FLUDARABINE

Packaging designed to be informative

**Carton and Label are DescriptIV™**
- Unique label design to help with accurate product selection
- Full-color carton coordinates with vial label
- Prominent, easy-to-read drug name and strength
- Cytotoxic caution on label and carton to alert caregivers who handle the product
- Available in 50 mg per 2 mL single-dose vials
- Preservative-free, AP rated, bar coded and not made with natural rubber latex

FLUDARABINE Phosphate Injection, USP

Please see full prescribing information, including boxed warning, for FLUDARABINE Phosphate Injection, USP, enclosed.

Every SAGENT® Product Features...

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* Product requires refrigeration between 2° and 8° C (36° and 46° F).

This SAGENT® product meets stringent FDA requirements and is AP rated, preservative-free and not made with natural rubber latex.

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FLUDARABINE Phosphate Injection, USP

INDICATIONS
Fludarabine Phosphate Injection, USP 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, USP in previously untreated or non-refractory CLL patients have not been established.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE BONE MARROW SUPPRESSION, 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 injection can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, fludarabine phosphate injection 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/m²/day for 5 to 7 days) than the recommended dose. Similar severe central nervous system toxicity, including coma, seizures, agitation and confusion, has been 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 phenomena such as hemolytic anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have been reported to occur after one or more cycles of treatment with fludarabine phosphate injection. Patients undergoing treatment with fludarabine phosphate injection should be evaluated and closely monitored for hemolysis.

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.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
• Dose Dependent Neurologic Toxicities. Clear dose dependent toxic effects are seen with fludarabine phosphate. Dose levels approximately 4 times greater (96 mg/m²/day for 5 to 7 days) than that recommended for CLL (25 mg/m²/day for 5 days) were associated with delayed blindness, coma and death. Thirteen of 36 patients 36% who received fludarabine phosphate at high doses developed this severe neurotoxicity. Fludarabine phosphate may reduce the ability to drive or use mechanical equipment.
• Bone Marrow Suppression. Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. Administration of fludarabine phosphate injection requires careful hematologic monitoring even though chemotherapy induced myelosuppression is often reversible.
• Autoimmune Reactions. Instances of life threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have been reported 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. Patients undergoing treatment should be closely monitored for hemolysis, and in the event of hemolysis, therapy should be discontinued.
• Transfusion Associated Graft- versus-Host Disease. This disorder has been observed after transfusion of nonirradiated blood in fludarabine phosphate treated patients.
• Pulmonary Toxicity. An unacceptably high incidence of fatal pulmonary toxicity was reported in a clinical investigation using fludarabine phosphate in combination with pentostatin for treatment of refractory chronic CLL. Therefore, this drug combination is not recommended.
• Pregnancy Category D. Fludarabine phosphate can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid pregnancy.
• Male Fertility. Fludarabine phosphate may cause testicular tissue and spermatozoa damage. Males should use contraception during and after cessation of fludarabine phosphate therapy.
• Tumor Lysis. Tumor lysis syndrome has been associated with fludarabine phosphate treatment in CLL patients with large tumor burdens.
• Renal Impairment. Administer fludarabine phosphate injection cautiously in patients with renal impairment. Patients with creatinine clearance 30 to 79 mL/min should be closely monitored, and if creatinine clearance is less than 30 mL/min, fludarabine phosphate should not be administered.

ADVERSE REACTIONS
• Very common adverse events include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, fatigue, weakness, infection, pneumonia, cough, nausea, vomiting and diarrhea.
• Other commonly reported events include malaise, mucositis and anorexia.
• Serious and sometimes fatal infections, including opportunistic infections and latent viral infection reactivations such as herpes zoster virus, Epstein-Barr virus and JC virus, have occurred in CLL patients treated with fludarabine phosphate.
• Edema, pericardial effusion, heart failure, arrhythmia, hemorrhagic cystitis, skin rashes, Steven-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, pemphigus, and elevated liver enzymes have been reported. Some have resulted in fatal outcomes.

OVERDOSAGE
High doses of fludarabine phosphate have been associated with an irreversible central nervous system toxicity characterized by delayed blindness, coma and death. High doses are associated with myelosuppression. There is no antidote for fludarabine phosphate overdosage. Treatment consists of drug discontinuation and supportive therapy.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full prescribing information for FLUDARABINE Phosphate Injection, USP.

