For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated. Please read carefully before using a new pack.

Fludarabine Phosphate Powder for Solution for Injection or Infusion

FLUDARA®

NAME OF THE MEDICINAL PRODUCT

Fludara 50 mg powder for solution for injection/infusion

COMPOSITION

Active ingredient: Each vial contains 50 mg fludarabine phosphate I.P. 1 ml of reconstituted solution for injection/infusion contains 25 mg fludarabine phosphate.

Excipients: Mannitol, Sodium hydroxide (to adjust the pH to 7.7).

INDICATIONS

Fludara is indicated for the treatment of patients with B -cell chronic lymphocytic leukemia (CLL) who have not responded to at least one standard alkylating-agent containing regimen.

DOSAGE AND METHOD OF ADMINISTRATION

Method of administration

Fludara must be administered only intravenously. No cases have been reported in which paravenously administered Fludara led to severe local adverse reactions. However, unintentional paravenous administration must be avoided.

Dosage regimen

Adults

Fludara solution for injection/infusion should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

The recommended dose is 25 mg fludarabine phosphate/m² body surface given daily for 5 consecutive days every 28 days by the intravenous route. Each vial is to be made up in 2 ml water for injection. Each ml of the resulting solution for injection/infusion will contain 25 mg fludarabine phosphate (see section ‘Instructions for use/handling’).

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 0.9 % sodium chloride. Alternatively, for infusion, the required dose drawn up in a syringe may be diluted into 100 ml 0.9 % sodium chloride and infused over approximately 30 minutes.

The duration of treatment depends on the treatment success and the tolerability of the drug.

In CLL patients, Fludara should be administered up to the achievement of best response (complete or partial remission, usually 6 cycles) and then the drug should be discontinued.

In patients with Lg-NHL, treatment with Fludara is recommended up to the achievement of best response (complete or partial remission). Two cycles of consolidation should be considered after best response has been reached. In clinical trials with Lg-NHL, the majority of patients underwent not more than 8 cycles.

SPECIAL POPULATIONS

Children and adolescents
Fludara is not recommended for the use in children below age 18 due to a lack of data on safety and efficacy.

Geriatric patients
Since there are limited data for the use of Fludara in elderly persons (> 75 years), caution should be exercised with the administration of Fludara in these patients (see section 'Special warnings and precautions for use').

Patients with 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 hematological monitoring should be used to assess toxicity. For further information see section 'Special warnings and precautions for use'.

Fludara treatment is contraindicated if creatinine clearance is < 30 ml/min.

Patients with hepatic impairment
The safety and efficacy have not been studied in patients with hepatic impairment.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Renal impairment with creatinine clearance < 30 ml/min
- Decompensated hemolytic anemia

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Neurotoxicity
When used at high doses in dose-ranging studies in patients with acute leukemia, Fludara was associated with severe neurologic effects, including blindness, coma and death. Symptoms appeared from 21 to 60 days from last dose. This severe central nervous system toxicity occurred in 36 % of patients treated intravenously with doses approximately four times greater (96 mg/m²/day for 5-7 days) than the recommended dose. In patients treated at doses in the range of the dose recommended for chronic lymphocytic leukaemia and Lg-NHL, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion) (see section 'Undesirable effects').

In postmarketing experience neurotoxicity has been reported to occur earlier or later than in clinical trials.

The effect of chronic administration of Fludara on the central nervous system is unknown. However, patients tolerated the recommended dose in some studies for relatively long treatment times (for up to 26 courses of therapy). Patients should be closely observed for signs of neurologic effects.

Administration of Fludara can be associated with leukoencephalopathy (LE), acute toxic leukoencephalopathy (ATL) or reversible posterior leukoencephalopathy syndrome (RPLS).

These may occur:

- at the recommended dose
  - when Fludara is given following, or in combination with, medications known to be associated with LE, ATL or RPLS,
  - or when Fludara is given in patients with other risk factors such as cranial or total body irradiation, Hematopoietic Cell Transplantation, Graft versus Host Disease, renal impairment, or hepatic encephalopathy.
- at doses higher than the recommended dose

LE, ATL or RPLS symptoms may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, and focal neurological deficits. Additional effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/ quadriparesis, muscle spasticity and incontinence.
LE/ ATL/ RPLS may be irreversible, life-threatening, or fatal.

