PRODUCT MONOGRAPH

[Pr]AJ-FLUDARABINE
FLUDARABINE PHOSPHATE INJECTION

House Standard

(Fludarabine Phosphate)

25 mg/mL
(2 mL per vial)

Antineoplastic

Date of Preparation:
July 18, 2013

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Submission Control No: 165926

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(Fludarabine Phosphate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous infusion	Solution/ 25 mg/mL	Mannitol, sodium hydroxide, water for injection

INDICATIONS AND CLINICAL USE

AJ-FLUDARABINE (Fludarabine Phosphate Injection) is indicated for:

- Second line therapy in patients with chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin's lymphoma (Lg-NHL) who have failed other conventional therapies. Such patients should be treated only by physicians skilled in the use of chemotherapeutic agents.

Geriatrics (> *75* years of age):
Since there are limited data for the use of fludarabine phosphate in elderly persons (> 75 years), caution should be exercised with the administration of AJ-FLUDARABINE in these patients. The total body clearance of the principal plasma metabolite 2F-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 kidney 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 70 mL/min). Since renal impairment is frequently present in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 mL/min, the dose should be reduced by up to 50%, and close hematologic monitoring should be used to assess toxicity. Fludarabine phosphate treatment is contraindicated, if creatinine clearance is <30 mL/min. (See **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Pediatrics:
The safety and effectiveness of fludarabine phosphate in children have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Renally impaired patients with creatinine clearance <30 mL/min.
- Patients with decompensated hemolytic anemia
- Pregnancy
- Lactation
- In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory CLL, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate in combination with pentostatin is contraindicated.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

AJ-FLUDARABINE should be administered under the supervision of, or prescribed by, 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, intravenous fludarabine phosphate was associated with severe irreversible 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 (96 mg/m^2/day for 5-7 days) than the recommended dose. In patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin's lymphoma (Lg-NHL), 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.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur during or after treatment with fludarabine phosphate. The causality of the development of this complication has not been identified. Patients undergoing treatment with AJ-FLUDARABINE should be evaluated and closely monitored for signs of autoimmune hemolytic anemia (a decline in hemoglobin linked with hemolysis and a positive Coombs' test). Discontinuation of therapy with AJ-FLUDARABINE is recommended in the event of hemolysis. The transfusion of irradiated blood and the administration of corticosteroids are the most common treatment measures for autoimmune hemolytic anemia.

In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory CLL, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate in combination with pentostatin is contraindicated.

General

AJ-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 neutropenia, thrombocytopenia, anemia and leukopenia.

Vaccination with live vaccines should be avoided during and after treatment with AJ-FLUDARABINE.

Gastrointestinal

In clinical trials with oral fludarabine phosphate, nausea/vomiting and/or diarrhea were reported in approximately 38% of patients. In most cases, the severity was mild to moderate (WHO toxicity grading). Only a small percentage of patients, approximately 1 % with nausea/vomiting and 5% with diarrhea, required therapy. Patients with prolonged, clinically relevant, nausea/vomiting and diarrhea should be closely monitored to avoid dehydration.

Hematologic

In patients with an impaired state of health, AJ-FLUDARABINE should be given with caution and after careful risk/benefit consideration. This applies especially to patients with severe impairment of bone marrow function (thrombocytopenia, anemia, and/or granulocytopenia), immunodeficiency or with a history of opportunistic infection. Prophylactic treatment should be considered in patients at increased risk of developing opportunistic infections (see **ADVERSE REACTIONS**).

Bone marrow suppression, notably thrombocytopenia, anemia, leukopenia and neutropenia, may occur with administration of fludarabine phosphate and requires careful hematologic monitoring. 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 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 AJ-FLUDARABINE 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 cases reported has ranged from approximately 2 months to approximately 1 year. These episodes have occurred in both previously treated and untreated patients.

Instances of life-threatening and sometimes fatal autoimmune phenomena (e.g. autoimmune hemolytic anemia, autoimmune thrombocytopenia, thrombocytopenic purpura, pemphigus, acquired hemophilia and Evans' syndrome) have been reported to occur during or after treatment with fludarabine phosphate in patients with or without a previous history of autoimmune processes 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. One study was performed with 31 patients with hemolytic anemia related to the administration of fludarabine phosphate. Since the majority (90%) of these patients rechallenged with fludarabine phosphate developed a recurrence in the hemolytic process, rechallenge with AJ-FLUDARABINE should be avoided. The mechanisms which predispose patients to the development of this complication

have not been identified. Patients undergoing treatment with fludarabine phosphate should be evaluated and closely monitored for signs of autoimmune
hemolytic anemia (a decline in hemoglobin linked with hemolysis and a positive Coombs' test). Discontinuation of therapy with AJ-FLUDARABINE is recommended in the event of hemolysis. The transfusion of irradiated blood and the administration of corticosteroids are the most common treatment measures for autoimmune hemolytic anemia.

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.

Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) has been observed rarely after transfusion of non- irradiated blood in patients treated with fludarabine phosphate. 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 phosphate should receive irradiated blood only.

Disease progression and transformation (e.g. Richter's Syndrome) have been commonly reported in CLL patients.

Hepatic/Biliary/Pancreatic

No data are available concerning the use of fludarabine phosphate in patients with hepatic impairment. In this group of patients, AJ-FLUDARABINE should be used with caution and administered if the perceived benefit outweighs any potential risk.

Neurologic

When high doses of fludarabine phosphate were administered in dose-ranging studies in acute leukemia patients, a syndrome with delayed onset, characterized by blindness, coma, and death was identified. Symptoms appeared from 21 to 60 days post dosing (however, in post marketing experience, cases of neurotoxicity have been reported to occur both earlier and later than seen in clinical trials). Demyelination, especially of the occipital cortex of the brain was noted. The majority of these cases occurred in patients treated intravenously with doses approximately four times greater (96 mg/m^2/day for 5-7 days) than the recommended dose. Thirteen of 36 patients (36.1%) who received fludarabine phosphate at high doses ($\geq$ 96 mg/m^2/day for 5 to 7 days per course) developed severe neurotoxicity, while only one of 443 patients (0.2%) who received the drug at low doses ($\leq$ 40 mg/m^2/day for 5 days per course) developed the toxicity. In patients treated at doses in the range of the dose recommended for CLL and Lg-NHL, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion).

The effect of chronic administration of fludarabine phosphate on the central nervous system is unknown. In some studies, however, patients tolerated the recommended dose, for relatively long treatment periods (up to 26 courses of therapy). Periodic neurological assessments are recommended.

Renal
The total body clearance of the principal plasma metabolite 2F-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 70 mL/min). Therefore, if renal impairment is clinically suspected, or the patient is over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 mL/min, the dose should be reduced by up to 50% and close hematological monitoring should be used to assess toxicity. FLUDARABINE PHOSPHATE INJECTION treatment is contraindicated, if creatinine clearance is < 30 mL/min. (See **DOSAGE AND ADMINISTRATION**).

Sexual Function/Reproduction
Preclinical toxicology 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. The possible adverse effects on fertility in males and females in humans have not been adequately evaluated. Therefore, it is recommended that females of child-bearing potential and males take contraceptive measures during AJ-FLUDARABINE therapy, and for at least 6 months after the cessation of AJ-FLUDARABINE therapy.

Skin
Reversible worsening or flare-ups of pre-existing skin cancer lesions has been reported to occur in some patients during or after intravenous fludarabine phosphate therapy.

Special Populations

Pregnant Women: Fludarabine phosphate has been shown to be teratogenic in rats and in rabbits. A study in rats demonstrated a transfer of fludarabine phosphate and/or metabolites across the placental barrier.

One case of fludarabine phosphate use during early pregnancy leading to skeletal and cardiac malformation in the newborn has been reported.

AJ-FLUDARABINE should not be used during pregnancy.

Women of child-bearing potential should be advised to avoid becoming pregnant and to inform the treating physician immediately should this occur.

Nursing Women: It is not known whether fludarabine phosphate is excreted in human milk. However, there is evidence from animal data that fludarabine phosphate and/or metabolites transfer from maternal blood to milk. Therefore, breast-feeding should be discontinued during AJ-FLUDARABINE therapy.

Pediatrics: The safety and effectiveness of fludarabine phosphate in children have not been established.

Geriatrics (> 75 years of age): Since there are limited data for the use of fludarabine phosphate

in elderly persons (> 75 years), caution should be exercised with the administration of AJ-FLUDARABINE in these patients. The total body clearance of the principal plasma metabolite 2F-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 kidney 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 70 mL/min). Since renal impairment is frequently present in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 mL/min, the dose should be reduced by up to 50%, and close hematologic monitoring should be used to assess toxicity. Fludarabine phosphate treatment is contraindicated, if creatinine clearance is <30 mL/min. (See **DOSAGE AND ADMINISTRATION**).

Monitoring and Laboratory Tests

During treatment, the patient's hematologic (particularly neutrophils and platelets) and serum chemistry profiles should be monitored regularly.

Effects on Ability to Drive and Operate Machines

The effect of treatment with fludarabine phosphate on the patient's ability to drive or operate machinery has not been evaluated.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse events occurring with fludarabine phosphate use include myelosuppression (anemia, leukopenia, neutropenia and thrombocytopenia), leading to decreased resistance to infection, including pneumonia, cough, fever, fatigue, weakness, nausea, vomiting and diarrhea. Other commonly reported events include chills, edema, malaise, peripheral neuropathy, visual disturbances, anorexia, mucositis, stomatitis and skin rash. Serious opportunistic infections have occurred in 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 listed below according to body system regardless of their seriousness. Their frequency (very common ≥1/10, common ≥1/100 to < 1/10, uncommon ≥1/1000 to <1/100) is based on clinical trial data regardless of the causal relationship with fludarabine phosphate. The rare events (≥1/10000 to <1/1000) were mainly identified from post-marketing experience.

Body as a Whole

Infection, fever, fatigue and weakness have been reported very commonly in patients receiving fludarabine phosphate. Malaise and chills have been commonly reported.

Hematopoietic and Lymphatic System

Hematologic events (neutropenia, thrombocytopenia and anemia) have been reported in the majority of 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 of opportunistic infections, including those due to latent viral reactivation, eg. herpes zoster virus, Epstein-Barr-Virus (EBV) and progressive multifocal

leukoencephalopathy. Evolution of EBV-infection/reactivation into EBV-associated lymphoproliferative disorder has been observed in immunocompromised patients. Life-threatening and sometimes fatal autoimmune hemolytic anemia has been reported to occur in patients receiving fludarabine phosphate. The majority of patients rechallenged with fludarabine phosphate developed a recurrence in the hemolytic process. (See **WARNINGS AND PRECAUTIONS** section for information on autoimmune hemolytic anemia associated with fludarabine phosphate).

In rare cases, the occurrence of myelodysplastic syndrome (MDS) has been described in patients treated with fludarabine phosphate. The majority of these patients also received prior, concomitant or subsequent treatment with alkylating agents or irradiation. Monotherapy with fludarabine phosphate had not been associated with an increased risk of development of MDS.

Nervous System
Following administration of fludarabine phosphate at doses of 20-30 mg/m^2/day in 133 patients with CLL, reported events included weakness, visual disturbances, loss of hearing, numbness, agitation, confusion, seizure and coma. Peripheral neuropathy has been commonly observed. Confusion is uncommon. Coma, seizures and agitation occur rarely. There was one case of wrist drop. (See **WARNINGS AND PRECAUTIONS** section for information on neurotoxicity associated with high doses of fludarabine phosphate).

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.

Respiratory System
Pneumonia has been commonly reported. Pneumonia, a frequent manifestation of infection in CLL patients occurred in 16% and 22% of those treated with fludarabine phosphate in the MDACC and SWOG studies, respectively. Pulmonary hypersensitivity reactions to fludarabine phosphate (pulmonary infiltrates, pneumonitis, fibrosis) characterized by dyspnea, and cough are uncommon.

Digestive System
Gastrointestinal disturbances such as nausea and vomiting, anorexia, diarrhea, mucositis and stomatitis are commonly reported. Gastrointestinal bleeding, mainly related to thrombocytopenia, has been reported in patients treated with fludarabine phosphate.

Skin and Appendages
Skin rashes have been commonly reported in patients treated with fludarabine phosphate. In rare cases, a Stevens-Johnson syndrome or toxic epidermal necrolysis (Lyell's disease) may develop.