Fludarabine phosphate injection should be administered under the supervision of a qualified physician.

**2.1 Recommended Dose**

- The recommended adult dose is 50 to 79 mL/min 20 mg/m²/day for 5 days. 
- When used at high doses in dose-ranging studies, the recommended dose is approximately 4 times greater (96 mg/m²/day for 5 to 7 days) than that recommended for CLL patients.

**2.2 Dose Reduction**

- If the patient is unable to undergo the recommended dose regimen for any reason, an alternative treatment regimen (25 mg/m²/day for 5 days) should be considered.

**2.3 Concurrent Use**

- Fludarabine phosphate is recommended for chronic lymphocytic leukemia.

**3.1 Renal Impairment**

- Fludarabine phosphate is not recommended for patients with a creatinine clearance of less than 30 mL/min.

**3.2 Pediatric Use**

- Fludarabine phosphate is not recommended for children or adolescents under 18 years of age.

**4.1 Pregnancy**

- Fludarabine phosphate is a pregnancy category D drug.

**4.3 Contraindications**

- Fludarabine phosphate is contraindicated in patients with severe bone marrow suppression.

**4.7 Black Box Warning**

- Fludarabine phosphate contains a black box warning.

**5.2 Long-Term Administration**

- Long-term administration of fludarabine phosphate is associated with increased risk of second malignancies.

**5.6 Effects on Reproduction**

- Fludarabine phosphate is associated with decreased fertility in males and females.

**5.7 Male Fertility and Reproductive Toxicity**

- Fludarabine phosphate is associated with decreased male fertility.

**5.8 Male Fertility and Reproductive Toxicity**

- Fludarabine phosphate is associated with decreased male fertility.

**5.9 Reproduction**

- Fludarabine phosphate is associated with increased risk of congenital anomalies.

**5.11 Doses of Fludarabine Phosphate in Pregnancy**

- Fludarabine phosphate is not recommended for use during pregnancy.

**5.12 Tumorigenicity in Nursing Infants**

- Fludarabine phosphate is not recommended for use during breast-feeding.

**8.1 Use in Specific Populations**

- Fludarabine phosphate is not recommended for use in patients with renal impairment.

**8.5 Post-Marketing Experience**

- Fludarabine phosphate has been associated with increased risk of secondary malignancies.

**8.8 Adverse Reactions**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**8.9 Reference Standards**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**10.1 Effect of Overdose**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**10.2 Overdosage Treatment**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**10.3 Disposition**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**11.2 Clinical Trials**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**11.3 Veterinary Medicine**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**11.4 Aging**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**11.5 Other Sites**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**11.6 Clinical Pharmacology**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**11.7 Other Use**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**Appendix**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**References**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.

**Notes**

- Fludarabine phosphate has been associated with increased risk of myelodysplastic syndromes.
Fludarabine phosphate is rapidly converted 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 understood. 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 with a transient decrease in seminal vesicle weights in dogs and monkeys and necrosis of the testis in mice. See CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics for further discussion of spermatogenic epithelium of the testes in mice, rats and dogs. No animal carcinogenicity studies with fludarabine have been conducted.

11.4.2 Human Studies

A dose of fludarabine phosphate for injection was used in 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 one study conducted by the Southwest Oncology Group (SWOG), 37 patients were treated with a dose of 22 to 25 mg/m² daily for 5 days every 28 days. Another study conducted by M.D. Anderson Cancer Center (MDAH), 48 patients were treated with a dose of 22 to 25 mg/m² daily for 5 days every 28 days. The complete response rate in both studies was 13%; the partial response rate was 28% and 35% in the MDAH study and 19% in the SWOG study. These response rates were obtained using 28 days. The overall objective response rates were 48% and 32% in the MDAH and SWOG studies, respectively. The median duration of disease control was 43 weeks and 52 weeks in the MDAH and SWOG studies, and 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. The median survival of all refractory CLL patients treated with fludarabine phosphate was 40 mg/m² 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/m² daily for 5 days every 28 days. The overall survival of all patients treated with fludarabine phosphate was 14.1 Adults

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. The median survival of all refractory CLL patients treated with fludarabine phosphate was 40 mg/m² 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/m² daily for 5 days every 28 days. The overall survival of all patients treated with fludarabine phosphate was 14.1 Adults

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