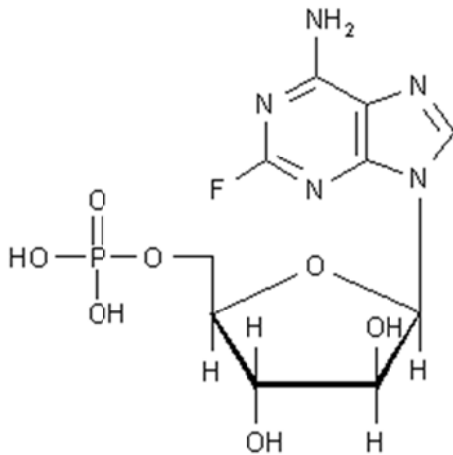


**Fludarabine Ebewe Solution for Injection,
fludarabine phosphate 25 mg/mL**

Name of the Medicine

Fludarabine phosphate, Structural Formula



Chemical Name

9-β-D-arabinofuranosyl-2-fluoroadenine 5'-(dihydrogen phosphate).

Molecular Formula

$C_{10}H_{13}FN_5O_7P$

Molecular Weight

365.2

Description

Each vial of FLUDARABINE EBEWE contains 50 mg of the active ingredient fludarabine phosphate together with sodium phosphate – dibasic dihydrate, and sodium hydroxide in water for injections to give a solution containing 25 mg/mL of fludarabine phosphate for intravenous administration.

Pharmacology

Fludarabine phosphate, a fluorinated nucleotide analogue of the antiviral agent vidarabine, (9-β-D-arabinofuranosyladenine) that is relatively resistant to deamination by adenosine deaminase.

Fludarabine phosphate is rapidly dephosphorylated to fludarabine (2F-ara-A) which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, fludarabine triphosphate (2F-ara-ATP). This metabolite has been shown to inhibit ribonucleotide reductase, DNA polymerase α, δ and ε, DNA primase and DNA ligase thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occurs.

Whilst some aspects of the mechanism of action of fludarabine triphosphate are as yet unclear, 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. In addition, *in vitro* studies have shown that exposure of chronic lymphocytic leukaemia (CLL) lymphocytes to fludarabine (2F-ara-A) triggers extensive DNA fragmentation and cell death characteristic of apoptosis. Fludarabine phosphate has also been shown to trigger these changes in normal (non-malignant) lymphoid cells.

Pharmacokinetics

The pharmacokinetics of fludarabine (2F-ara-A) has been studied after intravenous administration by rapid bolus injection, short term infusion and following continuous infusion as well as after peroral dosing of fludarabine phosphate (2F-ara-AMP).

No clear correlation was found between fludarabine pharmacokinetics and treatment efficacy in cancer patients. However, occurrence of neutropenia and haematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses haematopoiesis in a dose dependent manner.

Distribution and Metabolism

Fludarabine phosphate (2F-ara-AMP) is a water soluble prodrug of fludarabine (2F-ara-A), which is rapidly and quantitatively dephosphorylated in humans to the nucleoside fludarabine.

After single dose infusion of 25 mg fludarabine phosphate per m² to CLL patients for 30 minutes, fludarabine (2F-ara-A) reached mean maximum concentrations in the plasma of 3.5 -3.7 μM at the end of the infusion. Corresponding fludarabine (2F-ara-A) levels after the fifth dose showed a moderate accumulation with mean maximum levels of 4.4 - 4.8 μM at the end of infusion. During a 5 day treatment schedule, fludarabine (2F-ara-A) plasma trough levels increased by a factor of about 2. An accumulation of fludarabine (2F-ara-A) over several treatment cycles can be excluded. Post-maximum levels decayed in three disposition phases with an initial half life of approximately 5 minutes, an intermediate half life of 1 - 2 hours and a terminal half life of approximately 20 hours.

An interstudy comparison of fludarabine (2F-ara-A) pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 mL/min/m² (2.2 mL/min/kg) and a mean

volume of distribution (V_{ss}) of 83 L/m² (2.4 L/kg). Data showed a high inter-individual variability. After i.v. and peroral administration of fludarabine phosphate tablets in doses of 50 - 90 mg, the plasma concentration of fludarabine phosphate and the area under the plasma concentration time curve increased linearly with the dose. Additionally, after i.v. administration half lives, plasma clearance and volumes of distribution remained constant independent of the dose indicating a dose linear behaviour.

