HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fludarabine Phosphate Injection safely and effectively. See full prescribing information for Fludarabine Phosphate Injection.

Fludarabine Phosphate Injection
Initial U.S. Approval: 1991

WARNING: CNS TOXICITY, HEMOLYTIC ANEMIA, AND PULMONARY TOXICITY

See full prescribing information for complete boxed warning.

- **Severe central nervous system toxicity occurred in 36% of patients treated with doses approximately four times greater (96 mg/m^2/day for 5 to 7 days) than the recommended dose. This toxicity was seen in ≤0.2% of patients treated at the recommended dose levels (25 mg/m^2). (5.1)**
- **Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported after one or more cycles of treatment. (5.2)**
- **In a clinical investigation of the combination of fludarabine phosphate with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. (*5.6*)**

----------INDICATIONS AND USAGE----------

Fludarabine Phosphate Injection is a nucleotide metabolic inhibitor indicated for:

- The treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. Benefit in treatment-naïve or non-refractory CLL patients is not established. (*1.1*)

Important limitations:

- Fludarabine phosphate should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m^2). (*5.7*)

----------DOSAGE AND ADMINISTRATION----------

Chronic Lymphocytic Leukemia (CLL) (*2.1*):

- The recommended adult dose is 25 mg/m^2 administered intravenously over a period of approximately 30 minutes daily for five consecutive days.
- Each 5-day course of treatment should commence every 28 days.

Renal Insufficiency (*2.2*):

- Adult patients with moderate impairment of renal function (creatinine clearance 30 to 70 mL/min/1.73 m^2) should have 20% dose reduction.
- Not indicated in patients with severe renal impairment.

Use of Infusion Solutions (*2.3*):

- Fludarabine Phosphate Injection contains no antimicrobial preservative and should be used within 8 hours of opening. Care must be taken to assure sterility of infusion solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

----------DOSAGE FORMS AND STRENGTHS----------

- A 50 mg/2 mL (25 mg/mL), clear, colorless to almost colorless, sterile solution intended for intravenous administration.

----------CONTRAINDICATIONS----------

- None

----------WARNINGS AND PRECAUTIONS----------

- Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia. Monitor blood counts before and during treatment. (5.2)
- Transfusion-associated graft-versus-host disease. Use only irradiated blood products for transfusions. (*5.5*)
- Infections. Monitor for infection. (*5.3*)
- Renal Insufficiency. Reduce dose for moderate renal impairment and monitor closely. Do not administer to patients with severe renal impairment. (*5.7*)
- Tumor lysis syndrome (TLS). Take precautions for patients at high risk for TLS. (*5.4*)
- May cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant. (*5.9*)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence > 30%) include myelosuppression (neutropenia, thrombocytopenia and anemia), fever, infection, nausea and vomiting, fatigue, anorexia, cough and weakness (*6*).

To report SUSPECTED ADVERSE REACTIONS, contact EBEWE Pharma at 1-800-898-9948 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Fludarabine Phosphate Injection in combination with pentostatin is not recommended due to the risk of severe pulmonary toxicity (*5.6* and *7.1*).

----------USE IN SPECIFIC POPULATIONS----------

- Renal clearance represents approximately 40% of the total body clearance. Patients with moderate renal impairment (17 to 41 mL/min/m^2) receiving 20% reduced fludarabine phosphate dose had a similar exposure (AUC; 21 versus 20 nM•h/mL) compared to patients with normal renal function receiving the recommended dose (*2.2*, *5.7* and *8.6*)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CNS TOXICITY, HEMOLYTIC ANEMIA, AND PULMONARY TOXICITY

Fludarabine Phosphate Injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Fludarabine phosphate can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, 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 with doses approximately four times greater (96 mg/m^2/day for 5 to 7 days) than the recommended dose. Similar severe central nervous system toxicity has been rarely (≤0.2%) reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia. [*See Warnings and Precautions (5.1)*]

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with fludarabine phosphate. Patients undergoing treatment with Fludarabine Phosphate Injection should be evaluated and closely monitored for hemolysis. [*See Warnings and Precautions (5.2)*]

In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of Fludarabine Phosphate Injection in combination with pentostatin is not recommended [*See Warnings and Precautions (5.6)*]

1 INDICATIONS AND USAGE

1.1 Indication

Fludarabine Phosphate Injection is indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. The safety and effectiveness of Fludarabine Phosphate Injection in previously untreated or non-refractory patients with CLL have not been established.

