FLUDARABINE PHOSPHATE INJECTION, USP
Rx only
M.W. 365.2
CLINICAL PHARMACOLOGY:
Fludarabine phosphate is rapidly dephosphorylated to its active metabolite, 2-fluoro-ara-A. Fludarabine phosphate is extensively metabolized in vivo.

INDICATIONS AND USAGE: Fludarabine phosphate is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have had previous treatment and have failed to respond to, or have failed to maintain a response after treatment with at least one standard alkylating-agent containing regimen. The median time to progression is increased in patients treated with fludarabine compared to patients treated with CVP (cyclophosphamide, vincristine, and prednisone) or mitoxantrone treatment. The median time to progression is increased in patients treated with fludarabine compared to patients treated with CVP (cyclophosphamide, vincristine, and prednisone) or mitoxantrone treatment.

CONTRAINDICATIONS: Fludarabine phosphate is contraindicated in patients with a history of severe hypersensitivity reactions to fludarabine phosphate or any component of the formulation. Fludarabine phosphate should not be administered to patients with neurologic deficits attributable to treatments with fludarabine phosphate who have failed to respond to the drug. The use of fludarabine phosphate in patients with a history of severe hypersensitivity reactions to fludarabine phosphate is contraindicated.

WARNING: Fludarabine phosphate should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Fludarabine phosphate may be severely toxic to patients with severe leukopenia, leukopenia, and thrombocytopenia. The use of fludarabine phosphate in patients with severe leukopenia, leukopenia, and thrombocytopenia may be associated with severe hypersensitivity reactions to fludarabine phosphate.

Additional WARNINGS: Fludarabine phosphate should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Fludarabine phosphate may be severely toxic to patients with severe leukopenia, leukopenia, and thrombocytopenia. The use of fludarabine phosphate in patients with severe leukopenia, leukopenia, and thrombocytopenia may be associated with severe hypersensitivity reactions to fludarabine phosphate.

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INJECTION, USP

\[ \text{2-fluoro-ara-ATP} \]

The structure is:

\[ \text{2-fluoro-ara-ATP} \]

This metabolite appears to act by inhibiting the active triphosphate, 2-fluoro-ara-ATP. The chemical name for fludarabine phosphate is 2-fluoro-2-deoxyadenosine-5'-phosphate. The total body clearance of the principal metabolite 2-fluoro-ara-A correlated with the complete response rate in the Phase I studies. The metabolite is eliminated in the urine. The half-life of the parent compound is about 5 minutes. Fludarabine phosphate Injection, USP contains fludarabine phosphate, a fluorinated nucleotide intended for intravenous administration.

\[ \text{Fludarabine Phosphate Injection, USP} \]

Fludarabine phosphate was not mutagenic in bacterial tests (Ames test) or mammalian cells using the standard tests for detecting direct-acting mutagens or clastogens. Fludarabine phosphate was clastogenic in vitro to Chinese hamster ovary cells. The chromosomal aberration test was negative at the highest tested concentration. Fludarabine phosphate was reported to be clastogenic in the micronucleus assay but was not mutagenic to germ cells (demonstrated at test concentrations).

\[ \text{Fludarabine phosphate was not mutagenic} \]

instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with fludarabine. Fludarabine phosphate Injection, USP is a sterile solution containing 15 mg of fludarabine phosphate (10.5 mg/m^2), and 10 mmol sodium citrate, 0.1 mmol sodium bicarbonate, and 0.015 mmol sodium hydroxide (buffer). The pH is 4.5.

\[ \text{Fludarabine phosphate was not mutagenic} \]

Fludarabine phosphate Injection, USP in previously untreated adult patients with moderate impairment of renal function (creatinine clearance, 20 to 60 mL/minute) is contraindicated. Fludarabine phosphate Injection, USP must be administered cautiously in patients with renal insufficiency. Fludarabine phosphate Injection, USP is contraindicated for patients with severely impaired renal function (creatinine clearance, < 20 mL/minute) or for patients with line sepsis.

\[ \text{Fludarabine phosphate is a fluorinated} \]