Cardiovascular System
One patient developed a pericardial effusion possibly related to treatment with fludarabine phosphate. Rare instances of heart failure and arrhythmia have been reported in patients treated with fludarabine phosphate.

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

Metabolic an Nutritional Disorders
Tumor lysis syndrome has been reported in CLL patients treated with fludarabine phosphate. This complication may include hyperuricaemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria and renal failure. The onset of this syndrome may be heralded by flank pain and hematuria. Edema has been commonly reported. Changes in hepatic and pancreatic enzymes levels are uncommon.

The spectrum of adverse reactions reported in patients (n=3000) receiving fludarabine phosphate in studies of lymphomas, other leukemias and solid tumors is consistent with the above data.

DRUG INTERACTIONS

Serious Drug Interactions
In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory CLL, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate in combination with pentostatin is contraindicated.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations
Incompatibilities
The formulation for intravenous use must not be mixed with other drugs.

Recommended Dose and Dosage Adjustment
The usual starting dose of fludarabine phosphate is 25 mg/m^2 administered intravenously over a period of approximately 30 minutes, daily for five days every 28 days. Dosage may be decreased based on evidence of hematologic or nonhematologic toxicity.

Note that in patients with decreased renal function (creatinine clearance between 30 and 70 mL/min) the dose should be reduced by up to 50%. Fludarabine phosphate treatment is contraindicated, if creatinine clearance is <30 mL/min. (See **WARNINGS AND PRECAUTIONS**).

The duration of treatment depends on the treatment success and the tolerability of the drug. FLUDARABINE PHOSPHATE INJECTION should be administered up to the achievement of a maximal response (complete or partial remission, usually 6 cycles) and then the drug should be

discontinued.

Administration
Studies in animals have shown that even in cases of misplaced injections, no relevant local irritation was observed after paravenous, intraarterial, and intramuscular administration of an aqueous solution containing 7.5 mg fludarabine phosphate/mL.

It is strongly recommended that fludarabine phosphate should be only administered intravenously. No cases have been reported in which paravenously administered fludarabine phosphate led to severe local adverse reactions. However, unintentional paravenous administration should be avoided.

AJ-FLUDARABINE comes prepared for parenteral use. Each mL of the solution contains 25 mg of fludarabine phosphate, 25 mg of mannitol and 3.30 mg of sodium hydroxide. The pH range of the final solution is 6.0-7.1.

The product must be further diluted for intravenous infusion administration in PVC bags to a concentration of 1 mg/mL in 5% Dextrose Injection USP, or in 0.9% Sodium Chloride Injection USP.

Fludarabine Phosphate injection (25 mg/mL) is NOT for direct injection. Fludarabine Phosphate injection MUST be diluted with recommended intravenous infusion solutions.

Missed Dose
In the event that a dose is missed the opinion of an oncologist should be sought.

OVERDOSAGE
Higher than recommended doses of fludarabine phosphate have been associated with an irreversible central nervous system toxicity characterized by delayed blindness, coma and death. High doses are also associated with bone marrow suppression manifested by thrombocytopenia and neutropenia. There is no known specific antidote for fludarabine phosphate overdosage. Treatment consists of drug discontinuation and supportive therapy.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
AJ-FLUDARABINE is a fluorinated analog of adenine that is relatively resistant to deamination by adenosine deaminase.

Fludarabine phosphate (2F-ara-AMP) is a water-soluble prodrug, which is rapidly dephosphorylated to 2-fluoro-ara-A (2F-ara-A) and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate 2-fluoro-ara-ATP (2F-ara-ATP). The antitumor activity of this metabolite is the result of inhibition of DNA synthesis via inhibition of ribonucleotide reductase, DNA polymerase α, δ and g, DNA primase and DNA ligase. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occur. While some aspects of the mechanism of action of 2F-ara-ATP are as yet unclear, it is believed that effects on DNA, RNA and protein synthesis all contribute to the

inhibition of cell growth, with inhibition of DNA synthesis being the dominant factor. In addition, *in vitro* studies have shown that exposure of CLL lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and apoptosis.

Two open-label studies of fludarabine phosphate have been conducted in patients with CLL refractory to at least one prior standard alkylating agent-containing regimen. Overall objective response rates were 32% in one study, and 48% in the other, with median time to response at 21 and 7 weeks respectively.

Pharmacokinetics

Cellular pharmacokinetics of fludarabine triphosphate: Maximum 2F-ara-ATP levels in leukemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited considerable variation with a median peak concentration of approximately 20 μM. 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-A enrichment. Two independent investigations respectively reported median half-life values of 15 and 23 hours for the elimination of 2F-ara-ATP from target cells.

No clear correlation was found between 2F-ara-A pharmacokinetics and treatment efficacy in cancer patients; however, the occurrence of neutropenia and hematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses hematopoiesis in a dose-dependent manner.

Plasma and urinary pharmacokinetics of fludarabine (2F-ara-A): Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2F-ara-A, within minutes after intravenous infusion. Consequently, clinical pharmacology studies have focused on 2F-ara-A pharmacokinetics. After single doses of 25 mg 2F-ara-AMP/m^2 to cancer patients infused over 30 minutes, 2F-ara-A reached mean maximum concentrations in the plasma of 3.5 - 3.7 μM at the end of infusion. Corresponding 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 cycle, 2F-ara-A plasma trough levels increased by a factor of about 2. Accumulation of 2F-ara-A over several treatment cycles does not occur. 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 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). The data showed a high interindividual variability. After i.v. and peroral administration of fludarabine phosphate plasma levels of 2F-ara-A and areas under the plasma level time curves increased linearly with the dose, whereas half-lives, plasma clearance and volumes of distribution remained constant independent of the dose indicating a dose-linear behaviour.

After oral fludarabine phosphate doses, maximum 2F-ara-A plasma levels reached approximately 20-30% of corresponding i.v. levels at the end of infusion and occurred 1-2 hours after dosing. The mean systemic 2F-ara-A availability was in the range of 50-65% following

single and repeated doses and was similar after ingestion of a solution or an immediate release tablet formulation. After oral doses of 2F-ara-AMP with concomitant food intake a slight increase (<10%) of systemic availability (AUC), a slight decrease in maximum plasma levels (C_{max}) of 2F-ara-A and a delayed time to occurrence of C_{max} was observed; terminal half-lives were unaffected.

The mean steady-state volume of distribution (Vd_{ss}) of 2F-ara-A in one study was 96 L/m^2 suggesting a significant degree of tissue binding. Another study, in which Vd_{ss}, for patients was determined to be 44 L/m^2, supports the suggestion of tissue binding.

Based upon compartmental analysis of pharmacokinetic data, the rate-limiting step for excretion of 2F- ara-A from the body appears to be release from tissue binding sites. Total body clearance of 2F-ara-A has been shown to be inversely correlated with serum creatinine, suggesting renal elimination of the compound.

Special Populations and Conditions

Renal Insufficiency: A pharmacokinetic study in patients with and without renal impairment revealed that, in patients with normal renal function, 40 to 60% of the administered i.v. dose was excreted in the urine. Mass balance studies in laboratory animals with ^3H-2F-ara-AMP showed a complete recovery of radio-labelled substances in the urine. Another metabolite, 2F-ara-hypoxanthine, which represents the major metabolite in the dog, was observed in humans only to a minor extent. Patients with impaired renal function exhibited a reduced total body clearance, indicating the need for a reduced dose. Total body clearance of 2F-ara-A has been shown to be inversely correlated with serum creatinine, suggesting renal elimination of the compound. This was confirmed in a study of the pharmacokinetics of 2F-ara-A following administration of 2F-ara-AMP to cancer patients with normal renal function or varying degrees of renal impairment. The total body clearance of the principal metabolite 2F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Renal clearance represented on average 40% of the total body clearance. *In vitro* investigations with human plasma proteins revealed no pronounced tendency of 2F-ara-A protein binding.

STORAGE AND STABILITY

AJ-FLUDARABINE under refrigeration between 2°C and 8°C. Do not freeze. Discard unused portion.

AJ-FLUDARABINE should be used immediately upon dilution with the recommended infusion solutions and not stored.

AJ-FLUDARABINE contains no antimicrobial preservative and thus care must be taken to ensure the sterility of prepared solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

SPECIAL HANDLING INSTRUCTIONS

AJ-FLUDARABINE should not be handled by pregnant staff. Proper handling and disposal

procedures should be observed, with consideration given to the guidelines used for cytotoxic drugs. Any spillage or waste material may be disposed of by incineration.

Caution should be exercised in the preparation of AJ-FLUDARABINE 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Medicinal ingredients: Each vial contains 50 mg of fludarabine phosphate.

Non-medicinal ingredients: Each vial contains 50 mg mannitol and 6.60 mg sodium hydroxide and Water for Injection.

pH: 6.0-7.1

Availability :
AJ-FLUDARABINE is supplied as 2 mL per vial of 50 mg fludarabine phosphate, 50 mg of mannitol and 6.60 mg of sodium hydroxide and Water for Injection.

AJ-FLUDARABINE is a single use vial.

AJ-FLUDARABINE is supplied in a single vial carton.

AJ-FLUDARABINE uses a latex free stopper.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

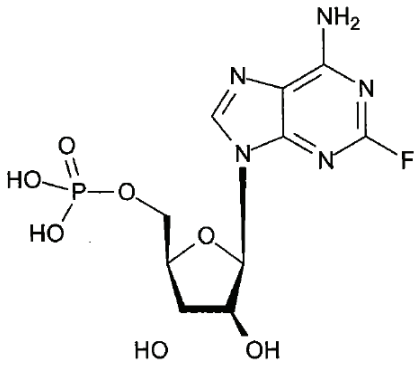
Drug Substance

Common name: Fludarabine Phosphate

Chemical name: 9H Purin-6-amine, 2-fluoro-9-(5-O-phosphone-β-D-arabinofuranosyl)

Molecular formula and molecular mass: $C_{10}H_{13}FN_5O_7P$ 365.2 g/mol

Structural formula:



Physicochemical properties: Fludarabine phosphate is a white to almost white, crystalline powder. It has pKa values of 3.2 ± 0.1 and 5.8 ± 0.1 and pH value of 2.0 (9mg/mL in water).

Fludarabine phosphate is freely soluble in dimethylsulphoxide and in dimethylacetamide; sparingly soluble in water; slightly soluble in methanol; insoluble in acetone and in dichloromethane.

CLINICAL TRIALS

Two single-arm open-label studies of fludarabine phosphate have been conducted in patients with CLL refractory to at least one prior standard alkylating-agent-containing regimen. In a study conducted by M.D. Anderson Cancer Center (MDACC), 48 patients were treated with a dose of 22-40 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 15-25 mg/m^2 for 5 days every 28 days. The overall objective response rates were 48% and 32% in the MDACC and SWOG studies, respectively. The complete response rate in both studies was 13%; the partial response rate was 35% in the MDACC 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 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 MDACC 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 (MDACC) and 65 weeks (SWOG). The median survival of all refractory CLL patients treated with fludarabine phosphate was 43 weeks and 52 weeks in the MDACC and SWOG studies, respectively. Normalized lymphocyte count, one measure of disease regression, occurred at a median of 2 weeks (complete responders), 2 weeks (partial responders) and 22 weeks (non-responders).

Rai stage improved to Stage II or better in 7 of 12 MDACC 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.

DETAILED PHARMACOLOGY

Mechanism of Action

The biological activity of 2F-ara-A was assessed in a number of models. 2F-ara-A has been shown to inhibit DNA synthesis in cultured mouse leukemia L1210 cells and in an *in vivo* mouse L1210 leukemia model. Total RNA synthesis in vitro was not inhibited by treatment with 2F-ara-A; however, protein synthesis was reduced substantially. It has been shown that 2F-ara-A is not deaminated by adenosine deaminase, contributing to the stability of the compound.

The activity, metabolism and toxicity of 2F-ara-A in the human lymphoblastoid T-cell line (CCRF-CEM) were compared with 9-β-D-arabinofuranosyl-adenine (ara-A). Inhibition of cell growth was equivalent for these two agents, provided that ara-A was protected from deamination. Similar studies conducted with CCRF-CEM showed that ara-A and 2F-ara-A exerted early killing effects preferentially during the S-phase of cell proliferation. Both compounds were converted to the triphosphate form, which accumulated intracellularly and inhibited DNA synthesis. This nucleoside metabolite, 2F-ara-ATP, was also shown to inhibit DNA polymerase α and to a lesser extent ribonucleotide reductase in mouse leukemia cells (L1210), human epithelial cells (HEp-2), and HeLa cells.

