SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE:

FLUDARABINE 50 TEVA (Concentrate for solution for injection or infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 2 ml vial of FLUDARABINE 50 TEVA contains fludarabine phosphate 25 mg/1 ml.

Excipient with known effect:

Contains sugar, 50,0 mg mannitol per 2 ml vial.

For full list of excipients, see **section 6.1**.

3 PHARMACEUTICAL FORM:

Concentrate for solution for injection or infusion.

FLUDARABINE 50 TEVA is a clear, colourless or lightly brownish-yellow solution, essentially free from particles.

4 CLINICAL PARTICULARS:

4.1 Therapeutic indications:

FLUDARABINE 50 TEVA is indicated for:

The treatment of patients with B-cell chronic lymphocytic leukaemia who have not responded to or have not progressed during treatment with at least one standard alkylating-agent containing regimen.

4.2 Posology and method of administration:

Posology:

Adults:

The recommended dose is 25 mg/m² body surface given daily for 5 consecutive days every 28 days by the intravenous route. The dose should not be exceeded as severe neurotoxicity may occur. The required dose (calculated on the basis of the patient's body surface) is drawn up into a syringe. For intravenous bolus injection this dose is further diluted into 10 ml of physiological saline. Alternatively, the required dose drawn up in a syringe may be diluted into 100 ml physiological saline and infused over approximately 30 minutes. Depending on the treatment success and the tolerability of the medicine, FLUDARABINE 50 TEVA should be administered in chronic lymphocytic leukaemia patients up to the achievement of best response (complete or partial remission, usually 6 cycles) and then the medicine should be discontinued.

Special populations:

Renal impairment:

Doses should be adjusted for patients with reduced kidney function. If creatinine clearance is between 30 and 70 ml/min, the dose should be reduced by up to 50 % and close haematological monitoring should be used to assess toxicity. For further information see **section 4.4**. FLUDARABINE 50 TEVA treatment is contraindicated if creatinine clearance is <30 ml/min (see **section 4.3**).

Elderly:

Caution should be exercised with the administration of FLUDARABINE 50 TEVA in elderly persons (>75 years), since there are limited data for the use of FLUDARABINE 50 TEVA in this patient group.

Paediatric population:

The safety and effectiveness of FLUDARABINE 50 TEVA in children has not been established (see **section 4.3**).

Method of administration:

FLUDARABINE 50 TEVA should be administered under the supervision of a qualified medical practitioner experienced in the use of antineoplastic therapy.

It is strongly recommended that FLUDARABINE 50 TEVA should be only administered intravenously. Unintentional paravenous administration must be avoided.

For instructions on handling and reconstitution of the medicine before administration, see **section 6.6**.

4.3 Contraindications:

- Hypersensitivity to fludarabine or to any of the excipients of FLUDARABINE 50 TEVA listed in **section 6.1**
- Pregnancy and breastfeeding (see **section 4.6**)
- Severe renal function impairment (patients with creatinine clearance <30 ml/minute) (see **section 4.3**)
- Haemolytic anaemia
- Chickenpox or herpes zoster
- The safety and effectiveness of FLUDARABINE 50 TEVA in children has not been established.

4.4 Special warnings and precautions for use:

Transfusion-associated graft-versus-host disease:

Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) has been observed rarely after transfusion of non-irradiated blood in FLUDARABINE 50 TEVA treated patients. Fatal outcome as a consequence of this disease has been

reported with a high frequency. Therefore patients who require blood transfusion and who are undergoing, or who have received, treatment with FLUDARABINE 50 TEVA should receive irradiated blood only.

FLUDARABINE 50 TEVA is teratogenic.

Renal impairment:

FLUDARABINE 50 TEVA treatment is contraindicated if creatinine clearance is <30 ml/minute (see **section 4.3**). The total body clearance of the principal plasma metabolite 2-F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Therefore, if renal impairment is clinically suspected, or in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 ml/min, the dose should be reduced by up to 50 % and close haematological monitoring should be used to assess toxicity.

Neurotoxicity:

Patients should be closely observed for signs of neurologic side-effects. The effect of chronic administration of FLUDARABINE 50 TEVA on the central nervous system is unknown.

Impaired state of health:

In patients with impaired state of health, FLUDARABINE 50 TEVA should not be given.

This applies especially for patients with severe impairment of bone marrow function (thrombocytopenia, anaemia, and/or granulocytopenia), immunodeficiency or with a history of opportunistic infection.

Myelosuppression:

Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with FLUDARABINE 50 TEVA.

While chemotherapy-induced myelosuppression is often reversible, administration of FLUDARABINE 50 TEVA requires careful haematologic monitoring. FLUDARABINE 50 TEVA is a potent antineoplastic medicine with potentially significant toxic side-effects. Patients undergoing therapy should be closely observed for signs of haematologic and non-haematologic toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anaemia, neutropenia and thrombocytopenia.

