PRODUCT MONOGRAPH

[Pr]FLUDARABINE PHOSPHATE FOR INJECTION

Fludarabine Phosphate

Sterile Solution for Injection

25 mg/mL
(2 mL per vial)

Antineoplastic

Teva Canada Limited
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M1B 2K9

Date of Revision:
March 1, 2016

Submission Control No: **190383**

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 - Product Information Summary

Route of Administration	**Dosage Form / Strength**	**Nonmedicinal Ingredients**
Intravenous infusion	Solution/ 25 mg/mL	Mannitol and sodium hydroxide

INDICATIONS AND CLINICAL USE

FLUDARABINE PHOSPHATE FOR INJECTION is indicated for:

- Second line treatment in patients with chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin's lymphoma (Lg-NHL) who have failed other conventional therapies.

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 FLUDARABINE PHOSPHATE FOR INJECTION 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 (area under the curve [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 FOR INJECTION 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.
- 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 FOR INJECTION in combination with pentostatin is contraindicated.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

FLUDARABINE PHOSPHATE FOR INJECTION should be administered under the supervision of, or prescribed by, a qualified physician experienced in the use of antineoplastic therapy.

Fludarabine phosphate is associated with:

- Myelosuppression, including fatal cases (see **WARNINGS AND PRECAUTIONS – Hematologic**)
- Irreversible CNS effects, including fatal cases (see **WARNINGS AND PRECAUTIONS – Neurologic**)
- Auto-immune hemolytic anemia, including fatal cases (see **WARNINGS AND PRECAUTIONS – Hematologic)**

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 FOR INJECTION in combination with pentostatin is contraindicated.

General
FLUDARABINE PHOSPHATE FOR INJECTION 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 FLUDARABINE PHOSPHATE FOR INJECTION.

Carcinogenesis and Mutagenesis
Disease progression and transformation (eg, Richter's Syndrome) have been commonly reported in CLL patients (see **WARNINGS AND PRECAUTIONS - Skin).**

Endocrine and Metabolism
Tumor lysis syndrome associated with fludarabine phosphate treatment has been reported in CLL patients with large tumor burdens. Since FLUDARABINE PHOSPHATE FOR INJECTION 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.

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, FLUDARABINE PHOSPHATE FOR INJECTION 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**).

Severe bone marrow suppression, notably thrombocytopenia, anemia, leukopenia and neutropenia, may occur with administration of FLUDARABINE PHOSPHATE FOR INJECTION 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 FLUDARABINE PHOSPHATE FOR INJECTION requires careful hematologic monitoring.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The duration of clinically significant cytopenia in the 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 FLUDARABINE PHOSPHATE FOR INJECTION should be avoided. The mechanisms which predispose patients to the development of this complication have not been identified. Patients undergoing treatment with FLUDARABINE PHOSPHATE FOR INJECTION 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 FLUDARABINE PHOSPHATE FOR INJECTION 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.

Hepatic/Biliary/Pancreatic

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

Immune

Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) has been observed after transfusion of nonirradiated 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 FOR INJECTION should receive irradiated blood only.

Neurologic

Administration of fludarabine phosphate can be associated with leukoencephalopathy (LE), acute toxic leukoencephalopathy (ATL), or posterior reversible encephalopathy syndrome (PRES)/ reversible posterior leukoencephalopathy syndrome (RPLS).

LE, ATL or PRES/RPLS may occur:

- at the recommended dose, most commonly

- when fludarabine phosphate is given following, or in combination with, medications known to be associated with LE, ATL or PRES/RPLS, or
- when fludarabine phosphate is given in patients with cranial or total body irradiation, Graft versus Host Disease, renal impairment, or following Hematopoietic Stem Cell Transplantation.

- at doses higher than the recommended dose.

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 ($\exists$ 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 (# 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, Lg-NHL, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion).

LE, ATL or PRES/RPLS symptoms may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, and focal neurological deficits. Additional effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/quadriparesis, muscle spasticity, incontinence, and coma.