In the systems tested, 2F-ara-ATP is the active metabolite which acts by inhibiting DNA polymerase α and ribonucleotide reductase thus preventing DNA synthesis. In addition, *in vitro* studies have shown that exposure of CLL lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and apoptosis.

Antitumor Activity

The effects of schedule and route of administration on the antitumor activity of fludarabine phosphate were examined using an *in vivo* mouse leukemia model (implanted L1210 leukemia cells). The drug was active following intraperitoneal administration on all treatment schedules.

Antitumor activity increased almost three-fold when the number of drug treatments was increased. In addition, the administration of several doses in one day was more effective than administration of one larger dose.

A single administration (900 mg/kg) on day 1 produced an increased life span (ILS) of 42% while administration of a smaller dose (250 mg/kg) 3 times a day on day 1 (total dose 750 mg/kg) gave a 98% ILS. This pattern of increased activity with administration of several doses in a day was also observed with the intermittent treatment schedule. A single administration on each of 3 days (total dose 2010 mg/kg) produced an ILS of 122% while administration of a smaller dose 3 times a day over 3 days (total dose 1125 mg/kg) produced the greatest activity, a 525% ILS with 6 long-term survivors (50 day) among the tumor-bearing mice.

With the administration of the drug 3 times a day on day 1, negative animal weight differences (body weight change over 5 days for test animals minus that for controls) of more than 4 grams at the highest dose evaluated suggests some acute drug toxicity. Based on equivalent total doses, administration of 3 smaller doses per day at 3-hour intervals was much more effective than a single administration for each day of treatment using the *in vivo* mouse leukemia model.

A single oral administration of fludarabine phosphate on day 1 was not effective against the L1210 leukemia. However, when given as 5 daily oral doses, the highest non-toxic dose of the drug, defined as the dose which results in at least 7 or 8 50-day survivors among the normal mice (800 mg/kg daily on days 1-5), was effective in a maximal ILS of 50%.

When the drug was administered i.v., it was more effective with daily administration for 5 days than it was with a single injection on day 1. Daily treatment for 5 days at a non-toxic dose level increased the life span of tumor-bearing mice by 71% and a higher, more toxic, treatment for 5 days produced an ILS of 95%; in contrast, in single i.v. treatment on day 1 produced a maximum ILS of 28%.

The intraperitoneally (i.p.) implanted L1210 leukemia was less sensitive to fludarabine phosphate when the drug was given either intravenously (i.v.) or orally than when compared to i.p. administration. A maximal ILS value of 122% was produced following i.p. administration of 266 mg/kg on days 1-5. This same dose given by i.v. administration on days 1-5 produced an ILS value of 95%. In contrast, a dose of 1600 mg/kg given orally on days 1-5 produced only a 75% ILS. However, with both i.p. and i.v. administration, the dose that produced the maximum ILS value was toxic to the non-tumored animals.

Fludarabine phosphate also demonstrated activity against the intraperitoneal implanted P388 leukemia. In two different experiments, the drug increased the life span of mice bearing the P388 leukemia by 115% and 53% following i.p. administration of 200 and 100 mg/kg injections, respectively, on days 1-9.

Cytotoxicity of Fludarabine Phosphate
Fludarabine phosphate has demonstrated significant antitumor activity against intraperitoneally (i.p.) implanted murine L1210 leukemia and the human LX-1 lung tumor xenograft. The drug has shown moderate activity against the murine subcutaneously (s.c.) implanted $CD8F_1$ mammary epithelioma and the i.p. implanted P388 lymphocytic leukemia. Fludarabine phosphate was not active against the i.p. implanted B16 melanoma, the s.c. implanted colon tumor, or the intravenously (i.v.) implanted Lewis lung epithelioma, nor was it effective against the human CX-1 colon or MX-1 mammary xenografts in the subrenal assay.

Effects on Bone Marrow Survival and Tumor Cell Sensitivity
Fludarabine phosphate was tested in an in vitro human bone marrow cell survival assay and tumor cell sensitivity assay. The sensitivity of normal human granulocyte-macrophage colony-forming units in culture (GM-CFUC) showed a simple negative exponential curve characterized by a logarithmic decrease in survival as a function of drug concentration. Fludarabine phosphate exhibited an LD_{63} of 0.51μg/mL for normal human granulocyte-macrophage colony-forming units in culture (GM-CFUC). In the tumor sensitivity assay, fludarabine phosphate demonstrated an LD_{40} and LD_{78} of 0.26 and 0.77 μg/mL, respectively.

Blood and bone marrow samples obtained from patients with relapsed leukemia and lymphoma after treatment with a single dose of 20-125 mg/m^2 fludarabine phosphate revealed that the area under the concentration-time curves for 2F-ara-A and 2F-ara-ATP were increased in proportion to the product dose. There was a high correlation between 2F-ara-ATP level in circulating leukemic cells and those in bone marrow cells aspirated at the same time. DNA synthetic capacity of leukemic cells was inversely related to the associated 2F-ara-ATP concentration. 2F-ara-ATP concentrations were three times higher in bone marrow cells from patients with lymphomatous bone marrow involvement than from those without evidence of marrow disease.

A dose response relationship between fludarabine phosphate concentration and inhibition of DNA synthesis in leukemia cells and bone marrow cells in culture was obtained.

Bone marrow progenitor cells from a normal subject and 10 patients with solid tumors, whose bone marrow was free of metastases, were treated with fludarabine phosphate and other cytotoxic drugs, using a bilayer soft agar culture. The in vitro effect of the drugs on bone marrow progenitor cells was not as toxic as expected relative to the myelosuppressive potency observed in vivo. In the case of fludarabine phosphate, it has been postulated that these findings might be related to incomplete in vitro phosphorylation to the triphosphate, 2F-ara-ATP.

Lymphocytotoxicity in Humans
Fludarabine phosphate was assessed for its lymphocytotoxicity in 11 patients receiving the investigational drug for treatment of nonhematologic cancers refractory to standard treatment. Fludarabine phosphate was administered by intravenous infusion at doses ranging from 18 mg/m^2/day to 40 mg/m^2/day, with each dose given on a 5-day dosing regimen.

Lymphocyte subsets were determined prior to treatment and on day 5 of treatment, 4 hours after the infusion. Observations indicated that lymphocytopenia developed rapidly but was reversible. Total T- lymphocyte counts fell during all treatment regimens, with a 90% decrease in mean absolute T-cell count. All major T-lymphocyte subsets were affected. B-lymphocyte counts decreased by 50% on average. Recoveries of total mononuclear cells, total T-cells and non-T,

non-B cells were reduced substantially by fludarabine phosphate treatment. B-cell recovery was not affected.

These results indicate that T-cells are more sensitive than B-cells to the cytotoxic effects of fludarabine phosphate.

Modulation of T-Cell Function by Fludarabine Phosphate
The effects of fludarabine phosphate on the growth and function of bone marrow and peripheral blood mononuclear cells (PBMC) from cancer patients were evaluated. Drug toxicity was dependent on time of incubation and concentration of fludarabine phosphate tested. After a 3-hour incubation of PBMC with 1 μg/mL of fludarabine phosphate, there was no effect on cell number whereas, after 48 hours, the cell count was 59% of control, untreated cells. In contrast, a 3-hour or 48-hour incubation of PBMC with 100 μg/mL of fludarabine phosphate reduced cell number to 65.7% or 63% of control, respectively.

Lymphocyte subpopulations of normal PBMCs were evaluated after treatment *in vitro* with fludarabine phosphate for 72 hours. A dose-dependent decrease in total T-cell number was noted. Incubation with 1 μg/mL of fludarabine phosphate reduced T-cells by 16.7%; 100 μg/mL reduced T-cells by 42%. The subset of T-cells predominantly affected was T-helper cells, reduced by 53.5% after incubation with 100μg/mL of fludarabine phosphate. B-cells, monocytes, and natural killer cells were not reduced, but rather increased relative to control. Fludarabine phosphate also inhibited the response of PBMC to mitogens in a dose-and time-dependent manner.

***In Vitro* Testing of Fludarabine Phosphate in Glioma Cell Cultures**
Fludarabine phosphate was tested for growth inhibitory effects on human glioma cells isolated from patient specimens. Cells were treated with 1-10 μM of fludarabine phosphate beginning 4 days after cells were plated. After 3 more days of incubation, cell number was determined. Inhibition of cell growth was dose-dependent and approximately equal to inhibition seen after treatment with the same concentrations of 5-fluorouracil. Dose-dependent growth inhibition was also observed when interferon-beta (1-1000 IU/mL) was incubated with glioma cell cultures. Although the combination of fludarabine phosphate and 5-fluorouracil or interferon-beta produced additive inhibitory effects, no synergistic effects were observed

Pharmacokinetics (Animals)
Fludarabine phosphate and its metabolites have been studied in mice, dogs, miniature pigs, and monkeys to elucidate their pharmacokinetic, distribution, and excretion profiles.

In the mouse, dog, and monkey, the pharmacokinetics of fludarabine phosphate and its major metabolite, 2F-ara-A, generally exhibited bi-compartmental characteristics after intravenous administration, with rapid clearance and relatively large volumes of distribution.

The pharmacokinetic parameters of fludarabine phosphate and its metabolites are presented in Table 1 and Table 2, located on the following pages.

Tissue Distribution, Metabolism and Excretion in Animals
Tissue distribution and excretion studies were conducted with fludarabine phosphate in mice, dogs, and monkeys at doses between 30 and 500 mg/m^2.

Fludarabine phosphate is metabolized to 2F-ara-A and, to a lesser extent, 2F-ara-HX in the mouse and monkey, while in the dog, 2F-ara-A and 2F-ara-HX are both major metabolites. The majority of the administered compound is metabolized and then eliminated in the urine within 24 hours after dose administration.

The metabolism, distribution and excretion information is presented in Table 3 located on the following pages.

Table 1
PHARMACOKINETIC PARAMETERS OF FLUDARABINE PHOSPHATE AND 2F-ARA-A

STUDY DETAIL				RESULTS					
Species	**Dose of Test Article (mg/m^2)**		**Route of Admin.**	**Metabolite**	**$t_{½\alpha}$**	**$t_{½\beta}$**	**Vd (mL)**	**Clearance mL/min/kg**	
Mouse (BDF_1) 18-25 grams	40	2F-ara-AMP	I.V.	2F-ara-AMP 2F-ara-A	0.7 min 31.1 min	21.2 min 113.9 min	73.4 60.6	2.40 0.37	In mice, 2F-ara-AMP is rapidly dephosphorylated to 2F-ara-A. 2F-ara-HX was also present in serum. HPLC (Waters Associates model) and TLC were used.
	500	2F-ara-AMP	I.V.	2F-ara-AMP 2F-ara-A	2.5 min 35.7 min	26.9 min 184.9 min	309.1 88.0	7.97 0.33	
Dog (Beagle) 7.8-10.8 kg	40	2F-ara-AMP	I.V.	2F-ara-AMP 2F-ara-A 2F-ara-HX	5.3 min 15.7 min 113.5 min	30.5 min 96.6 mi ----	142,960.0 9,552.7 ----	3,254.0 68.5 115.5	In dogs, 2F-ara-AMP is rapidly dephosphorylated to 2F-ara-A. A larger percentage of the metabolite 2F-ara-HX was found in dog serum when compared to mice. HPLC (Waters Associates model) and TLC were used.
	500	2F-ara-AMP	I.V.	2F-ara-AMP 2F-ara-A 2F-ara-HX	9.2 min 4.6 min 112.5 min	51.5 min 90.3 min ----	196,520.0 7,243.5 ---	2,646.0 55.6 111.2	
Dog (Beagle) 2 dogs	260	2F-ara-AMP	I.V.	2F-ara-A	13 min	96 min	0.712 L/kg Vd_{ss}	5.4 mL/min/kg	Total plasma clearance is more than 2-fold greater in dog than in man. The steady-state volume of distribution in man is approximately 70% larger than in dog. The terminal slope of 2F-ara-HX decay parallels the 2F-ara-A decay. Standard chromatographic and spectral assays were used.