1.2 Important Limitations

Fludarabine Phosphate Injection should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m^2). [*See Warnings and Precautions (5.7)*]

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Lymphocytic Leukemia (CLL)

The recommended adult dose of Fludarabine Phosphate Injection is 25 mg/m^2 diluted in 100 to 125 cc of 5% dextrose injection USP or 0.9% sodium chloride USP administered intravenously over a period of approximately 30 minutes daily for five consecutive days. Each 5-day course of treatment should commence every 28 days. Dosage may be decreased or delayed based on evidence of hematologic or nonhematologic toxicity. Physicians should consider delaying or discontinuing the drug if neurotoxicity occurs.

A number of clinical settings may predispose to increased toxicity from Fludarabine Phosphate Injection. These include advanced age, renal insufficiency, and bone marrow impairment. Such patients should be monitored closely for excessive toxicity and the dose modified accordingly.

The optimal duration of treatment has not been clearly established. It is recommended that three additional cycles of Fludarabine Phosphate Injection be administered following the achievement of a maximal response and then the drug should be discontinued.

2.2 Renal Impairment

Adult patients with moderate impairment of renal function (creatinine clearance 30 to 70 mL/min/1.73 m^2) should have a 20% dose reduction of Fludarabine Phosphate Injection. [*See Warnings and Precautions (5.7)*]

2.3 Use of Infusion Solutions

Fludarabine Phosphate Injection contains no antimicrobial preservative and should be used within 8 hours of opening. Care must be taken to assure sterility of infusion solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

3 DOSAGE FORMS AND STRENGTHS

50 mg/2 mL (25 mg/mL)

A clear, colorless or almost colorless, sterile solution intended for intravenous administration

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Neurotoxicity

There are clear dose dependent toxic effects seen with fludarabine phosphate. Dose levels approximately 4 times greater (96 mg/m^2/day for 5 to 7 days) than that recommended for CLL (25 mg/m^2/day for 5 days) were associated with a syndrome characterized by delayed blindness, coma and death. Symptoms appeared from 21 to 60 days following the last dose. Thirteen of 36 patients (36%) who received fludarabine phosphate at high doses (96 mg/m^2/day for 5 to 7 days) developed this severe neurotoxicity. This syndrome has been reported rarely in patients treated with doses in the range of the recommended CLL dose of 25 mg/m^2/day for 5 days every 28 days. The effect of chronic administration of fludarabine phosphate on the central nervous system is unknown; however, patients have received the recommended dose for up to 15 courses of therapy.

5.2 Hematological Adverse Reactions

Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I study in adult solid tumor patients, the median time to nadir counts was 13 days (range, 3 to 25 days) for granulocytes and 16 days (range, 2 to 32 days) for platelets. Most patients had hematologic 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 Injection requires careful hematologic 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 ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with fludarabine phosphate in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission from their disease. Steroids may or may not be effective in controlling these hemolytic episodes. The majority of patients rechallenged with fludarabine phosphate developed a recurrence in the hemolytic process. The mechanism(s) which predispose patients to the development of this complication has not been identified. Patients undergoing treatment with Fludarabine Phosphate Injection should be evaluated and closely monitored for hemolysis.

5.3 Infections

Of the 133 adult CLL patients in the two trials, there were 29 fatalities during study. Approximately 50% of the fatalities were due to infection and 25% due to progressive disease.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome associated with fludarabine phosphate treatment has been reported in CLL patients with large tumor 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.

5.5 Use of Transfusions

Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of non-irradiated blood in fludarabine phosphate treated patients. Consideration should, therefore, be given to the use of irradiated blood products in those patients requiring transfusions while undergoing treatment with Fludarabine Phosphate Injection.

5.6 Pulmonary Toxicity

In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL) in adults, there

was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of Fludarabine Phosphate Injection in combination with pentostatin is not recommended.

5.7 Renal Impairment

There are inadequate data on dosing of patients with renal insufficiency. Fludarabine Phosphate Injection must be administered cautiously in patients with renal insufficiency. The total body clearance of 2-fluoro-ara-A has been shown to be directly correlated with creatinine clearance. Patients with moderate impairment of renal function (creatinine clearance 30 to 70 mL/min/1.73 m^2) should have their fludarabine phosphate dose reduced by 20% and be monitored closely. Fludarabine phosphate is not recommended for patients with severely impaired renal function [(creatinine clearance less than 30 mL/min/1.73 m^2). [*See Dosage and Administration (2.2)*]

5.8 Monitoring

- Hematologic and Nonhematologic Toxicity

Fludarabine Phosphate Injection is an antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of hematologic and nonhematologic toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anemia, neutropenia and thrombocytopenia.