The onset of the neurologic symptoms can be delayed and may occur after discontinuation of fludarabine. Late-occurring encephalopathy has been reported up to 4.8 years following fludarabine.

LE/ ATL/ PRES/RPLS may be irreversible, life-threatening, or fatal.

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. Whenever LE, ATL or PRES/RPLS is suspected, FLUDARABINE PHOSPHATE FOR INJECTION treatment should be stopped. Patients should be monitored and should undergo brain imaging, preferably utilizing MRI. If the diagnosis is confirmed, FLUDARABINE PHOSPHATE FOR INJECTION therapy should be permanently discontinued.

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 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 hematological monitoring should be used to assess toxicity. FLUDARABINE PHOSPHATE FOR 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 men and women of child-bearing potential take contraceptive measures during FLUDARABINE PHOSPHATE FOR INJECTION therapy, and for at least 6 months after the cessation of FLUDARABINE PHOSPHATE FOR INJECTION therapy.

Skin

The worsening or flare-up of pre-existing skin cancer lesions, as well as new onset of skin cancer, has been reported to occur in patients during or after intravenous (i.v.) fludarabine phosphate therapy.

Special Populations

Pregnant Women: There are very limited data of fludarabine phosphate use in pregnant women in the first trimester: one newborn has been described with absent bilateral radii and normal thumbs, thrombocytopenia, fossa ovalis aneurysm and a small patent ductus arteriosus. Early pregnancy loss has been reported in fludarabine phosphate monotherapy as well as in combination therapy. Premature delivery has been reported.

FLUDARABINE PHOSPHATE FOR INJECTION should not be used during pregnancy unless clearly necessary (e.g., life-threatening situation, no alternative safer treatment available without compromising the therapeutic benefit, treatment cannot be avoided). It has the potential to cause fetal harm. Prescribers may only consider it to be used if the potential benefits justify the potential risks to the fetus. Women of childbearing potential must be apprised of the potential hazard to the fetus.

Women should avoid becoming pregnant while on FLUDARABINE PHOSPHATE FOR INJECTION therapy. Women of childbearing potential or fertile males must take effective contraceptive measures during and at least for 6 months after cessation of therapy.

Nursing Women: Breastfeeding should not be initiated during FLUDARABINE PHOSPHATE FOR INJECTION treatment. Nursing women should discontinue breastfeeding.

It is not known whether this drug is excreted in human milk. There is evidence from preclinical data that after intravenous administration to rats that fludarabine phosphate and/or metabolites transfer from maternal blood to milk.

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 FLUDARABINE PHOSPHATE FOR INJECTION 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 FOR INJECTION 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 or Operate Machines

FLUDARABINE PHOSPHATE FOR INJECTION may reduce the ability to drive or use machines, since fatigue, weakness, visual disturbances, confusion, agitation and seizures have been observed.

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 disturbance, 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 table below reports adverse events by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data regardless of the causal relationship with fludarabine phosphate.

Table 2 - Fludarabine Phosphate Clinical Trial Adverse Events (by MedDRA SOC)

System Organ Class MedDRA	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000
Infections and infestations	Infections / opportunistic infections (like latent viral reactivation, e.g., Herpes zoster virus, Epstein- Barr virus, Progressive multifocal leucoencephalopathy), pneumonia			Lymphoproliferative disorder (EBV-associated)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Myelodysplastic syndrome and acute myeloid leukaemia (mainly associated with prior, concomitant, or subsequent treatment with alkylating agents, topoisomerase inhibitors or irradiation)		
Blood and lymphatic system disorders	Neutropenia, anemia, thrombocytopenia	Myelosuppression		
Immune system disorders			Autoimmune disorder (including autoimmune hemolytic anemia, thrombocytopenic purpura, pemphigus, Evans syndrome, acquired hemophilia)	
Metabolism and nutrition disorders		Anorexia	Tumor lysis syndrome (including renal failure, hyperkalemia, metabolic acidosis, hematuria, urate crystalluria, hyperuricemia, hyperphosphatemia, hypocalcemia)	
Nervous system disorders		Neuropathy peripheral	Confusion	Agitation, seizures, coma
Eye disorders		Visual disturbance		Optic neuritis, optic