HPLC: High performance liquid chromatography

TLC: thin layer chromatography

Table 1 (Continued)
PHARMACOKINETIC PARAMETERS OF FLUDARABINE PHOSPHATE AND 2F-ARA-A

STUDY DETAIL				RESULTS					
Species	**Dose of Test Article (mg/m^2)**		**Route of Admin.**	**Metabolite**	**$t_{½\alpha}$**	**$t_{½\beta}$**	**Vd (mL)**	**Clearance mL/min/kg**	
Monkey (3 animals)	20	2F-ara-AMP	I.V.	2F-ara-AMP (plasma)	56 min	----	----	----	2F-ara-A crosses the blood-brain barrier with a lag time of 0.5 to 2.0 hours and accumulates in the CSF. To quantify the metabolites. HPLC was used.
				2F-ara-A (plasma)	2.5-3.1 h	21.3-35.6h	----	----	
				2F-ara-A (CSF)	1.1-1.8h	20.4-29.8h	-----	----	
Mouse (BDF_1) 25-31 grams	30	2F-ara- A	I.V.	2F-ara-A Metabolites	17 min 30 min	72 min 124 min	----- -----	---- ----	Standard chromatographic and spectral assays were used.
Dog (Beagle) 9.7-10.3 kg	30 400	2F-ara-A 2F-ara-A	I.V. I.V.	2F-ara-A 2F-ara-A	<5 min 130 min	112 min -----	 -----	 -----	Standard chromatographic and spectral assays were used.
Monkey (Rhesus) 3.9-4.6 kg	30 400	2F-ara-A 2F-ara-A	I.V. I.V.	2F-ara-A Phosphate Metabolites 2F-ara-A	26 min 131 min 15 min	125 min ----- 6.7h	----- ----- -----	----- ----- -----	12-14% of 2F-ara-A became serum protein bound.

HPLC: High performance liquid chromatography

TLC: thin layer chromatography

Table 2
PHARMACOKINETIC PARAMETERS OF FLUDARABINE PHOSPHATE AND METABOLITES

STUDY DETAILS			RESULTS				
Species/Test Model	**Test Article Dose**	**Route of Admin.**	**Metabolite**	**$t_{½}$**	**Time to C_{max}**	**C_{max}**	
Mouse ($BD2F_1$) P388 Tumor cell Model	1,485 mg/kg 2F-ara-AMP	I.P.	2F-ara-AMP 2F-ara-A 2F-ara-A 2F-ara-HX 2F-ara-HX	1.2 h ascites fluid 2.1 h ascites fluid 3.8 h plasma 3.0 h plasma ----	---- 4 h (ascites) 1-6 h (plasma) 4 h (plasma) 4 h (ascites)	---- ---- >1mM =0.4 mM ----	After separation of nucleotides by HPLC, metabolites were quantified by UV or radioactivity.
Mouse ($BD2F_1$) P388 Tumor cell Model	1,485 mg/kg 2F-ara-AMP	I.P.	---- 2F-ara-ATP 2F-ATP	---- 4.1 h (intracellular, P388 cells) 3.7 h (intracellular, P388 cells)	---- 6 h (intracellular, P388 cells) 6 h (intracellular, P388 cells)	---- 1,036 µM 27 µM	After separation of nucleotides by HPLC, metabolites were quantified by UV or radioactivity.
Swine Miniature (5 animals) 14-16.5 kg	10, 16, 25 mg/m^2 2F-ara-AMP	I.P.	2F-ara-A	----	5-140 min (peritoneal fluid) 120-240 min (plasma)	7.7-18 µg/mL (peritoneal fluid) 0.15-0.46 µg /mL (plasma)	HPLC was used.

C_{max}: maximal concentration
I.P.: intraperitoneal

Table 3
METABOLISM, DISTRIBUTION AND EXCRETION OF FLUDARABINE PHOSPHATE

Species	Design	Compound Administered	Dose (mg/m^2)	Metabolism and Distribution	Elimination	Metabolites
Mouse (BDF_1)	I.V. Administration	2F-ara-AMP	40 500	The major metabolite was 2F-ara-A in mice. The liver, spleen and kidney were the major organs containing the metabolites.	Elimination occurred exponentially from tissue, although the rate of elimination from serum was faster. All metabolites were excreted in the urine.	2F-ara-A 2F-ara-AMP 2F-ara-HX 2F-A Polyphosphorylated derivatives
Mouse	I.V. Administration	2F-ara-AMP	40 500	2F-ara-AMP undergoes dephosphorylation to 2F-ara-A in mice.	Elimination of 2F-ara-A from tissue occurs exponentially.	**Serum:** 2F-ara-A 2F-ara-HX **Tissue:** 2F-ara-A 2F-ara-HX 2F-A 2F-ara- AMP 2F-ara-ADP 2F-ara-ATP
Mouse ($BD2F_1$) P388 tumor cell implant model	I.P. Administration	2F-ara-AMP	1,485 (mg/kg)	Peak 2F-ara-A ascites conc. occurred at 4 hr. Peak 2F-ara-HX ascites conc. occurred at 4 hr. Peak 2F-ara-A plasma conc. (≥1 mM) occurred at 1-6 hr. Peak 2F-ara-HX plasma conc. (≈0.4mM) occurred at 4 hr.	2F-ara-A $t_{½}$ = 2.1 hr. (ascites) ---- 2F-ara-A $t_{½}$ = 3.8 hr. (plasma) 2F-ara-HX $t_{½}$ = 3 hr (plasma)	2F-ara-A (ascites & plasma) 2F-ara-HX (ascites & plasma) 2F-ara-ATP (intracellular) 2F-ara- AMP (intracellular)

Table 3 (Continued)
METABOLISM, DISTRIBUTION AND EXCRETION OF FLUDARABINE PHOSPHATE

Species	Design	Compound Administered	Dose (mg/m^2)	Metabolism and Distribution	Elimination	Metabolites
Mouse ($BD2F_1$) P388 tumor cell implant model	I.P. Administration	2F-ara-AMP	1,485 (mg/kg)	The peak concentration (1,036 µM) of the primary intracellular metabolite, 2F-ara-ATP, was reached 6 h post drug administration in P388 cells. Peak levels of 2F-ara-ATP were reached at 4-6 h in bone marrow and intestinal mucosa with 2F-ara-ATP accumulated 20-fold less than in P388 cells. 2F-ara-ATP has been determined the active metabolite.	2F-ara-ATP $t_{½}$ = 4.1 h (in P388 cells) 2F-ara-ATP $t_{½}$= 2 h (in host tissue)	---- ----
Mouse P388 tumor cell implant model	I.P. Administration	2F-ara-AMP	1,485 (mg/kg)	930 µM 2F-ara-ATP was the peak intracellular concentration observed in P388 cells. Peak 2F-ara-ATP concentrations of 34 nmol/µmol DNA accumulated in bone marrow. Peak 2F-ara-ATP concentrations of 23 nmol/µmol DNA accumulated in the intestinal mucosa. The metabolite 2F-ara-A passed rapidly from ascites to blood in concentrations proportional to dose. DNA synthesis was inhibited to 1% of controls at 6 h.	2F-ara-ATP disappeared from P388 cells with an intracellular half-life of 4.1 hr. 2F-ara-ATP disappeared from bone marrow and intestinal mucosa with a half-life of 1.5 hr. 2F-ara-A exhibited a plasma half-life of 3.5 hr.	2F-ara-A 2F-ara-ATP

Table 3 (Continued)
METABOLISM, DISTRIBUTION AND EXCRETION OF FLUDARABINE PHOSPHATE

Species	Design	Compound Administered	Dose (mg/m^2)	Metabolism and Distribution	Elimination	Metabolites
Dog (Beagle)	I.V. Administration	2F-ara-AMP	40 500	The dog metabolizes a greater % of the compound to 2F-ara-HX than does the mouse.	2F-ara-A, 2F-ara-HX, and 2F-A are all excreted in urine.	2F-ara-A 2F-ara-HX 2F-A
Dog (Beagle)	I.V. Administration	2F-ara-AMP	40 500	2F-ara-AMP undergoes dephosphorylation to 2F-ara-A in dogs.	----	2F-ara-A
Dog (Beagle)	I.V. Administration	2F-ara-AMP	260	Tissue binding of 2F-ara-A relative to plasma protein binding is substantially greater in the dog when compared to humans.	2F-ara-AMP is metabolized by dephosphorylation to 2F-ara-A with subsequent deamination to 2F-ara-HX	2F-ara-A 2F-ara-HX
Miniature Swine	I.P. Infusion	2F-ara-AMP	10 16 25	Peak I.P. levels of 2F-ara-A occurred at 5-140 minutes. Peak serum levels of 2F-ara-A occurred 120-240 minutes.	----	2F-ara-A
Monkey	I.V. Administration	2F-ara-AMP	20	Peak 2F-ara-A plasma levels occurred at 7-14 minutes. Peak 2F-ara-A CSF levels occurred at 31-127 minutes. 2F-ara-A crosses the blood-brain barrier accumulating in CSF with a lag time of 0.5-2 hr.	----	2F-ara-A
Mouse (BDF_1)	I.V. Administration	2F-ara-A	30	42% of radioactivity found in liver, 20% in spleen, pancreas, and colon, and 15% in lung and small intestines was a phosphorylated derivative of 2F-ara-A.	≥59% of drug is excreted in urine as 2F-ara-A at 24 hr. 12% of dose was excreted as metabolite at 24 hr.	2F-ara- AMP 2F-ara-ADP 2F-ara- ATP

Table 3 (Continued)
METABOLISM, DISTRIBUTION AND EXCRETION OF FLUDARABINE PHOSPHATE

Species	Design	Compound Administered	Dose (mg/m^2)	Metabolism and Distribution	Elimination	Metabolites
Mouse P388 tumor cell implant model	I.P. Administration	2F-ara- A	234 (mg/kg)	560 μM 2F-ara-ATP was the peak intracellular concentration observed. 2F-ara-A passed rapidly from ascites to blood in concentrations proportional to dose.	2F-ara-ATP disappeared with an intracellular half-life of 2.9 hr. 2F-ara-A exhibited a plasma half-life of 2.2 hr.	2F-ara-ATP
Dog (Beagle)	I.V. Administration	2F-ara- A	30	Dogs consistently metabolize greater portions of 2F-ara-A with higher levels detected in serum and urine when compared to mice.	27% of drug excreted unchanged in urine at 24 hr. 53% of drug excreted as metabolites in urine at 24 hr.	----
Dog (Beagle)	I.V. Administration	2F-ara- A	400	Dogs consistently metabolize greater portions of 2F-ara-A with higher levels detected in serum and urine when compared to mice.	18% of drug excreted unchanged in urine at 24 hr. 70% of drug excreted as metabolites in urine at 24 hr.	----
Monkey (Rhesus)	I.V. Administration	2F-ara- A	30	----	50% of drug excreted unchanged in urine at 24 hr. 26% of drug excreted as metabolites in urine at 24 hr.	----
Monkey (Rhesus)	I.V. Administration	2F-ara- A	400	----	58% of drug excreted unchanged at 24 hr. 25% of drug excreted as metabolites at 24 hr.	----

Pharmacokinetics (Humans)
The pharmacokinetics of fludarabine phosphate given intravenously have been determined in adult patients undergoing Phase I clinical trials at the University of Texas Health Science Center at San Antonio (UT), the University of Texas System Cancer Center at the M.D. Anderson Cancer Center (MDACC) and at Ohio State University (OSU). In addition, the pharmacokinetics of intraperitoneal fludarabine phosphate was also determined at UT and the pharmacokinetics of intravenous fludarabine phosphate in pediatric patients with leukemias and solid tumors were determined at the Children's Hospital of Los Angeles, the National Cancer Institute (NCI) and the Mayo Clinic.

Preliminary nonclinical and Phase I human studies demonstrated that fludarabine phosphate is rapidly converted to 2F-ara-A within minutes after intravenous infusion, and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2F-ara-ATP. Consequently, clinical pharmacology studies have focused on 2F-ara-A pharmacokinetics.

Described on the following pages are three principal pharmacokinetic studies that characterize the pharmacokinetic parameters of 2F-ara-A. Despite the differences in dosage and dosing schedules between these various studies discussed on the following pages, several consistent results were obtained. For the infusion studies, a mean terminal half-life of 9.2 hours was found in the population of patients studied at UT, and a median terminal half-life of approximately 8 hours was observed in the patients studied at MDACC. These values compare favorably to the 10.16-hour mean terminal half-life reported by the OSU investigators following large intravenous bolus injections. The terminal half-life of 2F-ara-A does not appear to be dose-dependent, as the doses used in these studies ranged from 18 to 260 mg/m^2.