- Hematopoietic Suppression

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression.

5.9 Pregnancy

Pregnancy Category D: Fludarabine phosphate may cause fetal harm when administered to a pregnant woman. Fludarabine phosphate was teratogenic in rats and in rabbits. Fludarabine phosphate was administered intravenously at doses of 0, 1, 10 or 30 mg/kg/day to pregnant rats on days 6 to 15 of gestation. At 10 and 30 mg/kg/day in rats, there was an increased incidence of various skeletal malformations. Fludarabine phosphate was administered intravenously at doses of 0, 1, 5 or 8 mg/kg/day to pregnant rabbits on days 6 to 15 of gestation. Dose-related teratogenic effects manifested by external deformities and skeletal malformations were observed in the rabbits at 5 and 8 mg/kg/day. Drug-related deaths or toxic effects on maternal and fetal weights were not observed. There are no adequate and well-controlled studies in pregnant women.

If Fludarabine Phosphate Injection is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, infection, and nausea and vomiting. Other commonly reported events include malaise, fatigue, anorexia, and weakness. Serious opportunistic infections have occurred in CLL patients treated with fludarabine phosphate. The most frequently reported adverse reactions and those reactions which are more clearly related to the drug are arranged below according to body system.

6.1 Hematopoietic Systems

Hematologic events (neutropenia, thrombocytopenia, and/or anemia) were reported in the majority of CLL patients treated with fludarabine phosphate. During fludarabine phosphate treatment of 133 patients with CLL, the absolute neutrophil count decreased to less than 500/mm^3 in 59% of patients, hemoglobin decreased from pretreatment values by at least 2 grams percent in 60%, and platelet count decreased from pretreatment values by at least 50% in 55%. Myelosuppression may be severe, cumulative, and may affect multiple cell lines. Bone marrow fibrosis occurred in one CLL patient treated with fludarabine phosphate.

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

Life-threatening and sometimes fatal autoimmune hemolytic anemias have been reported to occur in patients receiving fludarabine phosphate. [*See Warnings and Precautions (5.2)*] The majority of patients rechallenged with fludarabine phosphate developed a recurrence in the hemolytic process.

6.2 Metabolic

Tumor lysis syndrome has been reported in CLL patients treated with fludarabine phosphate. This complication may include hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and hematuria.

6.3 Nervous System

Objective weakness, agitation, confusion, visual disturbances, and coma have occurred in CLL patients treated with fludarabine phosphate at the recommended dose. Peripheral neuropathy has been observed in patients treated with fludarabine phosphate and one case of wrist-drop was reported. [*See Warnings and Precautions (5.1)*]

In post-marketing experience, cases of progressive multifocal leukoencephalopathy have been reported. Most cases had a fatal outcome. Many of these cases were confounded by prior and/or concurrent chemotherapy. The median time to onset was approximately one year.

6.4 Pulmonary System

Pneumonia, a frequent manifestation of infection in CLL patients, occurred in 16%, and 22% of those treated with fludarabine phosphate in the MDAH and SWOG studies, respectively. Pulmonary hypersensitivity reactions to fludarabine phosphate characterized by dyspnea, cough and interstitial pulmonary infiltrate have been observed.

In post-marketing experience, cases of severe pulmonary toxicity have been observed with Fludarabine Phosphate use which resulted in ARDS, respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, and respiratory failure. After an infectious origin has been excluded, some patients experienced symptom improvement with corticosteroids.

6.5 Gastrointestinal System

Gastrointestinal disturbances such as nausea and vomiting, anorexia, diarrhea, stomatitis and gastrointestinal bleeding have been reported in patients treated with fludarabine phosphate.

6.6 Cardiovascular

Edema has been frequently reported. One patient developed a pericardial effusion possibly related to treatment with fludarabine phosphate. No other severe cardiovascular events were considered to be drug related.

6.7 Genitourinary System

Hemorrhagic cystitis has been reported in patients treated with fludarabine phosphate.