System Organ Class MedDRA	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ l/10,000 to < 1/1000
				neuropathy, blindness
Cardiac disorders				Heart failure, arrhythmia
Respiratory, thoracic and mediastinal disorders	Cough		Pulmonary toxicity (including dyspnea, pulmonary fibrosis, pneumonitis)	
Gastrointestinal disorders	Nausea, vomiting, diarrhea	Stomatitis	Gastrointestinal hemorrhage, pancreatic enzymes abnormal	
Hepatobiliary disorders			Hepatic enzyme abnormal	
Skin and subcutaneous tissue disorders		Rash		Skin cancer, Stevens-Johnson syndrome, necrolysis epidermal toxic (Lyell type)
Renal and urinary disorder				Urinary tract hemorrhage (including hemorrhagic cystitis)
General disorders and administration site conditions	Fever, fatigue, weakness	Chills, malaise, edema, mucositis		

Post-Market Adverse Reaction

The following adverse reactions are based on post-marketing data regardless of the causal relationship with fludarabine phosphate.

Blood and lymphatic disorders: pancytopenia, myelosuppression, neutropenia, thrombocytopenia, anemia, cytopenia, tri-lineage bone marrow aplasia

Cardiac disorders: edema, heart failure, arrhythmia

Eye disorders: blindness, optic neuritis, optic neuropathy, eye hemorrhage including retinal

Gastrointestinal disorders: anorexia

General disorders and administrative conditions: chills

Genitourinary disorders (initial PI)/Metabolism and nutritional disorders: hematuria (context of TLS), hypocalcemia (context of TLS), hyperphosphatemia (context of TLS), hyperuricemia, renal failure (context of TLS), urate crystalluria (context of TLS), metabolic acidosis (context of TLS), hyperkalemia (context of TLS)

Hepatobiliary disorders: hepatic enzymes abnormal, pancreatic enzymes abnormal

Immune system disorders: transfusion-related GVHD, thrombocytopenic purpura, Evans syndrome, pemphigus, autoimmune hemolytic anemia, acquired hemophilia

Infections and infestations: opportunistic infections, herpes zoster virus, Epstein-Barr virus, latent viral reactivation, progressive multifocal leucoencephalopathy, human polyomavirus JC virus (context of PML), disease transformation CLL

Neoplasms, benign, malignant and unspecified: acute myeloid leukemia, Richter's syndrome, myelodysplastic syndrome, disease progressive CLL, lympho-proliferative disorder (EBV-associated)

Nervous system disorders: seizures, agitation, confusion, coma; leukoencephalopathy, acute toxic leukoencephalopathy, posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (see WARNINGS AND PRECAUTIONS, Neurologic).

Respiratory, thoracic and mediastinal disorders: pulmonary toxicity, pneumonitis, pulmonary fibrosis, dyspnea

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, rash, worsening of pre-existing skin cancer lesions, skin cancer, Stevens-Johnson syndrome

Vascular disorders: hemorrhage, pulmonary hemorrhage, gastrointestinal hemorrhage, urinary tract hemorrhage including hemorrhagic cystitis, cerebral hemorrhage

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 FOR INJECTION in combination with pentostatin is contraindicated.

Drug-Drug Interactions

The therapeutic efficacy of FLUDARABINE PHOSPHATE FOR INJECTION may be reduced by dipyridamole and other inhibitors of adenosine uptake.

Clinical studies and in vitro experiments showed that using fludarabine phosphate in combination with cytarabine may increase the intracellular concentration and intracellular exposure of Ara-CTP (active metabolite of cytarabine) in leukemic cells. Plasma concentrations of Ara-C and the elimination rate of Ara-C were not affected.

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 FOR INJECTION (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 FOR INJECTION (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 FOR INJECTION should be administered until 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 FOR INJECTION should only be 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.

