

**BRIEF SUMMARY**

**FLUDARABINE PHOSPHATE INJECTION  
FOR INTRAVENOUS USE ONLY**

**WARNING**

Fludarabine should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Fludarabine can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, fludarabine 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<sup>2</sup>/day for 5–7 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.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with fludarabine. Patients undergoing treatment with fludarabine should be evaluated and closely monitored for hemolysis.

In a clinical investigation using fludarabine 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 in combination with pentostatin is not recommended.

**CONTRAINDICATIONS**

Fludarabine phosphate injection is contraindicated in those patients who are hypersensitive to this drug or its components.

**WARNINGS (See boxed warning)**

There are clear dose-dependent toxic effects seen with fludarabine. Dose levels approximately 4 times greater (96 mg/m<sup>2</sup>/day for 5 to 7 days) than that recommended for CLL (25 mg/m<sup>2</sup>/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 at high doses (96 mg/m<sup>2</sup>/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<sup>2</sup>/day for 5 days every 28 days. The effect of chronic administration of fludarabine on the central nervous system is unknown; however, patients have received the recommended dose for up to 15 courses of therapy.

Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine. In a Phase I study in solid tumor 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 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 requires careful hematologic monitoring.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported. 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 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 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 should be evaluated and closely monitored for hemolysis.

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

In a clinical investigation using fludarabine 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 in combination with pentostatin is not recommended.

Of the 133 CLL adult 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.

**Pregnancy Category D**

Fludarabine 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 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.

**PRECAUTIONS**

**General**

Fludarabine is a potent 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.

Tumor lysis syndrome associated with fludarabine treatment has been reported in CLL patients with large tumor burdens. Since fludarabine 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. There are inadequate data on dosing of patients with renal insufficiency. Fludarabine 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 30–70 mL/min/1.73 m<sup>2</sup>) should have their fludarabine dose reduced by 20% and be monitored closely. Fludarabine is not recommended for patients with severely impaired renal function (creatinine clearance less than 30 mL/min/1.73 m<sup>2</sup>).

**Laboratory Tests**

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

**Drug Interactions**

The use of fludarabine in combination with pentostatin is not recommended due to the risk of severe pulmonary toxicity (see **WARNINGS** section).

**Carcinogenesis**

No animal carcinogenicity studies with fludarabine have been conducted.

**Mutagenesis**

Fludarabine phosphate was not mutagenic to bacteria (Ames test) or mammalian cells (HGPRT assay in Chinese hamster ovary cells) either in the presence or absence of metabolic activation. 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).

**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 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.

**Pregnancy**

*Teratogenic Effects: Pregnancy Category D*  
(See **WARNINGS** section).

**Nursing Mothers**

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

**Pediatric Use**

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

**ADVERSE REACTIONS**

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

**Hematopoietic Systems**

Hematologic events (neutropenia, thrombocytopenia, and/or anemia) were reported in the majority of CLL patients treated with fludarabine. During fludarabine treatment of 133 patients with CLL, the absolute neutrophil count decreased to less than 500/mm<sup>3</sup> 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.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in postmarketing 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 anemia have been reported to occur in patients receiving fludarabine (see **WARNINGS** section). The majority of patients rechallenged with fludarabine developed a recurrence in the hemolytic process.

**Metabolic**

Tumor lysis syndrome has been reported in CLL patients treated with fludarabine. 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.

**Nervous System**

(See **WARNINGS** section)

Objective weakness, agitation, confusion, visual disturbances, and coma have occurred in CLL patients treated with fludarabine at the recommended dose. Peripheral neuropathy has been observed in patients treated with fludarabine and one case of wrist-drop was reported.

**Pulmonary System**

Pneumonia, a frequent manifestation of infection in CLL patients, occurred in 16%, and 22% of those treated with fludarabine in the MDAH and SWOG studies, respectively. Pulmonary hypersensitivity reactions to fludarabine 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 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.

**Gastrointestinal System**

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

**Cardiovascular**

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

**Genitourinary System**

Rare cases of hemorrhagic cystitis have been reported in patients treated with fludarabine.

**Skin**

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

Data in the following table are derived from the 133 patients with CLL who received fludarabine in the MDAH and SWOG studies.

**PERCENT OF CLL PATIENTS REPORTING  
NON-HEMATOLOGIC ADVERSE EVENTS**

ADVERSE EVENTS	MDAH (N=101)	SWOG (N=32)
ANY ADVERSE EVENT	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	0
DEHYDRATION	1	6
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
HEMOPHTYSIS	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	0
DYSPHAGIA	1	3
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
MUSCULOSKELETAL	7	16
MYALGIA	4	16
OSTEOPOROSIS	2	0
ARTHRALGIA	1	0
TUMOR LYSIS SYNDROME	1	0

More than 3000 adult patients received fludarabine 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.

**SICOR Pharmaceuticals, Inc.**

Irvine, CA 92618



Issued: August 2003