Skin cancer lesions:

In some patients during or after FLUDARABINE 50 TEVA therapy, reversible worsening or flare up of pre-existing skin cancer lesions has been reported.

Tumour lysis syndrome:

Tumour lysis syndrome associated with FLUDARABINE 50 TEVA treatment has been reported in patients with large tumour burdens. Since FLUDARABINE 50 TEVA can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.

Autoimmune phenomena:

Patients undergoing treatment with FLUDARABINE 50 TEVA should be closely monitored for signs of autoimmune haemolytic anaemia (decline in haemoglobin linked with haemolysis and positive Coombs test).

Discontinuation of therapy with FLUDARABINE 50 TEVA is recommended in the case of haemolysis. Blood transfusion (irradiated) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

The elderly:

Caution should be exercised with the administration of FLUDARABINE 50 TEVA in elderly persons (>75 years), since there are limited data for the use of FLUDARABINE 50 TEVA in this patient group (see **section 4.2**).

4.5 Interaction with other medicines and other forms of interaction:

FLUDARABINE 50 TEVA may have interactions with the following medicines:

- Allopurinol
- Colchicine
- Probenecid
- Sulfinpyrazone
- Bone marrow depressants
- Dipyridamole and other inhibitors of adenosine uptake
- Pentostatin
- Corticosteroids
- Aminoglycosides
- Immunisation (using of vaccines) by patients using FLUDARABINE 50 TEVA should generally be avoided. It should only be undertaken with extreme caution after careful review of the patient's haematologic status and only with the knowledge and consent of the medical practitioner managing the FLUDARABINE 50 TEVA therapy. The interval between discontinuation of FLUDARABINE 50 TEVA and restoration of the patient's ability to respond to the vaccine

depends on the intensity and type of immunosuppression-causing medication used, the underlying disease and other factors; estimates vary from 3 months to 1 year.

4.6 Fertility, pregnancy and lactation:

Women of childbearing potential / Contraception in males and females:

Women of childbearing potential should be advised not to become pregnant. FLUDARABINE 50 TEVA is considered teratogenic (see **section 4.4**). Women should use effective contraceptive measures during treatment and for 6 months after stopping treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving FLUDARABINE 50 TEVA and for 3 months following completion of treatment.

Pregnancy:

FLUDARABINE 50 TEVA is contraindicated during pregnancy (see **section 4.3**).

Breastfeeding:

FLUDARABINE 50 TEVA is contraindicated during lactation (see **section 4.3**).

It is not known if FLUDARABINE 50 TEVA is excreted in breastmilk. Because of the potential for serious adverse reactions in infants, breastfeeding should be discontinued before starting treatment with FLUDARABINE 50 TEVA.

Fertility:

Due to the genotoxic risk of fludarabine phosphate women of childbearing potential must be apprised of the potential hazard to the foetus.

4.7 Effects on ability to drive and use machines:

FLUDARABINE 50 TEVA has minor or moderate influence on the ability to drive and use machines. Headaches, blurred vision and nausea have been reported during treatment with FLUDARABINE 50 TEVA, for this reason the patient should refrain from driving or using machines until the effects of FLUDARABINE 50 TEVA have been established.

4.8 Undesirable effects:

Blood and lymphatic system disorders:	
Frequent	Anaemia, leukopenia or neutropenia (black tarry stools, unusual bleeding or bruising, sores, ulcers or white spots on lips or in mouth), thrombocytopenia.
Less Frequent	Haemorrhage (bleeding gums, coughing up blood, prolonged bleeding from cuts), haemolytic anaemia, epistaxis.
Frequency unknown	Pancytopenia.
Gastrointestinal disorders:	
Frequent	Gastro-intestinal bleeding (bloody or black tarry stools), diarrhoea, nausea or vomiting, stomatitis.
Less Frequent	Constipation, cholelithiasis, dysphagia, oesophagitis, mucositis.
Skin and subcutaneous tissue disorders:	
Frequent	Skin rash.
Less Frequent	Pruritus, seborrhoea, loss of hair, Stevens-Johnson syndrome or toxic epidermal necrolysis.
Psychiatric disorders:	
Frequent	Depression.
Nervous system disorders:	
Frequent	Paraesthesia.