FLUDARABINE PHOSPHATE FOR INJECTION 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.

Use within 24 hours when kept at room temperature and 72 hours when refrigerated.

OVERDOSAGE

For management of suspected drug overdose, consult your regional poison control centre.

Higher than recommended doses of fludarabine phosphate have been associated with leukoencephalopathy, acute toxic leukoencephalopathy, or posterior reversible encephalopathy syndrome (PRES)/ reversible posterior leukoencephalopathy syndrome (RPLS). Symptoms, which may be delayed and irreversible, may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, focal neurological deficits, coma and death. Additional effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/ quadriparesis, muscle spasticity and incontinence. 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

Fludarabine phosphate 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 γ, 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 ΦM. 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 ΦM 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 ΦM 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 intravenously 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 intravenous (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} were 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 ^{3}H-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

Store FLUDARABINE PHOSPHATE FOR INJECTION under refrigeration between 2EC and 8EC. Do not freeze. Discard unused portion.

FLUDARABINE PHOSPHATE FOR INJECTION 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. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

SPECIAL HANDLING INSTRUCTIONS

FLUDARABINE PHOSPHATE FOR INJECTION 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 FLUDARABINE PHOSPHATE FOR INJECTION solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution 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.

pH: 6.0-7.1

Availability:
FLUDARABINE PHOSPHATE FOR INJECTION is supplied as 2 mL per vial of 50 mg fludarabine phosphate, 50 mg of mannitol and 6.60 mg of sodium hydroxide.

FLUDARABINE PHOSPHATE FOR INJECTION is a single use vial.

FLUDARABINE PHOSPHATE FOR INJECTION is supplied in a single vial carton.

FLUDARABINE PHOSPHATE FOR INJECTION uses a latex free stopper.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

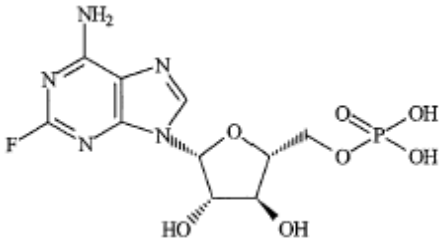
Proper name: Fludarabine Phosphate

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

Molecular formula: $C_{10}H_{13}FN_5O_7P$

Molecular mass: 365.21 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 at 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 days) 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, a 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 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 intraperitoneally 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 mcg/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 of 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 levels 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 mcg/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 mcg/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 mcg/mL of fludarabine phosphate reduced T-cells by 16.7%; 100 mcg/mL reduced T-cells by 42%. The subset of T-cells predominantly affected was T-helper cells, reduced by 53.5% after incubation with 100 mcg/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 3 and Table 4, 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.

Preclinical data in rats demonstrated a transfer of fludarabine phosphate and/or metabolites through the feto-placental barrier (see TOXICOLOGY).

The metabolism, distribution and excretion information is presented in Table 5 located on the following pages.

Lactation

There is evidence from preclinical data after intravenous administration to rats that fludarabine phosphate and/or metabolites transfer from maternal blood to milk. In a peri-/postnatal developmental toxicity study, fludarabine phosphate was intravenously administered to rats during late gestation and the lactation period at dose levels of 1, 10, and 40 mg/kg/day. The

offspring of the high-dose group showed a decrease in body weight gain and viability and a delay in skeletal maturation on day 4 post partum. However, it should be taken into account that the dosing period covered also the late prenatal development.