6.8 Skin

Skin toxicity, consisting primarily of skin rashes, has been reported in patients treated with fludarabine phosphate.

6.9 Adverse Reactions from Clinical Trials

Data in Table 1 are derived from the 133 patients with CLL who received fludarabine phosphate in the MDAH and SWOG studies.

TABLE 1: PERCENT OF CLL PATIENTS REPORTING NON-HEMATOLOGIC ADVERSE REACTIONS

ADVERSE REACTIONS	MDAH (N=101)	SWOG (N=32)
ANY ADVERSE REACTION	88	91
BODY AS A WHOLE	72	84
FEVER	60	69
CHILLS	11	19
FATIGUE	10	38
INFECTION	33	44
PAIN	20	22
MALAISE	8	6
DIAPHORESIS	1	13
ALOPECIA	0	3
ANAPHYLAXIS	1	0
HEMORRHAGE	1	0
HYPERGLYCEMIA	1	6
DEHYDRATION	1	0
NEUROLOGICAL	21	69
WEAKNESS	9	65
PARESTHESIA	4	12
HEADACHE	3	0
VISUAL DISTURBANCE	3	15
HEARING LOSS	2	6
SLEEP DISORDER	1	3
DEPRESSION	1	0
CEREBELLAR SYNDROME	1	0
IMPAIRED MENTATION	1	0
PULMONARY	35	69
COUGH	10	44
PNEUMONIA	16	22
DYSPNEA	9	22
SINUSITIS	5	0
PHARYNGITIS	0	9
UPPER RESPIRATORY INFECTION	2	16
ALLERGIC PNEUMONITIS	0	6
EPISTAXIS	1	0
HEMOPTYSIS	1	6
BRONCHITIS	1	0
HYPOXIA	1	0
GASTROINTESTINAL	46	63
NAUSEA/VOMITING	36	31
DIARRHEA	15	13
ANOREXIA	7	34
STOMATITIS	9	0
GI BLEEDING	3	13
ESOPHAGITIS	3	0
MUCOSITIS	2	0
LIVER FAILURE	1	0
ABNORMAL LIVER FUNCTION TEST	1	3
CHOLELITHIASIS	0	3
CONSTIPATION	1	3
DYSPHAGIA	1	0
CUTANEOUS	17	18
RASH	15	15
PRURITUS	1	3
SEBORRHEA	1	0
GENITOURINARY	12	22
DYSURIA	4	3
URINARY INFECTION	2	15
HEMATURIA	2	3
RENAL FAILURE	1	0
ABNORMAL RENAL FUNCTION TEST	1	0
PROTEINURIA	1	0
HESITANCY	0	3
CARDIOVASCULAR	12	38
EDEMA	8	19
ANGINA	0	6
CONGESTIVE HEART FAILURE	0	3
ARRHYTHMIA	0	3
SUPRAVENTRICULAR TACHYCARDIA	0	3
MYOCARDIAL INFARCTION	0	3
DEEP VENOUS THROMBOSIS	1	3
PHLEBITIS	1	3
TRANSIENT ISCHEMIC ATTACK	1	0
ANEURYSM	1	0
CEREBROVASCULAR ACCIDENT	0	3
MUSCULOSKETAL	7	16
MYALGIA	4	16
OSTEOPOROSIS	2	0
ARTHRALGIA	1	0
TUMOR LYSIS SYNDROME	1	0

More than 3000 adult patients received fludarabine phosphate in studies of other leukemias, lymphomas, and other solid tumors. The spectrum of adverse effects reported in these studies was consistent with the data presented above.

7 DRUG INTERACTIONS

7.1 Pentostatin

The use of Fludarabine Phosphate Injection in combination with pentostatin is not recommended due to the risk of severe pulmonary toxicity. [*See Warnings and Precautions (5.6)*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. [*See Warnings and Precautions (5.9)*]

8.3 Nursing Mothers

It is not known whether fludarabine phosphate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions including tumorigenicity in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

8.4 Pediatric Use

Data submitted to the FDA was insufficient to establish efficacy in any childhood malignancy.

