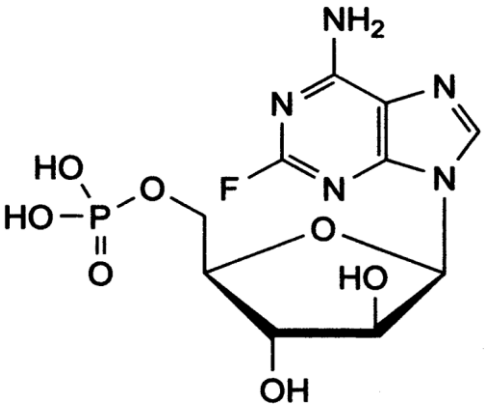
Product Information
FLUDARABINE EBEWE 50 mg/2 mL Injection

NAME OF THE MEDICINE

Fludarabine phosphate



Chemical Name: 2-Fluoro-9(5-O-phosphono-β-D-arabinofuranosyl)-9H-purin-6-amine
Molecular formula: $C_{10}H_{13}FN_5O_7P$
Molecular weight: 365.2
CAS number: 75607-67-9

DESCRIPTION

Fludarabine phosphate is a white or almost white, hygroscopic crystalline powder, slightly soluble in water, freely soluble in dimethylformamide, and very slightly soluble in anhydrous ethanol.

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

Fludarabine Ebewe is a sterile, clear, colourless solution containing 50mg fludarabine phosphate, sodium phosphate – dibasic dihydrate, and sodium hydroxide in water for injections.

PHARMACOLOGY

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.

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

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 m^2 to CLL patients for 30 minutes, fludarabine (2F-ara-A) reached mean maximum concentrations in the plasma of 3.5-3.7μM 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/m^2 (2.2 mL/min/kg) and a mean volume of distribution (V_{ss}) of 83 L/m^2 (2.4 L/kg). Data showed a high interindividual variability. After i.v. and peroral administration of fludarabine phosphate tablets in doses of 50-90mg, 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.

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 ^{3}H-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 25mg 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 25mg/m^2/day, the second 20mg/m^2/day and the third 15mg/m^2/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 leukemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited a considerable variation with a median peak concentration of approximately 20μM. 2F-ara-ATP levels in leukemic 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 leukemic 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 25mg/m^2 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/m^2 orally on days 1,15 plus methylprednisolone 40mg/m^2 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 months	26	21	Hazard ratio = 0.53 (0.35,0.79)
Median survival months	>48	>48	

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

Table 2

IV Fludarabine - TRIAL 2 (Inveresk) - duration 6 cycles vs cyclophosphamide 750mg/m^2 IV on day 1 plus doxorubicin 50mg/m^2 IV on day 1 plus prednisone 40mg/m^2 orally on days 1-5 every 28 days (CAP).			
	Fludarabine n=53	**C/MP n=52**	**Difference (95% CI)**
Complete response rate %[2]	17	8	9 (6,28)
Median time to progression months	41	17	Hazard ratio = 0.46 (0.30,0.71)
Median survival months	65	53	

[2] International Workshop on CLL criteria 1989 (IWCLL) criteria

Table 3

IV Fludarabine - TRIAL 3 (CALGB) - median duration 7 cycles vs chlorambucil 40mg/m^2 orally on day 1 every 28 days			
	Fludarabine n=175	**Chlorambucil n=178**	**Difference (95% CI)**
Complete response rate %[3]	15	3	12(4,19)
Median time to progression months	17	13	Hazard ratio = 0.55(0.39,0.76)
Median survival months	56	55	4

[3] 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 40mg/m^2 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 drug or its components, in renally impaired patients with creatinine clearance < 30mL/min and in patients with 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 (96mg/m^2/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). Patients should be closely observed for signs of neurologic side effects.

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

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, whereby up to 26 courses of therapy were administered.

Patients should be closely observed for signs of neurologic effects.

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

These may occur:

- at the recommended dose

- when fludarabine phosphate is given following, or in combination with, medications known to be associated with LE, ATL or RPLS

- when fludarabine phosphate is given to patients with other risk factors such as previous exposure to 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. Treating physicians should diagnose and monitor the patient with appropriate techniques (ideally brain imaging, MRI etc).