After peroral fludarabine phosphate (2F-ara-AMP) doses, maximum fludarabine (2F-ara-A) plasma levels reached approximately 20 - 30% of corresponding i.v. levels at the end of infusion and occurred 1 - 2 hours post dose. The mean systemic fludarabine (2F-ara-A) availability was in the range of 50 - 65% following single and repeated doses and was similar after ingestion of a solution or immediate release tablet formulation. After peroral dosing of fludarabine phosphate (2F-ara-AMP) with concomitant food intake a slight increase (<10%) of systemic availability (AUC), a slight decrease of maximum plasma levels (C_{max}) of fludarabine (2F-ara-A) and a delayed time of occurrence of C_{max} was observed. Terminal half lives were unaffected.

In vitro investigations with human plasma proteins revealed no pronounced tendency of fludarabine (2F-ara-A) protein binding.

Elimination

Fludarabine (2F-ara-A) elimination is largely by renal excretion. 40 - 60% of the administered i.v. dose was excreted in the urine. Mass balance studies in laboratory animals with ³H-2F-ara-AMP showed a complete recovery of radiolabelled substances in the urine.

Impaired Renal Function

Individuals with impaired renal function exhibited a reduced total body clearance, indicating the need for a dose reduction. Three groups of CLL/non-Hodgkin's lymphoma patients with differing creatinine clearance, >70 (n = 10), 30 - 70 (n = 9), <30 (n = 2) mL/min, were compared. After a single dose of 25 mg fludarabine by 30 minute IV infusion, AUC increased 16% in the second group and 116% in the third group relative to the first group. Multiple adjusted IV doses were then given over 5 days. The first group received 25 mg/m²/day, the second 20 mg/m²/day and the third 15 mg/m²/day. AUC was equivalent in the first and second groups, but increased 41% in the third group. [Note - Fludarabine is not recommended for patients in the third group (see CONTRAINDICATIONS).] There was a statistically significant inverse correlation between fludarabine AUC and creatinine clearance.

Cellular Pharmacokinetics of Fludarabine Triphosphate

Fludarabine (2F-ara-A) is actively transported into leukaemic cells, whereupon it is rephosphorylated to the monophosphate and subsequently to the di- and triphosphate. The triphosphate 2F-ara-ATP is the major intracellular metabolite and the only metabolite known to have cytotoxic activity. Maximum 2F-ara-ATP levels in leukaemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited a considerable variation with a median peak concentration of approximately

20 µM. 2F-ara-ATP levels in leukaemic cells were always considerably higher than maximum 2F-ara-A levels in the plasma indicating an accumulation at the target sites. In-vitro incubation of leukaemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and duration of incubation) and intracellular 2F-ara-ATP enrichment. 2F-ara-ATP elimination from target cells showed median half life values of 15 and 23 hours.

Clinical Trials

The following information refers to the use of fludarabine phosphate in first line chronic lymphocytic leukaemia.

Intravenous fludarabine 25 mg/m² on days 1 - 5 of a 28 day cycle significantly delayed disease progression compared with comparators in the first line treatment of B-cell CLL in three randomised controlled trials (Tables 1 - 3). A difference in survival was not shown due to insufficient follow up and confounding as a result of cross-overs. There was a median 7 and maximum 21 treatment cycles.

TABLE 1. IV FLUDARABINE - TRIAL 1 (Spirano) - median duration 8 cycles vs chlorambucil 30mg/m² orally on days 1, 15 plus methylprednisolone 40mg/m² intramuscularly on days 1 to 5 and 15 to 19 every 28 days (C/MP)

	Fludarabine n = 75	C/MP n = 75	Difference (95% CI)
Complete response rate ¹ %	25	21	4 (-10, 18)
Median time to progression <i>mths</i>	26	21	Hazard ratio = 0.53 (0.35, 0.79)
Median survival <i>mths</i>	> 48	> 48	

¹ US National Cancer Institute Working Group 1988 (NCI) criteria.