Limited pharmacokinetic data for fludarabine phosphate are available from a published study of children (ages 1 to 21 years) with refractory acute leukemias or solid tumors (Children's Cancer Group Study 097).When fludarabine phosphate was administered as a loading dose over 10 minutes immediately followed by a 5-day continuous infusion, steady-state conditions were reached early. [*See Clinical Studies (14.2)*]

8.6 Patients with Renal Impairment

The total body clearance of the principal metabolite 2-fluoro-ara-A correlated with the creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the drug. Renal clearance represents approximately 40% of the total body clearance. Patients with moderate renal impairment (17 to 41 mL/min/m^2) receiving 20% reduced fludarabine phosphate dose had a similar exposure (AUC; 21 versus 20 nM•h/mL) compared to patients with normal renal function receiving the recommended dose. The mean total body clearance was 172 mL/min for normal and 124 mL/min for patients with moderately impaired renal function.

10 OVERDOSAGE

High doses of fludarabine phosphate [*See Indications and Usage (1.1) and Warnings and Precautions (5.1, 5.2)*] have been associated with an 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 fludarabine phosphate overdosage. Treatment consists of drug discontinuation and supportive therapy.

11 DESCRIPTION

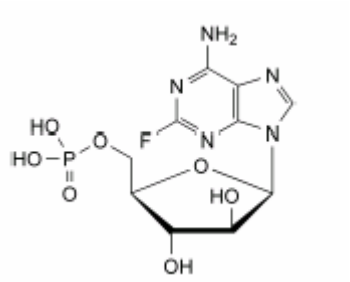
Fludarabine Phosphate Injection contains fludarabine phosphate, a nucleotide metabolic inhibitor. Fludarabine phosphate is a fluorinated nucleotide analog of the antiviral agent vidarabine, 9-β-D-arabinofuranosyladenine (ara-A), that is relatively resistant to deamination by adenosine deaminase.

Each mL contains 25 mg of the active ingredient fludarabine phosphate, 1.78 mg disodium phosphate dihydrate, water for injection, qs; and sodium hydroxide to adjust pH to 7.5. The pH range for the final product is 7.3 to 7.7. Fludarabine Phosphate Injection is a sterile solution intended for intravenous administration.

The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono-β-D-arabinofuranosyl)(2-fluoro-ara-AMP).

The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$ (MW 365.2) and the structure is provided in Figure 1

Figure 1: Chemical Structure of Fludarabine Phosphate



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted.

12.2 Pharmacodynamics

Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2-fluoro-ara-A, within minutes after intravenous infusion.

12.3 Pharmacokinetics

Clinical pharmacology studies have focused on 2-fluoro-ara-A pharmacokinetics. After the five daily doses of 25 mg 2-fluoro-ara-AMP/m^2 to cancer patients infused over 30 minutes, 2-fluoro-ara-A concentrations show a moderate accumulation. During a 5-day treatment schedule, 2-fluoro-ara-A plasma trough levels increased by a factor of about 2. The terminal half-life of 2-fluoro-ara-A was estimated as approximately 20 hours. *In vitro*, plasma protein binding of fludarabine ranged between 19% and 29%. A correlation was noted between the degree of absolute granulocyte count nadir and increased area under the concentration x time curve (AUC).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal carcinogenicity studies with fludarabine have been conducted.

Fludarabine phosphate was clastogenic *in vitro* to Chinese hamster ovary cells (chromosome aberrations in the presence of metabolic activation) and induced sister chromatid exchanges both with and without metabolic activation. In addition, fludarabine phosphate was clastogenic *in vivo* (mouse micronucleus assay) but was not mutagenic to germ cells (dominant lethal test in male mice). Fludarabine phosphate was not mutagenic to bacteria (Ames test) or mammalian cells (HGRPT assay in Chinese hamster ovary cells) either in the presence or absence of metabolic activation.

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 mice and rats with a trend toward decreased testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. The possible adverse effects on fertility in humans have not been adequately evaluated.

14 CLINICAL STUDIES

14.1 Adults

Two single-arm open-label studies of fludarabine phosphate have been conducted in adult patients with CLL refractory to at least one prior standard alkylating-agent containing regimen. In a study conducted by M.D. Anderson Cancer Center (MDAH), 48 patients were treated with a dose of 22 to 40 mg/m^2 daily for 5 days every 28 days. Another study conducted by the Southwest Oncology Group (SWOG) involved 31 patients treated with a dose of 15 to 25 mg/m^2 daily for 5 days every 28 days. The overall objective response rates were 48% and 32% in the MDAH and SWOG studies, respectively. The complete response rate in both studies was 13%; the partial response rate was 35% in the MDAH study and 19% in the SWOG study. These response rates were obtained using standardized response criteria developed by the National Cancer Institute CLL Working Group and were achieved in heavily pre-treated patients. The ability of fludarabine phosphate to induce a significant rate of response in refractory patients suggests minimal cross-resistance with commonly used anti-CLL agents.