The CLL adult patients in the two Phase I studies who received fludarabine at or above the dose-limiting toxicities (DLT) for fludarabine were considered to be at high risk of developing severe myelosuppression. Hematologic toxicity is the most frequent dose-limiting toxicities observed in patients treated with fludarabine. The most frequently reported adverse events and those reactions that resulted in treatment discontinuation are summarized in the table below.

\[ \text{Fludarabine phosphate is a fluorinated} \]

The most common adverse events include myelosuppression (neutropenia, thrombocytopenia, anemia, and coagulation disorders). Data from two Phase II studies in patients with chronic lymphocytic leukemia (CLL) who have thrombocytopenia at baseline.

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In the Phase II studies, neutropenia and neutropenic fever were reported in 13% of patients treated with fludarabine at doses of 5 mg/m^2/day for 5 days every 28 days. The median time to onset of neutropenia was 10 days. In the combined two Phase II studies, neutropenias were grade 3 or 4 in 19% of patients. The complete response rate in both studies was not influenced by the presence or absence of neutropenia.

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Patients with moderate renal impairment (MDAH study), severe renal impairment (SWOG study), and patients with a creatinine clearance below 20 mL/minute were not enrolled in the Phase I studies. Fludarabine phosphate Injection, USP should be administered cautiously to patients with renal impairment. The best supportive care should be provided to these patients. Fludarabine phosphate Injection, USP should be administered in the following manner: 30 mg/kg/day to pregnant rats on days 6 to 15 of gestation. Dose-related teratogenic effects observed in this study were dose-limiting toxicities. In the MDAH study, the most common adverse events were mucositis, nausea, vomiting, diarrhea, stomatitis, and leukopenia.

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Several instances of oligospermia have been reported. The patients who received fludarabine at high doses (98 to 150 mg/m^2/day for 1 to 7 days) developed this severe myelotoxicity. This syndrome has been reported in the range of the recommended DLT doses of fludarabine. Patients who have received fludarabine at doses of 12 to 15 mg/m^2/day for 5 days (four of six patients) and at doses of 20 mg/m^2/day for 5 days (two of six patients) have experienced myelosuppression (neutropenia, thrombocytopenia, and anemia). The median time to nadir was 7 to 10 days. Fludarabine phosphate Injection, USP should be used with caution in patients with severe renal impairment (creatinine clearance, < 20 mL/minute).

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The use of fludarabine in combination with other hematopoietic growth factors has been established. The use of fludarabine in combination with other hematopoietic growth factors has been established. For patients with CLL refractory to at least one prior standard therapy, the use of fludarabine in combination with pentostatin is not recommended. For patients with CLL refractory to at least one prior standard therapy, the use of fludarabine in combination with pentostatin is not recommended. In the MDAH study, the most common adverse events were mucositis, nausea, vomiting, diarrhea, stomatitis, and leukopenia. The most common adverse event was mucositis.

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The SWOG study included 18 patients with chronic lymphocytic leukemia. The median time to nadir was 7 to 10 days. The most common adverse events were mucositis, hand-foot syndrome, nausea, vomiting, diarrhea, and stomatitis.

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In the Phase I studies, fludarabine was administered at a loading dose over 10 days, followed by 5 days of continuous infusion, steady-state conditions were reached approximately 5 days later. At present, decreased titers in patients with acute leukemia. Fludarabine was associated with severe neurologic effects, including blindness, coma, and death. Symptoms appeared 21 to 60 days following the dose. Thirty-one patients (16%) who received fludarabine at high doses (98 to 150 mg/m^2/day for 1 to 7 days) developed this severe myelotoxicity. This syndrome has been reported in the range of the recommended DLT doses of fludarabine. Patients who have received fludarabine at doses of 12 to 15 mg/m^2/day for 5 days (four of six patients) and at doses of 20 mg/m^2/day for 5 days (two of six patients) have experienced myelosuppression (neutropenia, thrombocytopenia, and anemia). The median time to nadir was 7 to 10 days. Fludarabine phosphate Injection, USP should be used with caution in patients with severe renal impairment (creatinine clearance, < 20 mL/minute).

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