Table 3: 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**	**Comments**
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 was 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 min ----	142,960.0 9,552.7 ----	3,254.0 68.5 115.5	In dogs, 2F-ara-AMP was 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 was more than 2-fold greater in dogs than in man. The steady-state volume of distribution in man is approximately 70% larger than in dogs. 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 3(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**	**Comments**
Monkey (3 animals)	20	2F-ara-AMP	i.v.	2F-ara-AMP (plasma) 2F-ara-A (plasma) 2F-ara-A (CSF)	56 min 2.5-3.1 h 1.1-1.8h	---- 21.3-35.6h 20.4-29.8h	---- ---- -----	---- ---- ----	2F-ara-A crossed the blood-brain barrier with a lag time of 0.5 to 2.0 hours and accumulated in the CSF. To quantify the metabolites, HPLC was used.
Mouse (BDF$_1$) 25-31 g	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 4: 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}**	**Comments**
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 ΦM 27 ΦM	After separation of nucleotides by HPLC, metabolites were quantified by UV or radioactivity.
Miniature swine (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 Φg/mL (peritoneal fluid) 0.15-0.46 Φg/mL (plasma)	HPLC was used.

C_{max}: maximal concentration
i.p.: intraperitoneal

TABLE 5: METABOLISM, DISTRIBUTION AND EXCRETION OF FLUDARABINE PHOSPHATE

Species	Design	Compound Admin-istered	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 underwent 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. ($\exists$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 5 (Continued): **METABOLISM, DISTRIBUTION AND EXCRETION OF FLUDARABINE PHOSPHATE**

Species	Design	Compound Admin-istered	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 times 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 of DNA accumulated in bone marrow. Peak 2F-ara-ATP concentrations of 23 nmol/μmol of DNA accumulated in the intestinal mucosa. The metabolite 2F-ara-A passed rapidly from ascites to blood in concentrations proportional to the 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 h. 2F-ara-ATP disappeared from bone marrow and intestinal mucosa with a half-life of 1.5 h. 2F-ara-A exhibited a plasma half-life of 3.5 h.	2F-ara-A 2F-ara-ATP

TABLE 5 (Continued): **METABOLISM, DISTRIBUTION AND EXCRETION OF FLUDARABINE PHOSPHATE**

Species	Design	Compound Admin-istered	Dose (mg/m^2)	Metabolism and Distribution	Elimination	Metabolites
Dog (Beagle)	i.v. Administration	2F-ara-AMP	40 500	The dog metabolized a greater % of the compound to 2F-ara-HX than the mouse.	2F-ara-A, 2F-ara-HX, and 2F-A were 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 underwent 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 compared to plasma protein binding was 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 crossed the blood-brain barrier accumulating in the CSF with a lag time of 0.5-2 h.	----	2F-ara-A
Mouse (BDF_1)	i.v. Administration	2F-ara-A	30	42% of radioactivity found in the liver, 20% in spleen, pancreas, and colon, and 15% in the lung and small intestine 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 5 (Continued): METABOLISM, DISTRIBUTION AND EXCRETION OF FLUDARABINE PHOSPHATE

Species	Design	Compound Admin-istered	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 metabolized greater portions of 2F-ara-A with higher levels detected in the serum and urine when compared to mice.	27% of the drug was excreted unchanged in urine at 24 hr. 53% of the drug was excreted as metabolites in urine at 24 hr.	----
Dog (Beagle)	i.v. Administration	2F-ara- A	400	Dogs consistently metabolized greater portions of 2F-ara-A with higher levels detected in the serum and urine when compared to mice.	18% of the drug was excreted unchanged in the urine at 24 hr. 70% of the drug was excreted as metabolites in the urine at 24 hr.	----
Monkey (Rhesus)	i.v. Administration	2F-ara- A	30	----	50% of the drug was excreted unchanged in 24 hr. 26% of the drug was excreted as metabolites at 24 hr.	----
Monkey (Rhesus)	i.v. Administration	2F-ara- A	400	----	58% of the drug was excreted unchanged at 24 hr. 25% of the drug was excreted as metabolites at 24 hr.	----
Rat (Sprague Dawley)	i.v. Administration	^{3}H-2F-ara-AMP	60 (10mg/kg)	After intravenous administration of ^{3}H-2F-ara-AMP to lactating rats, levels of radioactivity in milk was about 30% of that in maternal blood. Thus, 2F-ara-AMP and/or metabolites are transferred into milk.	The half-life of disposition of radioactivity from blood is about 2 h. This is mirrored by the estimated half-life of 3 h calculated for excretion in milk.	----
Rat (Sprague Dawley)	i.v. Administration	^{3}H-2F-ara-AMP	60 (10mg/kg)	^{3}H-2F-ara-AMP and/or metabolites cross the feto-placental barrier and reached levels in fetus similar to as in maternal blood.	No long-lasting retention of the ^{3}H-labelled substances could be observed in fetus and in maternal tissues examined.	----