TABLE 2. IV FLUDARABINE - TRIAL 2 (Inveresk) - duration 6 cycles vs cyclophosphamide 750 mg/m² IV on day 1 plus doxorubicin 50 mg/m² IV on day 1 plus prednisone 40 mg/m² orally on days 1 - 5 every 28 days (CAP).

	Fludarabine n = 53	CAP n = 52	Difference (95% CI)
Complete response rate ¹ %	17	8	9 (6 ,28)
Median time to progression <i>mths</i>	41	17	Hazard ratio = 0.46 (0.30, 0.71)
Median survival <i>mths</i>	65	53	

¹ International Workshop on CLL criteria 1989 (IWCLL) criteria.

TABLE 3. IV FLUDARABINE - TRIAL 3 (CALGB) - median duration 7 cycles vs chlorambucil 40 mg/m² orally on day 1 every 28 days

	Fludarabine n = 175	Chlorambucil n = 178	Difference (95% CI)
Complete response rate ¹ %	15	3	12 (4, 19)
Median time to progression <i>mths</i>	17	13	Hazard ratio = 0.55 (0.39, 0.76)
Median survival <i>mths</i>	56	55	4

¹ Modified US National Cancer Institute Working Group 1988 criteria

Fludarabine tablets were assessed in an uncontrolled trial in 81 patients for first line treatment of B-cell CLL. The dose was 40 mg/m² on days 1 - 5 of each 28 day treatment cycle for a mean of 6 cycles. Fewer patients in this trial had Rai stage III/IV disease (22%) than in the intravenous fludarabine trials (35 - 50%). The median time to disease progression had not been reached at the time of the analysis, but exceeded 38 months, which is comparable or better than the result in the intravenous trials. The NCI complete response rate was 12% and overall response rate 80%. In a subgroup analysis, patients with Rai stage III or IV disease had a response rate of 61% which is comparable to that observed in this subgroup in the IV studies. There were no data on survival.

Indications

FLUDARABINE EBEWE is indicated for the treatment of B-cell chronic lymphocytic leukaemia.

Contraindications

FLUDARABINE EBEWE is contraindicated in those patients who are hypersensitive to this medicine or its components, in renally impaired patients with creatinine clearance < 30 mL/min and in patients with decompensated haemolytic anaemia.

FLUDARABINE EBEWE is contraindicated during pregnancy and lactation.

Precautions

Neurotoxicity

When used at high doses in dose-ranging studies in patients with acute leukaemia, fludarabine phosphate was associated with severe neurologic effects, including blindness, coma and death. 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 dose recommended for treatment of CLL. In patients treated at doses in the range of the dose recommended for CLL, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion).

In postmarketing experience, neurotoxicity has also been reported to occur earlier or later than in clinical trials, with a latency ranging from 7 to 225 days after the last dose of fludarabine phosphate.

The effect of chronic administration of fludarabine phosphate 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.

Myelosuppression

Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I study in solid tumour patients, the median time to nadir counts was 13 days (range 3 - 25 days) for granulocytes and 16 days (range 2 - 32) 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 haematological monitoring.

Fludarabine phosphate is a potent antineoplastic agent 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. In such cases, as a general rule, the dose of myelosuppressive agents should be reduced or the dosage interval extended.

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 ranged from approximately 2 months to 1 year. These episodes have occurred both in previously treated or untreated patients.

As with other cytotoxics, caution should be exercised with fludarabine phosphate, when further haematopoietic stem cell sampling is considered.

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 has been observed after transfusion of non-irradiated blood in fludarabine phosphate 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, to minimise the risk of transfusion associated graft-versus-host disease, patients who require blood transfusion and who are undergoing, or who have received, treatment with FLUDARABINE EBEWE should receive irradiated blood only.

Skin Cancer Lesions

The worsening or flare up of pre-existing skin cancer lesions as well as new onset of skin cancer has been reported in patients during or after fludarabine phosphate therapy.