Less Frequent	Neurological effects including agitation or confusion, peripheral neuropathy and delayed neurological effects (blindness or coma), sleep disorder, life-threatening neurotoxicity.
Frequency unknown	Multifocal leukoencephalopathy, demyelinating disease.
Musculoskeletal and connective tissue disorders:	
Frequent	Myalgia.
Less Frequent	Arthralgia, osteoporosis.
Respiratory, thoracic and mediastinal disorders:	
Frequent	Haemoptysis, pneumonia, allergic pneumonitis, cough, dyspnoea, pharyngitis.
Less Frequent	Sinusitis, bronchitis, hypoxaemia resulting in hypoxia.
Frequency unknown	Severe pulmonary toxicity, pneumocystis pneumonia, fibrosis.
Eye disorders:	
Less Frequent	Blurred vision, optic neuritis, optic neuropathy and blindness.
Vascular disorders:	
Frequent	Oedema.
Less Frequent	Cerebrovascular accident, deep vein thrombosis, hypoxia, phlebitis.
Metabolism and nutrition disorders:	
Frequent	Anorexia, hyperglycaemia, dehydration.
Less Frequent	Hyperphosphatemia, hypocalcaemia, metabolic acidosis, hyperkalaemia.
Ear and labyrinth disorders:	
Less Frequent	Loss of hearing.
Renal and urinary disorders:	
Frequent	Urinary infection.

Less Frequent	Haematuria, urinary hesitancy, haemorrhagic cystitis, urate crystalluria, tumour lysis syndrome including hyperuricemia, renal failure, dysuria, proteinuria.
Infections and infestations:	
Frequency unknown	Listeriosis, mycobacterial infections and opportunistic fungal and viral infections.
Hepato-biliary disorders:	
Less Frequent	Liver failure.
Frequency unknown	Changes in hepatic and pancreatic enzyme levels.
Cardiac disorders:	
Frequent	Angina.
Less Frequent	Aneurysm, dysrhythmia, congestive heart failure, supraventricular tachycardia.
General disorders and administration site conditions:	
Frequent	Pain, chills, diaphoresis, fatigue, fever, malaise, weakness.
Less frequent	Anaphylaxis, headache.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

There is no known specific antidote for FLUDARABINE 50 TEVA.

High doses of FLUDARABINE 50 TEVA have been associated with an irreversible central nervous system toxicity characterised by delayed blindness, coma, and death. High doses are also associated with severe thrombocytopenia and neutropenia due to bone marrow suppression.

Treatment consists of discontinuation of treatment and supportive therapy.

5 PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A 26 Cytostatic agent

Pharmacotherapeutic group: Antineoplastic agents, purine analogues ATC-code: L01B B05

Mechanism of action:

Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite has been shown to inhibit ribonucleotide reductase, DNA polymerase alpha/delta and epsilon, DNA primase and DNA ligase thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occurs. It is assumed that effects on DNA, RNA and protein synthesis all contribute to inhibition of cell growth with inhibition of DNA synthesis being the dominant factor.

5.2 Pharmacokinetics properties:

Absorption:

After intravenous doses, fludarabine phosphate is rapidly dephosphorylated to fludarabine in the plasma, which is taken up by lymphocytes and rephosphorylated to the active triphosphate nucleotide.

Distribution:

The terminal half-life of fludarabine is approximately 20 hours.

Elimination:

The compound is primarily eliminated by renal excretion, and approximately 40 – 60 % appears in the urine as fludarabine because of its relative resistance to deamination by adenosine deaminase. The pharmacokinetics of fludarabine exhibits considerable interindividual variation.

6 Pharmaceutical particulars:

6.1 List of excipients:

Mannitol

Water for injection

6.2 Incompatibilities:

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life:

Unopened vial: 36 months

Reconstituted and diluted solution: When diluted to final concentration range of 0,3 to 6,0 mg/ml in 5 % glucose for injection or in 0,9 % sodium chloride for injection the solution has to be used within 72 hours, when stored at 5 C ± 3 °C or at ambient room temperature and light conditions.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 °C to 8 °C or 8 hours at room temperature.

6.4 Special precautions for storage:

Store between 2 - 8 °C. Do not freeze. Inspect visually prior to use. Only clear solutions without particles should be used. FLUDARABINE 50 TEVA is for single use only. Any unused solution should be discarded.

For storage conditions of the reconstituted or diluted medicine, see **section 6.3**.

6.5 Nature and contents of container:

FLUDARABINE 50 TEVA is packed in a tubular type I glass, colourless injection vial (2R or 2 ml) with grey bromobutyl rubber stopper; silver aluminium flip-off seal and blue polypropylene snap-cap. One vial is packed in an outer carton.

6.6 Special precautions for disposal and other handling:

Pregnant staff should not handle FLUDARABINE 50 TEVA.

Procedures for proper handling and disposal should be observed. Consideration should be given to handling and disposal according to guidelines used for cytotoxic medicine. Any spillage or waste material may be disposed of by incineration.

Caution should be exercised in the handling and preparation of the FLUDARABINE 50 TEVA solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution comes into contact with the skin or mucous membranes, the area should be washed thoroughly with soap and water. In the event of contact with the eyes, rinse them thoroughly with copious amounts of water. Exposure by inhalation should be avoided.

7 HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8 REGISTRATION NUMBER:

FLUDARABINE 50 TEVA: 43/26/0009

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION:

Date of registration: 05 August 2011

10 DATE OF REVISION OF THE TEXT:

16 May 2025.