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 were 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 to 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/L) 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 the University of Texas, San Antonio

Methods

The pharmacokinetic parameters of the principal metabolite of fludarabine phosphate, 2F-ara-A, were determined in 7 adult patients (6 male; 1 female) who received fludarabine phosphate at doses of 18 or 25 mg/m^2/day as a 30-minute intravenous infusion daily for 5 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 the two-compartment open model.

Pharmacokinetic Parameters

Peak plasma concentrations of 2F-ara-A ranged from 0.199 to 0.876 mcg/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 mcg/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 mcg/mL, respectively. There was no drug accumulation during the 5-day treatment period.

The pharmacokinetic parameters derived from this study are presented in Table 6.

Table 6: 2F-ARA-A KINETIC PARAMETERS

Patient	BSA (m^2)	Dose		Duration of Infusion (min)		Peak conc. (mcg/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 SD								9.1 3.8	20.1 10.9	96.2 26.0	37.8 15.4	0.60[d] -	9.24[d]

[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 7, approximately 24% of the parent compound, fludarabine phosphate, was excreted in the urine as 2F-ara-A during the 5-day treatment period.

Table 7: **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	35	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 8, 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 8: 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 5 consecutive days. Ten of the patients were diagnosed as having lymphoma and 9 as having leukemia. In this study, 5 patients received doses of 20 mg/m^2/day, 5 patients received doses of 25 mg/m^2/day, 1 patient received 30 mg/m^2/day, 4 patients received 50 mg/m^2/day, 2 patients received 100 mg/m^2/day, and an additional 2 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 2 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 3 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 nos. 5-12) are presented in Table 9.

Table 9: 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
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 10). 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 10: **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[e]	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
	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 3 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, 1 patient received a dose of 160 mg/m^2, 8 patients received a dose of 120 mg/m^2, 4 patients received 100 mg/m^2, and an additional 6 patients received 80 mg/m^2. Plasma concentrations of fludarabine phosphate could not be detected 5 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 a 3-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 11. 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 ($Vd_{ss}/C1_T$) was 10.4 hours and total body clearance ($C1_T$) ranged from 26.5 to 120.4 mL/min/m^2 with a mean of 68.98 mL/min/m^2.

Table 11: **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)	$C1_T$ (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

MRT: mean residence time
C.V.: coefficient of variation

Table 12: **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 12. 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 the drug from the deep tissue compartment to be the rate-determining step in the elimination of 2F-ara-A from the body. Table 13 lists the microscopic rate constants for the first 9 patients studied.

Table 13: 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
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 #0.011). A positive correlation of Cl_T, with hemoglobin and hematocrit was observed (p#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. Table 14 and Table 15 list the correlation coefficients and *p* values for the above correlations.

Table 14: **CORRELATION OF 2F-ARA-A PHARMACOKINETIC PARAMETERS WITH CREATININE CLEARANCE AND SERUM CREATININE**

	Pharmacokinetic Parameter	Correlation Coefficient (r)[a]	P Value	N
Creatinine	Cl_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	Cl_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 15: 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 9 patients enrolled in the study showed good agreement with the corresponding severity of neutropenia developed by each patient (Table 16). Thus, the capacity of the compound to depress hematopoiesis appears to be dose-related.

Table 16: 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 17 and Table 18), long-term toxicity (Table 19), mutagenicity (Table 20), and reproductive studies (Table 21) is presented in the following pages.

The results from intravenous embryotoxicity studies in rats and rabbits indicated an embryolethal and teratogenic potential of fludarabine phosphate as manifested in skeletal malformations, fetal weight loss, and postimplantation loss.