The discrepancies between the studies regarding the biphasic or triphasic elimination patterns appear to be due to differences in sampling schedules and duration of intravenous administration. In addition, sampling duration has an impact upon the calculated value of the terminal half-life ($t_{½\gamma}$). The majority of pharmacokinetic studies use a blood sampling duration of 24 to 30 hours, which gives a calculated terminal half-life ($t_{½\gamma}$) of 8 - 10 hours. However, when the sampling duration is increased to 72 hours, the additional time points give a calculated $t_{½\gamma}$ of up to 31 hours. Because the plasma concentration of 2F-ara-A declines more than 50-fold from the peak concentration before this long elimination phase, the consequences of the relatively low 2F-ara-A concentration remaining in the plasma after 24 hours (<0.1 pmol) remain uncertain, as far as drug scheduling is concerned.

In addition, both the UT and OSU investigators found a positive correlation between area under concentration-time curves and degree of neutropenia reinforcing the assertion that toxicity (myelosuppression) is dose related.

Phase I-II Study of Fludarabine in Hematologic Malignancies (Study No. T83-1275) conducted at University of Texas, San Antonio

Methods

The pharmacokinetic parameters of the principal metabolite of fludarabine phosphate, 2F-ara-A, were determined in seven adult patients (6 male; 1 female) who received fludarabine phosphate at doses of 18 or 25 mg/m^2/day as a thirty-minute intravenous infusion daily for five consecutive days. Blood and urine samples were analyzed by HPLC for concentrations of 2F-ara-A.

The plasma concentration-time data, which were determined by HPLC, were analyzed by non-linear least squares regression analysis (NONLIN) using a zero order infusion input with first order elimination from the central compartment. Both a two and a three compartment model were tested and the data fitted to the two compartment open model.

Pharmacokinetic Parameters

Peak plasma concentrations of 2F-ara-A ranged from 0.199 to 0.876 μg/mL and appeared to be related to the dose and rate of infusion. Mean plasma concentrations of 2 fluoro-ara-A on days 1 and 5 in patients receiving 18 mg/m^2/day were 0.39 and 0.51 μg/mL, respectively. Mean plasma concentrations of 2F-ara-A on days 1 and 5 in patients receiving 25 mg/m^2/day were 0.57 and 0.54 μg/mL, respectively. There was no drug accumulation during the five-day treatment period.

The pharmacokinetic parameters derived from this study are presented in Table 4.

Table 4
2F-ARA-A KINETIC PARAMETERS

Patient	BSA (m^2)	Dose		Duration of Infusion (min)		Peak conc. (μg/mL)		Clearance rates (L/h/m^2)		Volumes of distribution (L/m^2)		$t_{½}$ (h)	
		mg/m^2	mg	Day 1	Day 5	Day 1	Day 5	Plasma	Tissue	Vd_{ss}	Vd	α	β
1	1.57	18	27	32	30	0.285	0.285	13.43	28.3	115.4	48.6	0.59	7.0
2[a]	1.74	18	31	25	30	0.199	0.377	1.51	28.1	1629.9	75.3	1.69	787.5
3	1.62	18	29	38	30	0.693	0.856	4.35	19.8	59.8	16.1	0.37	10.7
4	1.90	25	48	30	30	0.876	0.611[b]	10.38	23.8	91.9	22.9	0.39	7.8
5	1.94	25	48	35	30	0.509	0.550	8.30	5.1	86.4	46.8	1.99	10.6
6	1.74	25	43	33	30	0.550	–[c]	5.28	9.9	88.6	37.0	1.26	13.9
7	2.06	25	51	30	30	0.336	0.458[b]	12.71	33.8	135.2	55.2	0.59	8.44
Mean								9.1	20.1	96.2	37.8	0.60[d]	9.24[d]
SD								3.8	10.9	26.0	15.4	-	

[a]Patient omitted from calculation of mean and SD
[b]Day 5 levels drawn on day 4
[c]Day 5 levels not studied
[d]Harmonic mean half-life

The mean central compartment volume of distribution (Vd) was 37.8 L/m^2 with a mean steady-state volume of distribution (Vd_{ss}) of 96.2 L/m^2. The mean tissue clearance was 20.1 L/h/m^2 and the mean plasma clearance was 9.1 L/h/m^2. Plasma concentrations declined bi-exponentially with a harmonic mean initial half-life ($t_{½\alpha}$) of 0.6 hours and a harmonic mean terminal half-life ($t_{½\beta}$) of 9.2 hours. As presented in Table 5, approximately 24% of the parent compound,

fludarabine phosphate, was excreted in the urine as 2F-ara-A during the five-day treatment period.

Table 5
URINARY EXCRETION OF 2F-ARA-A

Patient	% Dose in Urine						Creatinine Clearance (mL/min.)
	Day 1	Day 2	Day 3	Day 4	Day 5	5-Day Average	
1	14	25	31	7	53	26	76
2	72	16	19	14	9	25	73
3	28	29	29	24	7	24	37
4	25	12	20	38	-	24	77
5	20	20	14	20	13	17	59
6	14	23	27	18	357	23	50
7	17	25	35	45	8	26	73
Mean	27	21	25	24	21	24	63
S.D.	21	6	7	13	19	3	15

Correlation of Pharmacokinetic Parameters with Clinical Parameters
As presented in Table 6, a correlation was observed between decreasing absolute granulocyte count and the area under the concentration-time curve (AUC). The Spearman rank correlation coefficient between absolute granulocyte count and AUC was -0.94 which was statistically significant ($p<0.02$). The Spearman rank correlation coefficient was also calculated between absolute granulocyte count and total plasma clearance (TPC). Here the correlation coefficient was 0.94 which was also statistically significant ($p<0.02$). The correlation coefficient between creatinine clearance and TPC was 0.828 ($0.05<p<0.1$). No correlation was observed between TPC and any of the liver function measurements.

Table 6
COMPARISON OF AUC WITH ABSOLUTE GRANULOCYTE NADIR AND CREATININE CLEARANCE

Patient	Dose (mg/m^2 per day X 5)	AUC[a] (mg · h/L)	AGC[b]	Creatinine Clearance (mL/min)
1	18	6.4	3,999	76
7	25	9.73	1,916	73
4	25	12.2	624	77
5	25	14.9	608	59
6	25	23.4	299	50
3	18	20.5	176	37

[a]Days 0 - 5
[b]Absolute granulocyte count

Summary and Conclusions
Intravenous doses of 18 and 25 mg/m^2/day for 5 days exhibited bi-exponential decay with a mean initial half-life ($t_{½\alpha}$) of 0.6 hours and a mean terminal half-life ($t_{½\beta}$) of 9.2 hours. The mean

plasma clearance was 9.1 L/h/m^2 and the mean tissue clearance was 20.1 L/h/m^2. The mean Vd_{ss} was 96.2 L/m^2, which is approximately twice body weight, suggesting that tissue binding of the drug occurs. In addition, there was a significant inverse correlation between AUC and absolute granulocyte count ($r=-0.94$, $p<0.02$) suggesting that myelosuppression is dose related.

Phase I-II Study of Fludarabine in Hematologic Malignancies (Study No. T83-1275) conducted at the M.D. Anderson Cancer Center

Methods

The pharmacokinetic parameters of the fludarabine phosphate metabolite, 2F-ara-A, were determined in 19 adult patients (12 male; 7 female) who received the drug as a 30-minute intravenous infusion daily for five consecutive days. Ten of the patients were diagnosed as having lymphoma and nine as having leukemia. In this study, five patients received doses of 20 mg/m^2/day, five patients received doses of 25 mg/m^2/day, one patient received 30 mg/m^2/day, four patients received 50 mg/m^2/day, two patients received 100 mg/m^2/day, and an additional two patients received 125 mg/m^2/day. Pharmacokinetic profiles were generally determined after the first dose of fludarabine phosphate. Plasma concentrations of 2F-ara-A and intracellular concentrations of 2F-ara-ATP were determined by HPLC. Intracellular concentrations were determined for mononuclear cells obtained from blood and bone marrow samples. The incorporation of 2F-ara-ATP into nucleic acids was determined using HPLC and liquid scintillation counting methods.

Pharmacokinetic Parameters

Plasma concentrations of fludarabine phosphate were undetectable at the times when the first samples were obtained. Of the patients receiving 20 or 25 mg/m^2/day, only two had detectable peak 2F-ara-A concentrations (1.4 and 2.2 μM) and, in this group of patients, 2F-ara-A levels were completely undetectable three hours after the completion of infusion of fludarabine phosphate.

At fludarabine phosphate dose levels of 50-125 mg/m^2/day, the disappearance of 2F-ara-A was biphasic and independent of dose with a median initial half-life ($t_{½\alpha}$) of 1.41 hours and a median terminal half life ($t_{½\beta}$) of approximately 8 hours. Plasma pharmacokinetic parameters for patients with relapsed leukemia (N=8, Patients #5-12) are presented in Table 7.

Table 7
PHARMACOLOGICAL CHARACTERISTICS FOR 2F-ARA-A IN THE PLASMA OF PATIENTS WITH RELAPSED LEUKEMIA

Patient	Fludarabine phosphate dose (mg/m^2)	2F-ara-A Parameters		
		$t_{½\alpha}$[a] (h)	$t_{½\beta}$[b] (h)	AUC[c] (μM·h)
5	50	3.30[d]	23.90	14
6	50	0.49	>24.00	28
7	50	1.42	7.77	10
8	50	1.25	7.76	16
Median	50	1.34	7.76[e]	15
9	100	1.40	8.90	15
10	100	1.87	6.88	37

Patient	Fludarabine	2F-ara-A Parameters		
11	125	0.93[d]	13.00	94
12	125	2.20	6.22	37
Median	112.5	1.64	7.89	37

[a] Initial rate of elimination
[b]Terminal rate of elimination
[c]Area under the concentration-time curve calculated to 24 h
[d]As the 2-h sample was the earliest obtained, this value is based on extrapolation of the line to 30 minutes
[e]The median value excluding patients 5 and 6 whose elevated creatinine levels may signal impaired renal function and thus a longer $t_{½\beta}$

A wide range of variation of pharmacokinetic parameters of 2F-ara-ATP in circulating leukemic cells was observed; however, when the median peak 2F-ara-ATP concentrations of 24 hour AUC values were compared at each dosage increment (20 or 25 mg/m^2, 50 mg/m^2, and 100 or 125 mg/m^2), a clear dose-dependence emerged (Table 8). Cellular elimination was not dose-dependent, with a half-life of approximately 15 hours at all dose levels. There was a strong correlation between the 2F-ara-ATP levels in leukemic cells obtained from peripheral blood and those found in bone marrow (r=0.84, p=0.01) suggesting that there were no pharmacological barriers in the bone marrow. Those patients with bone marrow involvement had the highest 2F-ara- ATP levels. In addition, intracellular 2F-ara-ATP levels in circulating leukemic cells at 12-14 hours after fludarabine phosphate infusion were inversely related to the DNA synthetic capacity of the cells relative to pretreatment. DNA synthesis remained maximally inhibited (>80%) until cellular concentrations of 2F-ara-ATP fell below 90 µM.