Tumour Lysis Syndrome

Tumour lysis syndrome associated with fludarabine phosphate treatment has been reported in CLL patients with large tumour burdens. Since fludarabine phosphate 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

Irrespective of any previous history of autoimmune processes or Coombs test status, life threatening and sometimes fatal autoimmune phenomena (e.g. autoimmune haemolytic anaemia, autoimmune thrombocytopenia, thrombocytopenic purpura, pemphigus, Evans' syndrome) have been reported to occur during or after treatment with fludarabine phosphate. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with fludarabine phosphate.

Patients undergoing treatment with FLUDARABINE EBEWE should be closely monitored for signs of haemolysis. Discontinuation of therapy with FLUDARABINE EBEWE is recommended in case of haemolysis. Blood transfusion (irradiated) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

Use in Specialised Groups

Impaired state of health

Patients who have advanced stage disease, hypoalbuminaemia, reduced platelet count or haemoglobin levels, white cell count above $50 \times 10^9/L$, significant hepatic or spleen enlargement, extensive prior therapy or poor performance status are at risk of serious and sometimes fatal toxicity during the first 6 months of treatment.

Fludarabine treatment may be associated with a spectrum of infections different from those seen with neutropenia from standard chemotherapy medicines. Prophylactic treatment should be considered in patients at increased risk of developing

opportunistic infections, which include, but are not limited to, pneumocytis, fungi and herpes virus infections.

The dose of 25 mg/m²/day for 5 days by intravenous infusion may be greater than needed in some patients, especially those at risk, and consideration should be given to using a lower dose in such patients.

Reduced renal function

There are limited data in dosing of patients with renal insufficiency. Careful monitoring for haematological toxicity is required and possible dose reductions of FLUDARABINE EBEWE in patients with renal impairment, patients with depressed white cell count and platelet counts, or patients with infection or bleeding may be required.

The total body clearance of 2-fluoro-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Patients with reduced renal function demonstrated an increased total body exposure (AUC of 2F-ara-A). Limited clinical data are available in patients with impairment of renal function (creatinine clearance below 70 mL/min). FLUDARABINE EBEWE 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 in proportion to the reduced creatinine clearance and close haematological monitoring should be used to assess toxicity. FLUDARABINE EBEWE treatment is contraindicated if creatinine clearance is < 30 mL/min.

Impaired hepatic function

No data are available concerning the use of FLUDARABINE EBEWE in patients with hepatic impairment. In this group of patients FLUDARABINE EBEWE should be used with caution, and administered if the potential benefit outweighs any potential risk.

The elderly

Since there are limited data for the use of FLUDARABINE EBEWE in elderly persons (> 75 years), caution should be exercised with the administration of FLUDARABINE EBEWE in these patients. In patients aged 65 years or older, creatinine clearance should be measured before start of treatment.

Vaccination

During and after treatment with FLUDARABINE EBEWE, vaccination with live vaccines should be avoided.

Effects on Ability to Drive and Use Machinery

FLUDARABINE EBEWE may reduce the ability to drive or use machines, since fatigue, weakness, visual disturbances, confusion, agitation and seizures have been observed. Patients experiencing such adverse effects should avoid driving and using

machines. Reactions can be particularly impaired due to insufficient sleep duration, individual sensitivity and dosage.

Use in Pregnancy

Category D

Fludarabine is contraindicated in pregnancy (see CONTRAINDICATIONS). FLUDARABINE EBEWE should not be used during pregnancy.

One case of fludarabine phosphate use during early pregnancy leading to skeletal and cardiac malformation in the newborn has been reported. Premature delivery has been reported

Fludarabine phosphate has been shown to be embryotoxic and/or teratogenic in animal studies. Preclinical data in rats demonstrated a transfer of fludarabine phosphate and/or metabolites through the foeto-placental barrier. In view of the small exposure margin between teratogenic doses in animals and the human therapeutic dose as well as in analogy to other antimetabolites which are assumed to interfere with the process of differentiation, the therapeutic use of fludarabine phosphate is associated with a relevant risk of teratogenic effects in humans.

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

Women should avoid becoming pregnant while on FLUDARABINE EBEWE therapy. Women of child-bearing potential must be apprised of the potential hazard to the foetus.

Women of child-bearing potential or fertile males must take contraceptive measures during and at least for 6 months after cessation of therapy. If the patient becomes pregnant while taking this medicine, the patient should be advised of the potential hazard to the foetus.

