erythematous skin rash, pruritus, and facial oedema) are rare.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms:

Common symptoms after overdosage are nausea, vomiting, diarrhoea, severe bone marrow depression (including anaemia, thrombocytopenia, leukopenia, and agranulocytosis), acute renal insufficiency as well as irreversible neurologic toxicity (paraparesis / quadriparesis), Guillan-Barré syndrome, and Brown-Séquard syndrome. Acute, irreversible neuro- and nephrotoxicity have been

described in individual patients treated at a dose which was ≥ 4 times higher than the recommended regimen for hairy cell leukaemia.

Treatment:

No specific antidotal therapy exists. Immediate discontinuation of therapy, careful observation, and initiation of appropriate supportive measures (blood transfusions, dialysis, haemofiltration, antiinfectious therapy, etc.) are the indicated treatment of overdosage of LITAK. Patients who have been exposed to overdosage of LITAK should be monitored haematologically for at least four weeks.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class:

A 26 Cytostatics

Pharmacotherapeutic group and ATC code:

Purine analogues, L01BB04

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

Mechanism of action:

Cellular Resistance and Sensitivity

Cladribine is a prodrug, which is taken up 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.

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 and ATP concentration even in resting cells. Furthermore CdATP inhibits ribonucleotide reductase, the enzyme responsible for the conversion of ribonucleotides into deoxyribonucleotides. Cell death occurs from energy depletion and apoptosis.

5.2 Pharmacokinetic properties

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/day). The clinical relevance of the different peak plasma concentrations after intravenous and subcutaneous administration of cladribine has not been examined.

Intracellular concentration of cladribine exceeds plasma drug concentration by 128 to 375 times.
The mean volume of distribution of cladribine is 9,2 l/kg. Plasma protein binding of cladribine 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 body weight/day).

Metabolism

Intracellular cladribine is metabolised predominantly by deoxycytidine kinase to 2-chlorodeoxyadenosine-5'-monophosphate that is further phosphorylated to the diphosphate by nucleoside monophosphate kinase and to the active metabolite 2-chlorodeoxyadenosine- 5'-triphosphate (CdATP) by nucleoside diphosphate kinase.

Elimination

Pharmacokinetic studies in humans showed that the plasma concentration curve of cladribine fits a 2- or 3-compartment model with α- and β- half-lifes of on average 35 minutes and 6,7 hours, respectively. The terminal plasma half-life $t_{1/2}$ amounted to 7 - 10 hours after continuous intravenous administration for 7 days (0,10 mg/kg body weight/day) and was on average 19,5 hours after intermittent 2-hour intravenous infusion on 5 consecutive days (0,14 mg/kg body weight/day). The biexponential decline of the serum concentration of cladribine after subcutaneous bolus injection is comparable to elimination parameters after 2-hour intravenous infusion with an initial and terminal half-life of approximately 2 hours and 11 hours, respectively. The intracellular retention time of cladribine nucleotides *in vivo* is clearly prolonged as compared to the retention time in the plasma: Half-lifes $t_{1/2}$ 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 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 LITAK in patients with renal or hepatic impairment *(see also section 4.2 and section 4.4).* The use of LITAK in children and patients older than 75 years has not been investigated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections

Sugar free

6.2 Incompatibilities

LITAK must not be mixed with other medicines except those mentioned in section 4.2.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store between +2 °C and +8 °C.

Solutions prepared for I.V. administration may be stored refrigerated between 2 °C and 8 °C for not more than 8 hours prior to administration.

Do not freeze.

Any remaining solution after administration must be discarded.

6.5 Nature and contents of container

1.3.1.1.1 Professional Information

5 ml solution in a 10 ml clear neutral Type I glass vial with a bromobutyl stopper and sealed with an aluminium cap. One or five vials are packed in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 – 11th avenue

Houghton Estate

2198

RSA

8 REGISTRATION NUMBER(S)

Date: 27 June 2025 Signature:

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date of registration of the medicine: 18 April 2008

Date of the most recent amendment to the professional information as approved by the Authority: 27 June 2025

10 DATE OF REVISION OF TEXT

27 June 2025