The median time to response in the MDAH and SWOG studies was 7 weeks (range of 1 to 68 weeks) and 21 weeks (range of 1 to 53 weeks), respectively. The median duration of disease control was 91 weeks (MDAH) and 65 weeks (SWOG). The median survival of all refractory CLL patients treated with fludarabine phosphate was 43 weeks and 52 weeks in the MDAH and SWOG studies, respectively.

Rai stage improved to Stage II or better in 7 of 12 MDAH responders (58%) and in 5 of 7 SWOG responders (71%) who were Stage III or IV at baseline. In the combined studies, mean hemoglobin concentration improved from 9.0 g/dL at baseline to 11.8 g/dL at the time of response in a subgroup of anemic patients. Similarly, average platelet count improved from 63,500/mm^3 to 103,300/mm^3 at the time of response in a subgroup of patients who were thrombocytopenic at baseline.

14.2 Pediatrics

Fludarabine phosphate was evaluated in 62 pediatric patients (median age 10, range 1 to 21) with refractory acute leukemia (45 patients) or solid tumors (17 patients). The fludarabine phosphate regimen tested for pediatric acute lymphocytic leukemia (ALL) patients was a loading bolus of 10.5 mg/m^2/day followed by a continuous infusion of 30.5 mg/m^2/day for 5 days. In 12 pediatric patients with solid tumors, dose-limiting myelosuppression was observed with a loading dose of 8 mg/m^2/day followed by a continuous infusion of 23.5 mg/m^2/day for 5 days. The maximum tolerated dose was a loading dose of 7 mg/m^2/day followed by a continuous infusion of 20 mg/m^2/day for 5 days. Treatment toxicity included bone marrow suppression. Platelet counts appeared to be more sensitive to the effects of fludarabine phosphate than hemoglobin and white blood cell counts. Other adverse reactions included fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. There were no reported occurrences of peripheral neuropathy or pulmonary hypersensitivity reaction.

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NDC 68842-007-01: 50 mg/2 mL (25 mg/mL)

16.2 Storage

Store at 2° to 8°C (36° to 46°F).

16.3 Handling and Disposal

Procedures for proper handling and disposal should be considered. Consideration should be given to handling and disposal according to guidelines issued for cytotoxic drugs. Several guidelines on this subject have been published.[1-4] Caution should be exercised in the handling and preparation of Fludarabine Phosphate Injection 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 contacts the skin or mucous membranes, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Avoid exposure by inhalation or by direct contact of the skin or mucous membranes.

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Ebewe PHARMA

EBEWE Pharma Ges.m.b.H. Nfg.KG
A-4866 Unterach, AUSTRIA

17 PATIENT COUNSELING INFORMATION

17.1 Monitoring

Patients should be informed of the importance of periodic assessment of their blood count to detect the development of anemia, neutropenia and thrombocytopenia.

17.2 Laboratory Tests

During treatment, the patient's hematologic profile (particularly neutrophils, red blood cells, and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. [*See Warnings and Precautions (5.1)*]

17.3 Pregnancy

Fludarabine phosphate may cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant. [*See Warnings and Precautions (5.9)*]

Revised Carton
NDA 22-137: Fludarabine Phosphate Injection

Faltschachtel ● (X) / Faltschachtelzuschnitt: ●

Artikelnummer: 742560 – 01 (inkl. Klischeevermerk):
Format: 38 x 38 x 70 mm FS-Norm: _____
Farben: ● Pantone 320 C ● Pantone 185 C
● Schwarz C ● _____
Schmuckfarbe Spannung über 1,1 ja (X) / nein ●
Code: 905 Besonderheit: _____

Revised Vial Label
NDA 22-137: Fludarabine Phosphate Injection

Etikette AMP ● / DST X
CARINI Standard 2007
Artikelnummer: 733413 – 01 (inkl. Klischeevermerk):
Format: 62 x 21 mm
Farben: ● Pantone 320 C ● Pantone 185 C
● Schwarz C ●
Eindruckfeld rechts: 6 mm X 8 mm ●
Code: 1358 Seite: rechts(DST) X links (AMP) ●
Stellung: M4