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 Ebewe 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 of blood products:
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, 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 Ebewe 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 autoimmune haemolytic anaemia (decline in haemoglobin linked with haemolysis and positive Coombs test). 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 $50x\ 10^9$ /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 drugs. 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/m^2/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 and 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 70mL/min). Fludarabine Ebewe must be administered cautiously in patients with renal insufficiency. 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 70mL/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 < 30mL/min.

Impaired hepatic function:
No data are available concerning the use of fludarabine phosphate 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.

Vaccination:
During and after treatment with Fludarabine Ebewe, vaccination with live vaccines should be avoided.

Effects on ability to drive and use machinery:
The effect of treatment with fludarabine phosphate on the patient's ability to drive or operate machinery has not been evaluated. However, fludarabine phosphate treatment may be associated with fatigue or visual disturbances. Patients experiencing such adverse effects should avoid driving and using machines.

Effects on 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.

Use in pregnancy:

Category D.

Fludarabine is contraindicated in pregnancy (see CONTRAINDICATIONS). Fludarabine Ebewe should not be used during pregnancy. There are very limited data of Fludarabine Ebewe use in pregnant women in the first trimester.

One case of fludarabine phosphate use during early pregnancy leading to skeletal and cardiac malformation in the newborn has been reported. Early pregnancy loss has been reported in Fludarabine phosphtate monotherapy as well as in combination therapy. 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 should avoid becoming pregnant while on fludarabine therapy.

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

Australian categorisation definition of Category D:
Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Use in 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. Because of the potential for serious adverse reactions in nursing infants from Fludarabine Ebewe, breast feeding should be discontinued for the duration of Fludarabine Ebewe therapy.

Breastfeeding should not be initiated during Fludarabine Ebewe therapy.

Paediatric use:
The safety and effectiveness of fludarabine phosphate in children has not been established. Therefore, treatment with fludarabine phosphate in children and adolescents is not recommended.

Use in the elderly:
Since there are limited data for the use of fludarabine phosphate 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.

Carcinogenicity/Genotoxicity:
No animal carcinogenicity studies with fludarabine phosphate have been conducted. However, positive findings in carcinogenicity studies with other cytotoxic drugs and the positive genotoxicity findings with fludarabine phosphate suggest that it 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.

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 drug 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.

The therapeutic efficacy of fludarabine phosphate may be reduced by dipyridamole and other inhibitors of adenosine uptake.

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

ADVERSE EFFECTS

Based on the experience with the intravenous use of fludarabine phosphate, the most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anaemia) fever, chills and 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. Serious opportunistic infections have occurred in CLL patients treated with fludarabine phosphate. Fatalities as a consequence of serious adverse events have been reported.

The most frequently reported adverse events and those reactions which are more clearly related to the drug are arranged below according to body system.

Their frequencies (common >1%, uncommon >0.1% and <1%) are based on clinical trial data regardless of the causal relationship with fludarabine phosphate. The rare events (<0.1%) were mainly identified from post marketing experience.

Haematopoietic System:
Haematologic events (neutropenia, thrombocytopenia, and anaemia) have been reported in the majority of CLL patients treated with fludarabine phosphate. Myelosuppression may be severe and cumulative. The prolonged effect of fludarabine phosphate on the decrease in the number of T-lymphocytes may lead to increased risk for opportunistic infections, including those due to latent viral reactivation, e.g. Herpes zoster, Epstein-Barr-Virus (EBV) or progressive multifocal leukoencephalopathy. Evolution of EBV-infection/reactivation into EBV associated lymphoproliferative disorder has been observed in immunocompromised patients.

Commonly, the occurrence of myelodysplastic syndrome (MDS) and acute myeloid leukaemia has been described in patients treated with fludarabine phosphate. The majority of these patients also received prior, concomitant or subsequent treatment with alkylating agents, topisomerase inhibitors or irradiation. Monotherapy with fludarabine phosphate has not been associated with an increased risk for the development of MDS.