Whenever LE, ATL or RPLS is suspected, fludarabine treatment should be stopped. Patients should be monitored and should undergo brain imaging, preferably utilizing MRI. If the diagnosis is confirmed, fludarabine therapy should be permanently discontinued.

Impaired state of health
In patients with impaired state of health, Fludara should be given with caution and after careful risk/benefit consideration. This applies especially for patients with severe impairment of bone marrow function (thrombocytopenia, anemia, and/or granulocytopenia), immunodeficiency or with a history of opportunistic infection. Prophylactic treatment should be considered in patients at increased risk of developing opportunistic infections (see section ‘Undesirable effects’).

Myelosuppression
Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, has been reported in patients treated with Fludara. In a Phase I study in adult solid tumor patients, the median time to nadir counts was 13 days (range 3-25 days) for granulocytes and 16 days (range 2-32 days) for platelets. Most patients had haematologic impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate requires careful haematologic monitoring.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The duration of clinically significant cytopenia in the reported cases has range from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

Disease progression

Disease progression and transformation (e.g. Richter's Syndrome) have been commonly reported in CLL patients.

Transfusion associated graft-versus-host disease
Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) has been observed after transfusion of non irradiated blood in Fludara treated patients. Fatal outcome as a consequence of this disease has been reported with a high frequency. Therefore, to minimize the risk of transfusion-associated graft-versus-host disease, patients who require blood transfusion and who are undergoing, or who have received treatment with Fludara should receive irradiated blood only.

Skin cancer
The worsening or flare up of preexisting skin cancer lesions as well as new onset of skin cancer has been reported in patients during or after Fludara therapy.

Tumor lysis syndrome
This syndrome has been reported in patients with large tumor burdens. Since Fludara can induce a response as early as the first week of treatment, precaution should be taken in those patients at risk of developing this complication.

Autoimmune phenomena
Irrespective of any previous history of autoimmune processes or Coombs test status, lifethreatening and sometimes fatal autoimmune phenomena (see section 'Undesirable effects') have been reported to occur during or after treatment with Fludara. The majority of patients experiencing hemolytic anemia developed a recurrence in the hemolytic process after rechallenge with Fludara.

Patients treated with Fludara should be closely monitored for signs of hemolysis.

Discontinuation of therapy with Fludara is recommended in case of hemolysis.

Renal impairment
There are limited clinical data available in patients with impairment of renal function (creatinine clearance <70 ml/min).

Fludara must be administered cautiously in patients with renal insufficiency. In patients with moderate impairment of renal function (creatinine clearance between 30 and 70 ml/min), the dose should be reduced by up to 50 % and the patient should be monitored closely (see section'Dosage and method of administration'). Fludara treatment is contraindicated if creatinine clearance is < 30 ml/min.

Geriatric patients
Since there are limited data for the use of Fludara in elderly persons (> 75 years), caution should be exercised with the administration of Fludara in these patients.

In patients aged 65 years or older, creatinine clearance should be measured before start of treatment, see 'Renal impairment' and section 'Dosage and method of administration'.

Pregnancy
Fludara should not be used during pregnancy unless clearly necessary (e.g. life threatening situation, no alternative safer treatment available without compromising the therapeutic benefit, treatment cannot be avoided). It has the potential to cause fetal harm (see sections 'Pregnancy and lactation'and 'Preclinical safety data'). Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.

Women should avoid becoming pregnant while on Fludara therapy.

Women of childbearing potential must be apprised of the potential hazard to the fetus (see sections 'Pregnancy and lactation'and'Preclinical safety data')

Contraception
Women of childbearing potential or fertile males must take effective contraceptive measures during and at least for 6 months after cessation of therapy (see section 'Pregnancy and lactation').

Lactation
Breastfeeding should not be initiated during Fludara treatment. Nursing women should discontinue breastfeeding.

Vaccination
During and after treatment with Fludara vaccination with live vaccines should be avoided.