Table 8
PHARMACOLOGICAL CHARACTERISTICS OF 2F-ARA-ATP IN CIRCULATING LEUKEMIC CELLS

Patient	Diagnosis	Fludarabine phosphate dose (mg/m^2)	2F-ara-ATP Parameters		
			Peak (µM)	$t_{½}$[a](h)	AUC[b](µM·h)
1	CLL[c]	20	42	13.3	600
2	DWDL[d]	20	51	16.8	840
3	DLCL[c]	25	15	13.7	220
4	NMCL[f]	25	24	>24.0	480
	Median	22.5	33	15.3	540
5	AMML[g]	50	58	10.7	780
6	AML[h]	50	47	>24.0	700
7	AML	50	147	14.1	2,060
8	ALL[i]	50	105	12.8	1,340
	Median	50	82	13.5	1,060
9	AML	100	112	>24.0	2,560
10	CML-BC[j]	100	1	6.0	10
11	ALL	125	747	5.2	3,470
12	ALL	125	226	>24.0	6,050

Patient	Diagnosis	Fludarabine phosphate dose (mg/m^2)	2F-ara-ATP Parameters		
			Peak (µM)	$t_{½}$[a](h)	AUC[b](µM·h)
	Median	112.5	169	15.0	3,015

[a]Elimination half-life
[b]Area under the concentration-time curves calculated to 24 h
[c]Chronic lymphocytic leukemia
[d]Diffuse, well-differentiated lymphoma
[e]Diffuse, large cell lymphoma
[f]Nodular mixed cell lymphoma
[g]Acute myelomonocytic leukemia
[h]Acute myeloblastic leukemia
[i]Acute lymphoblastic leukemia
[j]Chronic myelogenous leukemia in blast crisis

Summary and Conclusions

Intravenous doses of 20-125 mg/m^2/day exhibited bi-exponential decay in plasma with a median initial half-life ($t_{½\alpha}$) of 1.41 hours and a median terminal half-life ($t_{½\beta}$) of approximately 8 hours for 2F-ara-A. The median intracellular half-life for 2F-ara-ATP was approximately 15 hours. The terminal half-lives of both 2F-ara-A and 2F-ara-ATP were not dependent on the dose of fludarabine phosphate. In addition, there was a high correlation between 2F-ara-ATP levels in circulating leukemic cells and bone marrow cells aspirated at the same time. DNA synthetic capacity of leukemic cells was inversely related to intracellular 2F-ara-ATP levels. Finally, 2F-ara-ATP levels were approximately three times higher in bone marrow cells from patients with bone marrow involvement than from those patients without evidence of bone marrow disease, suggesting that tumor cells may have a greater capacity to accumulate and retain nucleoside analogue triphosphates than do normal cells.

Phase I - Pharmacokinetic Study of Fludarabine (NSC-312887) (Study No. W83-328) conducted at Ohio State University

Methods

Twenty-six patients participated in this study, in which fludarabine phosphate was administered as a rapid intravenous (I.V.) infusion of 2-5 minutes duration. Seven patients received fludarabine phosphate at a dose of 260 mg/m^2, one patient received a dose of 160 mg/m^2, eight patients received a dose of 120 mg/m^2, four patients received 100 mg/m^2, and an additional six patients received 80 mg/m^2. Plasma concentrations of fludarabine phosphate could not be detected five minutes after the discontinuation of the infusion. Plasma concentrations of 2F-ara-A, the principal metabolite of fludarabine phosphate, were determined by HPLC over a time period of 0-30 hours post dosing. The plasma concentration-time data were analyzed by the NONLIN computer program and fitted to a three-compartment open model with first-order elimination from the central (blood) compartment, using the equations for rapid intravenous infusion.

Pharmacokinetic Parameters

Harmonic mean half-lives, mean residence time and total body clearance of 2F-ara-A for each of the dose levels are shown in Table 9. This metabolite exhibited a very short initial half-life (mean $t_{½\alpha}$) of 5.42 minutes, followed by an intermediate half-life (mean $t_{½\beta}$) of 1.38 hours and terminal half-life (mean $t_{½\gamma}$) of 10.16 hours. In the 26 patients, the terminal half-lives ranged

from 4.92 to 19.7 hours. The harmonic mean residence time (Vd_{ss}/C1T) was 10.4 hours, and total body clearance (C1T) ranged from 26.5 to 120.4 mL/min/m^2 with a mean of 68.98 mL/min/m^2.

Table 9
2F-ARA-A HARMONIC MEAN HALF-LIVES, MEAN RESIDENCE TIME, AND TOTAL BODY CLEARANCE IN PATIENTS

Dose mg/m^2	No. of Patients	$t_{½\alpha}$ (min)	$t_{½\beta}$ (hour)	$t_{½\gamma}$ (hour)	MRT (hour)	C1T (mL/min/m^2)
260	7	6.85	1.67	9.86	9.26	72.34
160	1	4.87	1.52	9.03	8.76	66.50
120	8	4.12	1.20	11.77	12.55	58.33
100	4	5.77	1.15	8.26	9.30	85.11
80	6	6.41	1.55	10.44	10.49	68.93
Mean of all patients	26	5.42	1.38	10.16	10.36	68.98
C.V. (%)	-	-	-	-	-	33.7

C.V.: coefficient of variation

Table 10
2F-ARA-A MEAN VOLUME PHARMACOKINETIC PARAMETERS

Dose mg/m^2	No. of Patients	V_1 (L/m^2)	V_2 (L/m^2)	V_3 (L/m^2)	Vd_{ss} (L/m^2)	Vd_{γ} (L/m^2)
260	7	7.97	12.83	20.87	41.68	61.95
160	1	6.63	10.15	18.17	34.96	52.00
120	8	6.28	10.79	26.54	43.61	60.45
100	4	7.73	14.14	27.69	49.55	64.99
80	6	7.73	11.98	26.27	45.97	65.11
Mean of all patients	26	7.30	12.11	24.81	44.22	62.30
C.V. (%)		31.9	25.1	40.7	25.7	28.0

The mean volume parameters for each dosage level are shown in Table 10. The central compartment volume of distribution was approximately 20% of body weight (V_1 = 7.30 L/m^2). The steady-state volume of distribution indicated significant binding of the drug to tissue components (Vd_{ss}=44.22 L/m^2). The smallest of the microscopic rate constants was k_{31}, indicating release of drug from the deep tissue compartment to be the rate-determining step in the elimination of 2F-ara-A from the body. Table 11 lists the microscopic rate constants for the first nine patients studied.

Table 11
2F-ARA-A MICROSCOPIC RATE CONSTANTS (N= 9)

Patient	Dose mg/m^2	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{13} (min^{-1})	k_{31} (min^{-1})	k_{10} (min^{-1})
W.Y.	260	0.0402	0.0341	0.00650	0.00333	0.00786
R.E.	260	0.0940	0.0418	0.00375	0.00176	0.01644
H.W.	260	0.0470	0.0360	0.00588	0.00268	0.00632

Patient	Dose mg/m^2	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{13} (min^{-1})	k_{31} (min^{-1})	k_{10} (min^{-1})
E.P.	260	0.0556	0.0379	0.01102	0.00299	0.00733
N.R.	120	0.0421	0.0314	0.00708	0.00204	0.00828
M.M	80	0.0786	0.0301	0.00909	0.00327	0.01580
J.B.	80	0.0621	0.0401	0.00917	0.00289	0.01296
R.D.	80	0.0867	0.0414	0.01239	0.00323	0.00692
E.K.	80	0.0107	0.0213	0.00240	0.00160	0.00340
Mean		0.0574	0.0349	0.00748	0.00264	0.00948
C.V. (%)		45.6	18.9	43.7	25.4	47.6

Correlation of Pharmacokinetic Parameters with Clinical Parameters

Upon completion of the pharmacokinetic studies, a multivariate correlation analysis was undertaken of all pharmacokinetic parameters with the following clinical parameters: bilirubin, serum creatinine, creatinine clearance, BUN, SGOT, SGPT, LDH, alkaline phosphatase, hemoglobin, hematocrit, baseline WBC, baseline platelets, WBC nadir, platelet nadir, WBC toxicity grade, platelet toxicity grade, nausea and vomiting grade, age and sex. Pearson correlation coefficients were substantiated by Spearman correlations. Despite the small number of patients, total body clearance correlated well with creatinine clearance and serum creatinine indicating that renal excretion is important for the elimination of the drug from the body. The volume parameters, particularly Vd_{ss} and Vd_{γ}, correlated with creatinine clearance and serum creatinine ($p \leq 0.011$). A positive correlation of Cl_T, with hemoglobin and hematocrit was observed ($p \leq 0.035$) and may be due to the metabolism of 2F-ara-A in the RBC. In addition, apparent correlations of Vd_{γ} with WBC toxicity ($p=0.025$) and γ with hematocrit ($p=0.035$) were observed. Tables 12 and 13 list the correlation coefficients and p values for the above correlations.

Table 12
CORRELATION OF 2F-ARA-A PHARMACOKINETIC PARAMETERS WITH CREATININE CLEARANCE AND SERUM CREATININE

	Pharmacokinetic Parameter	Correlation Coefficient (r)[a]	P Value	N
Creatinine	$C1_T$	0.71	0.002	16
Clearance	V_3	0.62	0.011	16
	Vd_{ss}	0.72	0.002	16
	Vd_{γ}	0.77	<0.001	16
Serum	$C1_T$	-0.48	0.013	26
Creatinine	V_1	-0.44	0.025	26
	Vd_{ss}	-0.49	0.011	26
	Vd_{γ}	-0.67	<0.001	26

[a]Pearson correlation coefficients which were substantiated by Spearman correlations.

Table 13
CORRELATION OF 2F-ARA-A PHARMACOKINETIC PARAMETERS WITH OTHER CLINICAL PARAMETERS

Pharmacokinetic Parameter	Clinical Parameter	Correlation Coefficient (r)[a]	*P* Value	N
Cl_T	BUN	-0.48	0.012	26
Cl_T	Hgb	0.42	0.035	26
Cl_T	Hct	0.46	0.017	26
Vd_γ	BUN	-0.39	0.050	26
Vd_γ	WBC tox	-0.46	0.025	24
γ	Hct	0.41	0.035	26

[a]Pearson correlation coefficients which were substantiated by Spearman correlations.

A rank ordering of the areas under the plasma concentration-time curve (AUC) for the first nine patients enrolled in the study showed good agreement with the corresponding severity of neutropenia developed by each patient (Table 14). Thus, the capacity of the compound to depress hematopoiesis appears to be dos-related.

Table 14
AREAS UNDER THE PLASMA CONCENTRATION-TIME CURVE AND NEUTROPENIA GRADE

Patient	Dose (mg/m^2)	AUC (μM min x 10^{-3})	Neutropenia Grade
H.W.	260	13.29	3
E.P.	260	13.19	3
R.E.	260	8.16	2
W.Y.	260	7.41	3
N.R.	120	5.58	0
R.D.	80	5.08	0
E.K.	80	4.57	1
M.M.	80	2.65	2
J.B.	80	2.54	0

TOXICOLOGY

Toxicology information from acute toxicity (Table 15 and Table 16), long term toxicity (Table 17), mutagenicity (Table 18), and reproductive studies (Table 19) is presented in the following pages.

Table 15
ACUTE TOXICITY STUDIES – MOUSE

Study Type/ Route of Administration	Animal Information	No. of Animals	Dosage mg/kg/day	Results
Single Dose Lethality Intravenous Injection Study# SIB 6101.2	Mouse ($CD2F_1$) Age: 6-8 weeks Wt.: 18.3-23.6 g	180 (90 Males, 90 Females)	0 800 967 1,170 1,414 1,710 2,068 2,500 No treatment	Dose-related decrease in motor activity (reversible in survivors), tonic spasms and death. Lethal dose estimates (mg/kg) were: LD_{10} LD_{50} LD_{90} M 979.2 1,404.2 2,013.6 F 780.2 1,235.6 1,956.9 M & F 874.4 1,321.1 1,995.9
Five Daily Dose Lethality Intravenous Injection Study# SIB 6101.3	Mouse ($CD2F_1$) Age: 6-8 weeks Wt.: 17.1-23.8 g	270 (135 Males, 135 Females)	0 325 412 523 664 843 1,070 1,358 No treatment	Dose-related decrease in motor activity (reversible in survivors) and death. Lethal dose estimates (mg/kg/day) were LD_{10} LD_{50} LD_{90} M 404.6 593.3 870.0 F 355.4 496.8 694.5 M & F 372.5 542.7 790.7

Table 15 (Continued)
ACUTE TOXICITY STUDIES – MOUSE

Study Type/ Route of Administration	Animal Information	No. of Animals	Dosage mg/kg/day	Results
Single Dose Toxicity Intravenous Injection Study # SIB 6101.7	Mouse ($CD2F_1$) Age: 6-8 weeks Wt.: 18.6-23.2 g	100 (50 Males, 50 Females)	Males: 0 490[a] 979[b] 1404[c] No treatment Females: 0 390[a] 780[b] 1236[c] No treatment	Dose-dependent effects on nervous, hematopoietic, GI, renal, and male reproductive systems. LD_{50}: lethal to males and females, with females more acutely affected than males. LD_{10}: mildly toxic to renal and hematopoietic systems, with decreased mean relative testicular weights. $½LD_{10}$: decrease in motor activity in a few mice, decreased mean relative testicular weights.
Five Daily Dose Toxicity Intravenous Injection Study # SIB 6101.4	Mouse ($CD2F_1$) Age: 6-8 weeks Wt.: 17.3-22.2 g	100 (50 Males, 50 Females)	Males: 0 203[a] 405[b] 593[c] No treatment Females: 0 178[a] 355[b] 497[c] No treatment	Dose-dependent effects on hematopoietic, GI, renal, and male reproductive systems. LD_{50}: lethal to male and female mice. LD_{10}: delayed toxicity to the testes (decreased mean relative testicular weight). $½LD_{10}$: can be considered safe in the mouse.