Use in Lactation

It is not known whether this medicine is excreted in human milk. However there is evidence from preclinical data that fludarabine phosphate and/or metabolites transfer from maternal blood to milk. Because of the potential for serious adverse reactions in nursing infants from FLUDARABINE EBEWE, breast feeding should not be initiated during FLUDARABINE EBEWE treatment. Nursing women should discontinue breastfeeding for the duration of FLUDARABINE EBEWE therapy.

Paediatric Use

The safety and effectiveness of FLUDARABINE EBEWE in children has not been established. Therefore, treatment with fludarabine phosphate (Ph.Eur.) in children and adolescents is not recommended.

Interactions with Other Medicines

In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukaemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of FLUDARABINE EBEWE in combination with pentostatin is not recommended.

A pharmacokinetic interaction was observed in AML patients during combination therapy with fludarabine phosphate and Ara-C. Clinical studies and *in vitro* experiments with cancer cell lines demonstrated elevated intracellular Ara-CTP levels in combination with fludarabine phosphate treatment.

Dipyrimadole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of FLUDARABINE EBEWE.

In clinical investigation, pharmacokinetic parameters after peroral administration were not significantly affected by concomitant food intake.

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

Carcinogenesis/Mutagenesis

No animal carcinogenicity studies with FLUDARABINE EBEWE have been conducted. However, positive findings in carcinogenicity studies with other cytotoxic medicines and the positive genotoxicity findings with fludarabine phosphate suggest that FLUDARABINE EBEWE has carcinogenic potential. Fludarabine phosphate has been shown not to cause gene mutations in bacterial and mammalian cells *in vitro*. Chromosomal aberrations were observed in an *in vitro* assay using Chinese hamster ovary (CHO) cells under metabolically activated conditions. Fludarabine phosphate has also been shown to be clastogenic in the *in vivo* mouse micronucleus test. In addition, fludarabine phosphate was shown to cause increased sister chromatid exchanges using an *in vitro* sister chromatid exchange (SCE) assay under both metabolically activated and non-activated conditions

Impairment of Fertility

Studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. These results indicate that fludarabine phosphate may adversely affect male fertility, but this has not been directly investigated in studies of reproductive function. No information is available from animal studies on potential effects on female fertility. The possible adverse effects on fertility in humans have not been adequately evaluated.

Adverse Effects

Based on the experience with the intravenous use of fludarabine phosphate, the most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anaemia), infection including pneumonia, cough, fever, fatigue, weakness, nausea, vomiting and diarrhoea. Other commonly reported events include chills, oedema, mucositis, malaise, anorexia, peripheral neuropathy, visual disturbances, stomatitis, skin rashes, and mucositis. Serious opportunistic infections have occurred in CLL patients treated with fludarabine phosphate. 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 fludarabine phosphate. The rare adverse reactions were mainly identified from post marketing experience.

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			Lymphoproliferative 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)		Skin cancer

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
Blood and lymphatic system disorders	Neutropenia Anaemia Thrombocytopenia	Myelosuppression		
Immune system disorders			Autoimmune disorder (including autoimmune haemolytic anaemia, thrombocytopenic purpura, acquired haemophilia, pemphigus, Evan's syndrome, acquired haemophilia)	
Metabolism and nutrition disorders		Anorexia	Tumour lysis syndrome (including renal failure, hyperkalemia, metabolic acidosis, haematuria, urate crystalluria, hyperuricaemia, hyperphosphataemia, hypocalcaemia)	
Nervous system disorders		Neuropathy peripheral	Confusion	Agitation, Seizures Coma
Eye disorders		Visual disturbance		Optic neuritis Optic neuropathy Blindness
Cardiac disorders				Heart failure Arrhythmia
Respiratory, thoracic and mediastinal	Cough		Pulmonary toxicity (including dyspnoea,	

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
disorders			pulmonary fibrosis, pneumonitis)	
Gastrointestinal disorders	Nausea Vomiting Diarrhoea	Stomatitis	Gastrointestinal haemorrhage Pancreatic enzymes abnormal	
Hepatobiliary disorders			Hepatic enzyme abnormal	
Skin and subcutaneous tissue disorders		Rash		Skin cancer, Stevens-Johnson syndrome Necrolysis epidermal toxic (Lyell type)
Renal and urinary disorder				Haemorrhagic cystitis
General disorders and administration site conditions	Fever Fatigue Weakness	Chills Malaise Oedema Mucositis		

Dosage and Administration

Formulation for Intravenous Use

FLUDARABINE EBEWE should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

It is strongly recommended that FLUDARABINE EBEWE should only be administered intravenously. Paravenous administration must be avoided.