Retreatment options after initial Fludara treatment
Patients who primarily respond to Fludara have a good chance of responding again to Fludara monotherapy. A crossover from initial treatment with Fludara to chlorambucil for non responders to Fludara should be avoided because most patients who have been resistant to Fludara have shown resistance to chlorambucil.

INTERACTIONS

In a clinical investigation, using Fludara in combination with pentostatin (deoxycoformycin) for the treatment of CLL, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of Fludara in combination with pentostatin is not recommended.

Dipyridamole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of Fludara.

Clinical studies and in vitro experiments showed that using Fludara in combination with cytarabine may increase the intracellular concentration and intracellular exposure of Ara-CTP (active metabolite of cytarabine) in leukemic cells. Plasma concentrations of Ara-C and the elimination rate of Ara-C were not affected.

PREGNANCY

The results from intravenous embryotoxicity studies in rats and rabbits indicated an embyrolethal and teratogenic potential at the therapeutic doses. Preclinical data in rats demonstrated a transfer of Fludara and/or metabolites through the feto-placental barrier (see section 'Preclinical safety data').

There are very limited data of Fludara use in pregnant women in the first trimester:
One newborn has been described with absent bilateral radii and normal thumbs, thrombocytopenia, fossa ovalis aneurysm and a small patent ductus arteriosus. Early pregnancy loss has been reported in Fludara monotherapy as well as in combination therapy. Premature delivery has been reported.

Fludara should not be used during pregnancy unless clearly necessary (e.g, life threatening situation, no alternative safer treatment available without compromising the therapeutic benefit,treatment cannot be avoided). It has the potential to cause fetal harm. Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.

Women of childbearing potential must be apprised of the potential hazard to the fetus.

Women of childbearing potential must take effective contraceptive measures during and at least for 6 months after cessation of therapy. (see also sections 'Special warnings and precautions for use'and 'Preclinical safety data')

LACTATION

It is not known whether this drug is excreted in human milk. However, there is evidence from preclinical data that fludarabine phosphate and/or metabolites transfer from maternal blood to milk.

Therefore, breastfeeding should not be initiated during Flurdara treatment. Nursing women should discontinue breastfeeding.(see also section 'Special warnings and precautions for use')

EFFECTS ON ABILITY TO DRIVE OR USE MACHINES

Fludara may reduce the ability to drive or use machines, since e.g. fatigue, weakness, visual disturbances, confusion, agitation and seizures have been observed.

UNDESIRABLE EFFECTS

Serious opportunistic infections have occurred in patients treated with Fludara. Fatalities as a consequence of serious adverse events have been reported.

The table below reports adverse events by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data regardless of the causal relationship with Fludara. The rare adverse events were mainly identified from post marketing experience.

Table 1: Adverse events reported in clinical trials or during post-marketing surveillance in patients treated with Fludara

System Organ Class MedDRA	**Very Common** ≥1/10	**Common** ≥ 1/100 to <1/10	**Uncommon** ≥ 1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Infections and infestations	Infections / Opportunistic infections (like latent viral reactivation, e.g. Herpes zoster virus Epstein-Barr-virus, Progressive multifocal leucoencephalopathy), Pneumonia			Lympho-proliferative disorder (EBV-associated)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Myelodysplastic syndrome and Acute myeloid leukaemia (mainly associated with prior, concomitant or subsequent treatment with alkylating agents,		

		topoisomerase inhibitors or irradiation)		
Blood and lymphatic system disorders	Neutropenia, Anemia, Thrombocytopenia	Myelosuppression		
Immune system disorders			Autoimmune disorder (including Autoimmune hemolytic anemia, Thrombocytopenic purpura, Pemphigus, Evans syndrome, Acquired hemophilia)	
Metabolism and nutrition disorders		Anorexia	Tumor lysis syndrome (including Renal failure, Hyperkalemia, Metabolic acidosis, Hematuria, Urate crystalluria, Hyperuricemia, Hyperphosphatemia, Hypocalcemia)	
Nervous system disorders		Neuropathy peripheral	Confusion	Agitation, Seizures, Coma
Eye disorders		Visual disturbance		Optic neuritis, Optic neuropathy, Blindness
Cardiac disorders				Heart failure, Arrhythmia
Vascular disorders			Gastrointestinal hemorrhage	
Respiratory, thoracic and mediastinal disorders	Cough		Pulmonary toxicity (including Dyspnea, Pulmonary fibrosis, Pneumonitis)	
Gastrointestinal disorders	Nausea, Vomiting, Diarrhoea	Stomatitis	Pancreatic enzymes abnormal	
Hepatobiliary disorders			Hepatic enzyme abnormal	
Skin and subcutaneous tissue disorders		Rash		Skin cancer, Stevens-Johnson syndrome,