Clinically significant autoimmune phenomena (including autoimmune haemolytic anaemia, Evans syndrome, thrombocytopenic purpura, acquired haemophilia, pemphigus) are uncommon in patients receiving fludarabine phosphate.

Metabolic:
Tumour lysis syndrome has been reported uncommonly in CLL patients treated with fludarabine phosphate. This complication may include hyperuricaemia, hyperphosphataemia, hypocalcaemia, metabolic acidosis, hyperkalaemia, haematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and haematuria.

Changes of hepatic and pancreatic enzymes are uncommon.

Oedema has been commonly reported.

Nervous System:
Peripheral neuropathy has been commonly observed. Confusion is uncommon. Coma, agitation and seizures occur rarely.

Pulmonary System:
Pneumonia commonly occurs in association with fludarabine phosphate treatment. Pulmonary hypersensitivity reactions to fludarabine phosphate (pulmonary infiltrates/pneumonitis/fibrosis) associated with dyspnoea and cough are uncommon.

Gastrointestinal System:
Gastrointestinal disturbances such as nausea and vomiting, anorexia, diarrhoea, mucositis and stomatitis are common events. Gastrointestinal bleeding, mainly related to thrombocytopenia, has been uncommonly reported in patients treated with fludarabine phosphate.

Cardiovascular:
In rare cases, heart failure and arrhythmia have been reported in patients treated with fludarabine phosphate.

Genitourinary System:
Rare cases of haemorrhagic cystitis have been reported in patients treated with fludarabine phosphate.

Skin:
Skin rashes have been commonly reported in patients treated with fludarabine phosphate.

In rare cases a toxic epidermal necrolysis (Lyell's disease), Stevens-Johnson syndrome or skin cancer may develop.

Special senses:
Visual disturbances are commonly reported events in patients treated with fludarabine phosphate. In rare cases optic neuritis, optic neuropathy and blindness have occurred.

Body as a whole:
Fever, chills, infection, malaise, weakness and fatigue have been commonly reported.

Postmarketing Experience: Postmarketing experience with unknown frequency

- Nervous system disorders
  - Leukoencephalopathy (see PRECAUTIONS)
  - Acute toxic leukoencephalopathy (see PRECAUTIONS)
  - Reversible posterior leukoencephalopathy syndrome (RPLS) (see PRECAUTIONS)
- Vascular disorders
  - Haemorrhage (including cerebral haemorrhage, pulmonary haemorrhage, haemorrhagic cystitis)

DOSAGE AND ADMINISTRATION

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.

Product is for single use in one patient only. Discard any residue.

Adults:
The recommended dose is 25mg/m^2 body surface given daily for 5 consecutive days every 28 days by the intravenous route. Each vial contains 25mg 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 10mL of physiological saline. Alternatively, the required dose drawn up in a syringe may be diluted into 100mL physiological saline and infused over approximately 30 minutes.

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

Toxicity:
Dosage may be decreased or delayed based on evidence of haematological and non haematological toxicity. Physicians should consider delaying or discontinuing the drug 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** sections of this document.

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/m^2 every 28 days. Only one subject (2%) achieved a partial response.

Instructions For Use:
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 100mL or 125mL of 5% dextrose injection or 0.9% sodium chloride injection. The product may also be diluted with 5% glucose injection.

To reduce microbiological hazard, use as soon as practicable after preparation of infusion solutions. If storage is necessary, hold at 2-8°C 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 (see Handling and disposal, below). Any solutions which are discoloured, hazy or contain visible particulate matter should not be used.

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

Handling and disposal:
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 drugs. 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.

OVERDOSAGE:

Contact the Poisons Information Centre on (telephone Australia 13 11 26 or New Zealand 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 phosphate overdosage. Treatment consists of drug discontinuation and supportive therapy.

PRESENTATION AND STORAGE CONDITIONS

Fludarabine Ebewe 50mg/2mL injection – glass vial. Pack of 1 vial and of 5 vials.

Store at 2°C to 8°C (Refrigerate. Do not freeze).

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG):04/01/2008

DATE OF MOST RECENT AMENDMENT: 18/11/2016