[a]=$½LD_{10}$
[b]=LD_{10}
[c]=LD_{50}

Table 16
ACUTE TOXICITY STUDIES - RAT AND DOG

Study Type/ Route of Administration	Animal Information	No. of Animals	Dosage mg/kg/day	Results
Single Dose Toxicity Intravenous Injection Study # TBT03-008	Rat (Sprague Dawley) Age: 8-11 weeks Wt.: 200-269 g	24 (15 Males, 9 Females)	800 1,400 2,000	Dose-dependent signs of toxicity were hypoactivity, rough fur, squinted eyes, hypothermia, gross findings in lymph nodes, thymus, heart, lungs, and stomach and death. Estimated LD_{50} values were 910 mg/kg (males) and 1,050 mg/kg (females).
Single Dose Toxicity Intravenous Injection Study # SIB 6101.5	Dog (Beagle) Age: 8-10 months Wt.: 7.0-11.6 kg	20 (10 Males, 10 Females)	13.1[a] 131.2[b] 262.4[c] 393.6[d] 524.8[e]	Dose-dependent signs of toxicity included changes in clinical status and adverse effects on the hematopoietic, gastrointestinal, renal and hepatic systems. In addition, male dogs receiving 4 x $MELD_{10}$ had pancreatic and reproductive toxicity, and were sacrificed moribund. The 1/10 $MELD_{10}$ and $MELD_{l0}$ doses were considered safe, as effects seen were minimal and readily reversible.
Five Daily Dose Toxicity Intravenous Injection Study # SIB 6106.6 and 6101.6c	Dog (Beagle) Age: 8-9 months Wt.: 6.5-11.7 kg	24 (12 Males, 12 Females)	0 5.59[a] 55.85[b] 111.76[c] 167.7[d] 223.52[e]	Dose-dependent signs of toxicity included alterations in clinical status and adverse effects on the hematopoietic, renal, gastrointestinal, and hepatic systems resulting in moribund sacrifice or death by day 8 for all 4 x $MELD_{10}$ animals, as well as one female at the 3 x $MELD_{10}$dose level. The 1/10 $MELD_{10}$ and $MELD_{10}$ dose levels were considered safe, as effects seen were minimal and readily reversible.

MELD = Mouse Equivalent Lethal Dose
[a]=1/10 $MELD_{10}$
[b]=$MELD_{10}$
[c]=2 x $MELD_{10}$
[d]=3 x $MELD_{10}$
[e]=4 x $MELD_{10}$

Table 17
SUBCHRONIC STUDIES
INTRAVENOUS 13-WEEK TOXICITY STUDIES IN RATS AND DOGS

Study Type/ Route of Administration	Animal Information	No. of Animals	Dosage mg/kg/day	Results
13 Week Subchronic Toxicity Intravenous Study # TBT03-003	Rat (Sprague Dawley) Age: 8-14 weeks Wt.: 215-312 g	160 (80 Males, 80 Females)	0, 1, 10, 50	There were 9 mortalities across all dose groups throughout the 13 weeks. None were attributable to test article. At 50 mg/kg/day, toxicity was expressed as increased physical activity during dosing, increased incidence of piloerection, effects on body weights, food consumption, water consumption, and clinical chemistry parameters, and decreases in red blood cell parameters. Organ weight changes included decreased absolute testes weights (males) and increased (relative to body weight) adrenal, kidney, liver, and spleen weights in both sexes at this dose. There were correlated gross pathologic and histologic abnormalities in most of these organs. Fludarabine phosphate given intravenously to rats for 91 consecutive days at doses of 1 and 10 mg/kg/day was well tolerated.
13 Week Subchronic Toxicity Intravenous Study # TBT03-002	Dog (Beagle) Age: 12-16 months Wt.: 7.1-17.9 kg	16 (8 Males, 8 Females)	0, 1, 10, 50	One male dog in the 50 mg/kg/day group died on day 42. Signs of toxicity noted in the 50 mg/kg/day group included weight loss, decreases in some red and white blood cell parameters, possible decrease in testicular weight, lymphoid depletion of the thymus and chronic inflammation of the stomach. For the male that died during the study, additional findings included hemorrhage in numerous tissues. The only test article-related change in the 10 mg/kg/day group was mild lymphoid depletion of the thymus in one male, although testicular weights may have been slightly decreased. The “no toxic effect” dose level was 10 mg/kg/day in female dogs and 1 mg/kg/day in male dogs.

Table 18
MUTAGENICITY STUDIES

Study Type	System Used	Concentration Range	Results
Ames Mutagenesis Assay Study # TBT03-009	*Salmonella typhimurium* Strains TA 98 TA 100 TA 1,535 TA 1,537	Activated and Non-activated Assays: 0.0015; 0.005; 0.015; 0.05; 0.15; 0.5 mg/plate	Non-activated Assay Fludarabine phosphate, at concentrations of 0.0015-0.15 mg/plate, did not increase the mean number of revertants per plate over the negative control value for each of the four strains of bacteria tested. The highest concentration tested, 0.5 mg/plate, was toxic to all strains of bacteria utilized. Activated Assay At concentrations of 0.0015 to 0.15 mg/plate, the mean number of revertants per plate was not increased over the control value for any of the four strains of bacteria tested. At 0.5 mg/plate, fludarabine phosphate was toxic to one strain of bacteria (TA 1537). Fludarabine phosphate was non-mutagenic to *S. typhimurium* strains tested, under both activated and non-activated conditions.
Sister Chromatid Exchange Assay Study # TBT03-010	Chinese hamster ovary cells (CHO)	Non-activated Assay: 10; 15; 30; 50; 100; 150; 300; 500 µg/mL Activated Assay: 50; 125; 250; 500; 1,000; 1,500; 2,000; 2,500 µg/mL	Non-activated Assay A significant increase in sister chromatid exchanges (SCEs) was seen in cells exposed to fludarabine phosphate at a concentration of 50 µg/mL with higher concentrations precluded from analysis due to cellular toxicity. Concentrations of 15 and 30 µg/mL did not cause statistically significant increases in SCEs. Activated Assay Concentrations of 500 and 1,000 µg/mL caused significant increases in SCEs per cell. Concentrations of 125 and 250 µg/mL did not increase SCEs per cell. Concentrations higher than 1,000 µg/mL were toxic to cells and thus precluded from analysis. Fludarabine phosphate has been demonstrated to cause significant increases in SCEs under both activated and non-activated assay conditions.

Table 18 (Continued)
MUTAGENICITY STUDIES

Study Type	System Used	Concentration Range	Results
CHO/HGPRT Mammalian Cell Mutagenesis Assay Study # TBT03-012	Chinese hamster ovary cells (CHO)	Non-activated Assay: 0.3; 1; 3; 10; 30; 100; 300; 500 µg/mL Activated Assay: 3; 10; 30; 100; 300; 1,000; 1,500; 2,000; 2,500 µg/mL	Non-activated Assay At concentrations of 1 to 300 µg/mL, fludarabine phosphate was non-mutagenic as indicated by mean mutation frequencies not significantly different from the negative (solvent) control values. A concentration of 500 µg/mL produced significant cellular toxicity and could not be analyzed. Activated Assay Mean mutation frequencies were not significantly different from the solvent control value at fludarabine phosphate concentrations ranging from 3 to1,000 µg/mL. Higher concentrations were not selected for analysis due to toxicity to cells. It was concluded that fludarabine phosphate was non-mutagenic under both non-activated and activated conditions in the CHO/HGPRT system.
Chromosome Aberration Assay Study # TBT03-011	Chinese hamster ovary cells (CHO)	Non-activated Assay: 2.6, 4.5, 9, 13, 26.45, 90, 130,260 µg/mL Activated Assay: 30, 50, 100, 150, 300, 500, 1000, 1500, 2000 µg/mL	Non-activated Assay The concentrations of fludarabine phosphate analyzed, 9, 26, and 90 µg/mL, did not increase the percentage of aberrant cells (both excluding and including gaps). Concentrations of 130 and 260 µg/mL were toxic to cells. Activated Assay A significant increase in the percentage of cells with chromosomal aberrations (both excluding and including gaps) were detected at concentrations of 1,500 and 2,000 µg/mL. No significant increases in aberrant cells were noted at the other two concentrations analyzed, 150 and 500 µg/mL. Fludarabine phosphate has been demonstrated to increase chromosome aberrations under activated conditions but did not increase chromosome aberrations under nonactivated conditions in this assay.

Table 18 (Continued)
MUTAGENICITY STUDIES

Study Type	System Used	Concentration Range	Results
Mouse Micronucleus Test Study # PHRR AD76	Mouse, NMRI (SPF)	0; 100; 300; 1,000 mg/kg body weight cyclophosphamide (30 mg/kg) positive control	One day after application at the toxic dose level of 1,000 mg/kg, 3/20 mice showed moderate apathy, while on day 2, 2/20 died. In the 1,000 mg/kg dose group, a significant increase in the micronucleated polychromatic erythrocytes (PCE) and normochromatic erythrocyte (NCE) counts was observed at both sampling times. Additionally, in the mid-dose group, a significant increase in micronucleated PCE counts was observed 24 hours after administration. Furthermore, bone marrow depression was observed in all treatment groups at 24 hours post-administration and in the high- and mid-dose groups at 48 hours post-administration. The positive control gave the expected increase in the micronucleated cell counts. A significant decrease in the PCE/NCE ratio was also observed.
Dominant Lethal Test Study# PHRR AV36	Mouse, NMRI, BR (SPF)	0; 100; 300; 800 mg/kg body weight cyclophosphamide (120 mg/kg) positive control	Only the highest dose tested (800 mg/kg) was clearly toxic after single administration as demonstrated by a mortality rate of approximately 40%. Fludarabine phosphate showed no potential to induce germ cell mutations in male mice at any germ cell stage over complete spermatogenic maturation. No biologically relevant positive response for any of the parameters evaluated (number of total and those resulting in death per pregnant female, pre-implantation losses and fertility index) were observed at any mating interval at any dose-level. The positive control gave the expected mutagenic response demonstrating the sensitivity of the test system.

Table 19
REPRODUCTIVE STUDIES
INTRAVENOUS DEVELOPMENTAL TOXICITY STUDIES OF FLUDARABINE PHOSPHATE

Study Type/ Route of Administration	Animal Information	No. of Animals	Dosage mg/kg/day	Results
Range-Finding Developmental Toxicity Intravenous Injection (gestation days 6-15) Study # TBT03-004	Rat (Sprague Dawley) Age: 12 weeks Wt.: 227-266 g	30 Females	0 4 10 40 100 400	Mortality was 100% at the 400 mg/kg/day dose level; all other animals survived to scheduled sacrifice. Signs of toxicity in the 40, 100, and 400 mg/kg/day groups included lethargy, hypothermia, changes in the feces, decreased body weight gain or body weight loss, and decreased food consumption. Post-implantation loss was 100% and 30% at the 100 and 40 mg/kg/day dose levels respectively. Ten fetuses in two litters in the 40 mg/kg/day group had fetal malformations, which included omphalocele and various limb and tail anomalies. The 4 and 10 mg/kg/day dose levels produced no signs of maternal or developmental toxicity. The No Observable Adverse Effect Level (NOAEL) was 10 mg/kg/day.
Developmental Toxicity Intravenous Injection (gestation days 6-15) Study # TBT03-006	Rat (Sprague Dawley) Age: 12 months Wt.: 208-299 g	100 Females	0 1 10 30	No treatment-related deaths occurred during the study, nor were there any clinical signs of toxicity. Mean maternal body weight gain was slightly decreased early in the dosing phase, and mean fetal weight was low, for the 30 mg/kg/day group. The small number of malformations seen were considered not test article-related, due to a lack of a dose response; however, the 10 and 30 mg/kg/day groups showed dose-related increases in the incidence of several skeletal variations (rib and vertebrae anomalies), indicating developmental toxicity at both dose levels. A dose level of 1 mg/kg/day was considered the No Observable Adverse Effect Level (NOAEL).