				Necrolysis epidermal toxic (Lyell type)
General disorders and administration site conditions	Fever, Fatigue, Weakness	Chills, Malaise, Edema, Mucositis		

The most appropriate MedDRA term to describe a certain adverse event is listed. Synonyms or related conditions are not listed, but should be taken into account as well. Adverse event term representation is based on MedDRA version 12.0.

Postmarketing experience with frequency unknown

- Nervous system disorders
    - Leukoencephalopathy (see section"Special warnings and precautions for use")
    - Acute toxic leukoencephalopathy (see section "Special warnings and precautions for use")
    - Reversible posterior leukoencephalopathy syndrome (RPLS) (see section "Special warnings and precautions for use")

- Vascular disorders
    - Hemorrhage (including Cerebral hemorrhage, Pulmonary hemorrhage, Hemorrhagic cystitis)

OVERDOSE

High doses of Fludara have been associated with leukoencephalopathy, acute toxic leukoencephalopathy, or reversible posterior leukoencephalopathy syndrome (RPLS). Symptoms may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, and focal neurological deficits. Additional effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/ quadriparesis, muscle spasticity, incontinence, irreversible central nervous system toxicity characterized by delayed blindness, coma and death. High doses are also associated with severe thrombocytopenia and neutropenia due to bone marrow suppression.

There is no known specific antidote for Fludara overdosage. Treatment consists of drug discontinuation and supportive therapy.

INCOMPATIBILITIES

The formulation for intravenous use must not be mixed with other drugs.

SHELF LIFE

See outer carton for Shelf Life.

Fludara contains no antimicrobial preservative. Care must be taken to assure the sterility of prepared solutions for injection/infusion. 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 to 8 °C or 8 hours at room temperature.

SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^0C.For storage conditions of the reconstituted or diluted medicinal product, see section 'Shelf life'.

NATURE AND CONTENTS OF CONTAINTER

10 ml colourless Type I glass vials containing 50 mg fludarabine phosphate.
Each package contains 5 vials.

INSTRUCTIONS FOR USE / HANDLING

- ***Handling and disposal***

Fludara should not be handled by pregnant staff.

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

- ***Special instructions for the formulation for intravenous use***

Fludara should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2 ml of sterile water for injection, the solid cake should fully dissolve in 15 seconds or less. Each ml of the resulting solution for injection/infusion will contain 25 mg of fludarabine phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2 - 8.2. In clinical studies, the product has been diluted in 100 ml or 125 ml of 5 % dextrose injection or 0.9 % sodium chloride.

Caution should be exercised in the handling and preparation of the Fludara 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.

MANUFACTURED BY:

Baxter Oncology GmbH, Kantstrasse. 2, 33790 Halle/Westfalen, Germany

PACKED BY:

EUROAPI UK Ltd, 37, Hollands Road, Haverhill, Suffolk CB9 8PU, UK

IMPORTER:

Sanofi Healthcare India Private Limited

Gala No. 4, Ground Floor, Building No. B1, Citylink Warehousing Complex,

S.No.121/10/A,121/10/B & 69, NH3, Vadape, Tal: Bhiwandi-16 (Thane Z5) Pin: 421302

MARKETED BY:

Emcure Pharmaceuticals Ltd.

255/2, Hinjwadi, Pune – 411 057.

Updated: March 2022

Source: CCDS Version. No 26 dated 11 March 2014

Fludara is a registered trade mark exclusively licensed to Genzyme Corporation (A Sanofi Company)