Adults

The recommended dose is 25 mg/m² body surface given daily for 5 consecutive days every 28 days by the intravenous route. Each vial contains 25 mg fludarabine phosphate per mL (50mg in 2mL).

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 physiological saline. Alternately, the required dose drawn up in a syringe may be diluted into 100 mL physiological saline and infused over approximately 30 minutes.

The duration of treatment depends on the treatment success and the tolerability of the medicine. FLUDARABINE EBEWE should be administered up to achievement of best response (complete or partial remission, usually 6 cycles) and then it should be discontinued.

Toxicity

Dosage may be decreased or delayed based on evidence of haematological or non-haematological toxicity. Physicians should consider delaying or discontinuing the medicine if toxicity occurs.

Impaired State of health

A number of clinical settings may predispose to increased toxicity from FLUDARABINE EBEWE. These include advanced age, renal insufficiency and bone marrow impairment - see Precautions, Use in Specialised Groups, Impaired State of Health. Such patients should be monitored closely for excessive toxicity and the dose modified accordingly.

Impaired Renal Function

Dosage reduction is required in renally impaired patients. Refer to Pharmacokinetics - Impaired Renal Function and Precautions - Use in Specialised Groups.

Retreatment Options After Initial FLUDARABINE EBEWE Treatment

Patients who primarily respond to FLUDARABINE EBEWE have a good chance of responding again to FLUDARABINE EBEWE monotherapy. A crossover from initial treatment with FLUDARABINE EBEWE to chlorambucil for non responders to FLUDARABINE EBEWE should be avoided. In a clinical trial, 46 subjects who failed initial fludarabine therapy were treated with chlorambucil 40 mg/m² every 28 days. Only one subject (2%) achieved a partial response.

Instructions for Use/Handling

Each mL of Fludarabine Ebewe injection contains 25mg of fludarabine phosphate, with sodium phosphate (dibasic dihydrate) and sodium hydroxide in water for injections. The pH range for the product is 7.2 to 7.8. In clinical studies the product has been diluted in 100 mL or 125 mL of 5% dextrose injection or 0.9% sodium chloride. The product may also be diluted with 5% glucose injection.

FLUDARABINE EBEWE 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 medicines. Any spillage or waste material may be disposed of by incineration.

Caution should be exercised in the handling and preparation of the FLUDARABINE EBEWE 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.

Incompatibilities

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

Overdosage

Contact the Poisons Information Centre on 0800 POISON or 0800 764766 for advice on management of overdose.

High doses of fludarabine phosphate 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. There is no known specific antidote for FLUDARABINE EBEWE overdose. Treatment consists of discontinuation and supportive therapy.

Presentations and Storage Conditions

Presentation

Single dose clear glass vials containing 50 mg of fludarabine phosphate in 2mL. Available in packs of 1 vial, 5 vials and 10 vials.

Storage Conditions

Intravenous Formulation

Store at 2°C - 8°C (refrigerate, do not freeze).

FLUDARABINE EBEWE contains no antimicrobial preservative. To reduce microbiological hazards it is recommended that any dilution should be effected immediately prior to use and infusion commenced as soon as practicable after preparation of infusion solutions. If storage is necessary, store at 2°C - 8°C

(refrigerate, do not freeze) for not more than 24 hours after preparation. Administration should be completed within 24 hours of preparation of the infusion and any residue discarded according to the guidelines for the disposal of cytotoxic drugs. Any solutions which are discoloured, hazy or contain visible particulate matter should not be used.

Medicine Classification

Prescription Medicine

Name and Address

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(Distributor on behalf of Sandoz Pty Ltd)

Date of Preparation

30 August 2011