Table 19 (Continued)
REPRODUCTIVE STUDIES
INTRAVENOUS DEVELOPMENTAL TOXICITY STUDIES OF FLUDARABINE PHOSPHATE

Study Type/ Route of Administration	Animal Information	No. of Animals	Dosage mg/kg/day	Results
Range-Finding Developmental Toxicity Intravenous Injection (gestation days 6-18) Study # TBT03-005	Rabbit (New Zealand White) Age: 6 months Wt.: 3.0-3.9 kg	30 Females	0 1 5 10 25 50	Mortality was 100% for the 50 and 25 mg/kg/day groups. Signs of toxicity in the 10, 25, and 50 mg/kg/day groups included ataxia, lethargy, labored respiration, changes in the feces, maternal body weight losses, and decreased food consumption. The 5 mg/kg/day group also had slightly decreased food consumption early in the dosing phase. Post-implantation loss was slightly increased in the 10 mg/kg/day group. In addition, 30 of 35 fetuses in this group had external malformations, consisting primarily of craniofacial and/or limb and digit defects. The No Observable Adverse Effect Level (NOAEL) was considered to be 1 mg/kg/day.
Developmental Toxicity Intravenous Injection (gestation days 6-18) Study # TBT03-007	Rabbit (New Zealand White) Age: 6 months Wt.: 3.1-4.2 kg	80 Females	0 1 5 8	Maternal survival was not affected and no clinical signs of toxicity were apparent in any group. The 5 and 8 mg/kg/day groups showed dose-related inhibition of maternal body weight gain and food consumption. Post-implantation loss was increased and mean fetal body weight was low, at the 8 mg/kg/day dose level. External and skeletal malformations, generally specific to the head, limbs, digits and tail, were increased in the 8 mg/kg/day group. In addition, diaphragmatic hernia (a soft tissue malformation) was noted at a low frequency but in a dose-related pattern (3, 1 and 1 fetuses in the 8, 5 and 1 mg/kg/day groups, respectively). The incidence of skeletal variations was also increased in a dose-related manner in the 5 and 8 mg/kg/day groups. A dose level of 1 mg/kg/day was considered the No Observable Adverse Effect Level (NOAEL) for maternal toxicity but equivocal for fetal developmental toxicity, because of the appearance of a single fetus with diaphragmatic hernia at this dose level.

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PART III: CONSUMER INFORMATION

[Pr]AJ-FLUDARABINE
(Fludarabine phosphate injection)

This leaflet is part III of a three-part "Product Monograph" published when AJ-FLUDARABINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AJ-FLUDARABINE. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this leaflet carefully before you start using AJ-FLUDARABINE. Keep this leaflet. You may need to read it again, This leaflet will provide information about the benefits and risks of using AJ-FLUDARABINE. It will also advise you about how to take AJ-FLUDARABINE properly and when to tell your doctor about health-related conditions. If you have any questions or need more advice, ask you doctor, professional health care provider or pharmacist. This product has been prescribed for you personally and you should pass it on to others. It may harm them, even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:
AJ-FLUDARABINE is a cytotoxic (anti-cancer) drug. It is given by slow infusion (with a drip) into the veins (intravenously).

AJ-FLUDARABINE is used for the treatment of a type of cancer known as chronic lymphocytic leukemia (CLL). AJ-FLUDARABINE is usually used as a second line treatment of CLL, this is, if a previous treatment has failed or stopped working. It may also be used in to treat low-grade non-Hodgkin's lymphoma (Lg-NHL). CLL and Lg-NHL are cancers of a type of white blood cells called lymphocytes.

In CLL and Lg-NHL, too many abnormal lymphocytes are produced and lymph nodes start to grow in various regions of your body, The abnormal lymphocytes either do not work properly or are too young (immature) to fight infection well. If there are too many of these abnormal lymphocytes, they push aside healthy blood cells in the bone marrow where most of the new blood cells are formed. Without enough healthy blood cells, infections, anemia, bruising, excessive bleeding or even organ failure can result.

What it does:
All cells of the body produce new cells like themselves by dividing, For this purpose, the cells' genetic material (DNA) must be copied and reproduced. AJ-FLUDARABINE works by hindering the production of new DNA. Therefore, when the cancer cells take up AJ-FLUDARABINE, it stops the growth of new cancer cells. It has been discovered that fludarabine phosphate works especially well against some cancers of the type of white blood cells called lymphocytes.

When it should not be used:

You must not use AJ-FLUDARABINE if any of the following apply to you:

- Pregnant or breast-feeding
- Allergy (hypersensitivity) to any of the ingredients of this medication
- Kidney function is severely reduced
- Number of red blood cells is reduced due to a break down of these cells (hemolytic anemia).

AJ-FLUDARABINE should not be used with a drug called pentostatin (deoxycoformycin).

What the medicinal ingredient is:
Fludarabine Phosphate

What the nonmedicinal ingredients are:
Mannitol and sodium hydroxide and Water for Injection.

What dosage forms it comes in:
AJ-FLUDARABINE is supplied as 2 mL per vial of 50 mg fludarabine phosphate, 50 mg of mannitol and 6.60 mg of sodium hydroxide.

Fludarabine for intravenous administration is supplied in a single vial carton and is a single use vial.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- When used at doses four times greater than the recommended dose for chronic lymphocytic leukemia (CLL), a third of patients experienced severe central nervous effects including blindness, coma and death. Such effects are rare or uncommon but have been reported in patients who receive the recommended dose for CLL (see **Side Effects** section).
- Some patients treated with fludarabine phosphate have had rapid breakdown of red blood cells which in some cases was severe or resulted in death. This can happen whether you have previously been treated with AJ-FLUDARABINE or not (**Side Effects** section).
- This medicine should not be used with a drug called pentostatin (deoxycoformycin).

BEFORE you use AJ-FLUDARABINE talk to your doctor if:

- Your kidneys do not work well
- Your liver does not work well
- You are not feeling very well
- You are over 75 years old
- You have or have had herpes zoster (shingles)
- You need a blood transfusion and you are undergoing, or

have received treatment with AJ-FLUDARABINE.

Special regular check-ups will be necessary if you are over 75 years old or your liver or kidneys do not work well.

The number of normal blood cells may be reduced and so you will have regular blood tests during treatment.

Your ability to become pregnant or father a child may be affected by taking AJ-FLUDARABINE. It is important to discuss fertility with your doctor before you start treatment.

Men and women who may still be fertile must use a reliable form of contraception during, and for at least 6 months after stopping treatment.

Check with your doctor about any vaccinations you may need, because live vaccinations should be avoided during and after treatment with AJ-FLUDARABINE.

If your disease is very severe, your body may not be able to get rid of all the waste products from the cells destroyed by AJ-FLUDARABINE. This may cause dehydration, kidney failure and heart problems. Your doctor will be aware of this and may give you other drugs to stop this happening (see **Side Effects** section).

Reversible worsening or flare-up of pre-existing skin cancer has been reported in some patients during or after fludarabine phosphate therapy.

Progression of the disease has been commonly reported.

The effect of treatment with AJ-FLUDARABINE on the ability to drive and operate machines has not been evaluated. Do not drive or operate machines if fatigue or changes in vision occur.

INTERACTIONS WITH THIS MEDICATION

This medication should not be used with a drug called pentostatin (deoxycoformycin).

The effectiveness of AJ-FLUDARABINE may be reduced by medications containing dipyridamole and similar substances. If you are taking any other medicines regularly, tell your doctor.

PROPER USE OF THIS MEDICATION

AJ-FLUDARABINE (25 mg/mL) is NOT for direct injection. AJ-FLUDARABINE MUST be diluted with recommended intravenous infusion solutions.

Usual dose:

The following instructions apply to the use of AJ-FLUDARABINE, unless indicated otherwise by your physician. Please follow them carefully.

- How and when should AJ-FLUDARABINE be taken?

AJ-FLUDARABINE should be administered under the supervision of, or prescribed by, a qualified physician experienced in the use of anti-cancer treatment. The dose you receive or should take varies with your body surface area. Technically this is measured in square meters (m^2), but actually is worked out from your height and weight.

The recommended dose is 25mg/ m^2 of body surface area.

Your doctor will calculate your individual dose which has to be given daily in the form of a solution directly into the blood stream through a vein once a day for 5 consecutive days. This five day course of treatment will normally be repeated every 28 days as prescribed by your doctor. Usually six 28-day cycles are required.

The dosage may be decreased or the repeat course delayed if side effects are a problem. If you have kidney problems you will receive a reduced dose and you will have regular blood tests.

- How should AJ-FLUDARABINE be handled?

Due to the toxic nature of anti-cancer drugs such as AJ-FLUDARABINE, special protective measures for handling are advised. Please ask your doctor or pharmacist.

Overdose:
In the case of an overdose your doctor will stop the therapy and treat the symptoms.

Missed Dose:
Your doctor will set the times at which you are to receive this medicine. If you think you may have missed a dose, contact your doctor as soon as possible.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most frequently reported side effects and those that are more clearly related to the drug are reported below with their frequencies (very common: 10% and more; common: 1% and more, but less than 10%; uncommon: 0.1% and more, but less than 1%; rare: less than 0.1%).

The following side effects have been reported very commonly:

- infection (like latent viral reactivation, e.g., Herpes zoster

virus, Epstein-Barr-virus, Progressive multifocal leucoencephalopathy)
- pneumonia
- fever
- feeling tired
- feeling weak
- a reduction in the number of blood cells
- cough
- nausea
- vomiting
- diarrhea

Serious infections have occurred in patients treated with AJ-FLUDARABINE.

Prolonged vomiting and/or diarrhea or mouth sores and diarrhea may limit your fluid intake and you may be prone to dehydration. Contact your doctor if these symptoms persist for 24 hours.

The following side effects have been reported commonly:
- a reduction in blood cell production by the bone marrow (myelosuppression)
- loss of appetite
- numb or weak limbs
- visual problems (blurred vision)
- inflammation of the lining of the mouth
- skin rash
- generally feeling unwell
- chills
- build up of fluid in the body (edema)

Myelosuppression may result in anemia, abnormal bleeding or bruising and reduced resistance to infections.

The following side effects have been reported uncommonly:
- a significant reduction in the number of red blood cells
- bleeding in the digestive system
- confusion
- allergic type reaction (pulmonary hypersensitivity)
- pain in your side, blood in your urine

The following side effects have been reported rarely:
- coma
- seizures
- agitation
  - blindness
  - pain in the eye
  - heart failure
  - irregular heart beat
  - inflammation of the bladder
  - red and flaky skin (e.g., Stevens-Johnson syndrome or toxic epidermal necrosis)

When used at doses four times greater than the recommended dose for chronic lymphocytic leukemia (CLL), a third of patients experienced severe central nervous system effects including blindness, coma and death. Such effects are rare (coma, seizures and agitation) or uncommon (confusion) but have been reported in patients who receive the recommended dose for CLL. These effects usually begin from three to eight weeks after treatment has been given but may occur earlier or later.

If you notice any unwanted effects, or if you are unsure about the effect of this product, please inform your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	Vomiting, diarrhea (24 hours)/ dehydration		✓	
	Cough, trouble breathing, fever /pneumonia		✓	
	Fever, chills, feeling unwell, pain/ infection		✓	
	Numb or weak limbs/ motor disturbance		✓	
	Blurred vision/ changes in vision		✓	
Uncommon	Difficulty breathing, rash, itching/ allergic reaction			✓
	Pain in your side, blood in your urine/ infection		✓	
	Tar-coloured or bloody stool/ bleeding in the digestive system		✓	
Uncommon (cont'd)	Chest pain/ heart failure, irregular heartbeat		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate
	Extreme fatigue, unusual bruising excessive bleeding after injury/ reduction in blood cell production by the bone marrow		✓	
	Yellowing of the skin or eyes an/or red-brown urine/ rapid breakdown of red blood cells (also called hemolytic anemia)		✓	
	Confusion/ severe central nervous system effects		✓	
	Loss of hearing		✓	
Rare	Coma, seizures, agitation/ severe central nervous system effects		✓	
	Red and flaky skin/ severe skin disorder			✓
	Pain in your eyes, blindness		✓	

This is not a complete list of side effects. For any unexpected effects while taking AJ-FLUDARABINE, contact your doctor or pharmacist.

HOW TO STORE IT

Store all drugs properly and keep them out of the reach of children.

The expiry date is printed on the label. Do not use after this date.

Store AJ-FLUDARABINE under refrigeration between 2°C and 8°C. Do not freeze. Discard unused portion.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting:

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