In view of the small safety margin between teratogenic doses in animals and the human therapeutic dose, as well as in analogy to other antimetabolites which are assumed to interfere with the process of differentiation, the therapeutic use of FLUDARABINE PHOSPHATE FOR INJECTION is associated with a relevant risk of teratogenic effects in humans (see section WARNINGS AND PRECAUTIONS).

Table 17: 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 No. 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 StudyNo. 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 17 (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 No. 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 No. 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 18: 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 No. 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 No. SIB 6101.5	Dog (Beagle) Age: 8-10 months Wt.: 7.0-11.6 kg	20 (I0 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 No. 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 19: 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 No. 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 the 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 No. 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 20: MUTAGENICITY STUDIES

Study Type	System Used	Concentration Range	Results
Ames Mutagenesis Assay Study No. 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 No. TBT03-010	Chinese hamster ovary cells (CHO)	Non-activated Assay: 10; 15; 30; 50; 100; 150; 300; 500 mcg/mL Activated Assay: 50; 125; 250; 500; 1,000; 1,500; 2,000; 2,500 mcg/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 mcg/mL with higher concentrations precluded from analysis due to cellular toxicity. Concentrations of 15 and 30 mcg/mL did not cause statistically significant increases in SCEs. Activated Assay Concentrations of 500 and 1,000 mcg/mL caused significant increases in SCEs per cell. Concentrations of 125 and 250 mcg/mL did not increase SCEs per cell. Concentrations higher than 1,000 mcg/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 20 (Continued): MUTAGENICITY STUDIES

Study Type	System Used	Concentration Range	Results
CHO/HGPRT Mammalian Cell Mutagenesis Assay Study No. TBT03-012	Chinese hamster ovary cells (CHO)	Non-activated Assay: 0.3; 1; 3; 10; 30; 100; 300; 500 mcg/mL Activated Assay: 3; 10; 30; 100; 300; 1,000; 1,500; 2,000; 2,500 mcg/mL	Non-activated Assay At concentrations of 1 to 300 mcg/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 mcg/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 to 1,000 mcg/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 no. TBT03-011	Chinese hamster ovary cells (CHO)	Non-activated Assay: 2.6, 4.5, 9, 13, 26,45, 90, 130,260 mcg/mL Activated Assay: 30, 50, 100, 150, 300, 500, 1000, 1500, 2000 mcg/mL	Non-activated Assay The concentrations of fludarabine phosphate analyzed, 9, 26, and 90 mcg/mL, did not increase the percentage of aberrant cells (both excluding and including gaps). Concentrations of 130 and 260 mcg/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 mcg/mL. No significant increases in aberrant cells were noted at the other two concentrations analyzed, 150 and 500 mcg/mL. Fludarabine phosphate has been demonstrated to increase chromosome aberrations under activated conditions but did not increase chromosome aberrations under non-activated conditions in this assay.

Table 20 (Continued): MUTAGENICITY STUDIES

Study Type	System Used	Concentration Range	Results
Mouse Micronucleus Test Study No. 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 erythrocyte (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 no. 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 a complete spermatogenic maturation. No biologically relevant positive response for any of the parameters evaluated (number of total implantations 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 21: 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 no. 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 no. 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 No Observable Adverse Effect Level (NOAEL).

Table 21(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 No. 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 No. 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.

Table 21(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
Reproduction Toxicity (Peri-/Postnatal Study) Intravenous injection (gestation day 15 to day 21 post partum)	Rat (Jcl: Sprague Dawley)	96 females	0 1 10 40	Following daily IV administration during late gestation and the lactation period, fludarabine phosphate was well tolerated at dose levels of 1 and 10 mg/kg/d with no relevant changes observed in dams or offspring. Signs of maternal toxicity (decreased body weight gain and food consumption, soft feces/diarrhea and piloerection) occurred in the 40 mg/kg/d group. The offspring of the high dose group showed a decreased viability index on day 4 post partum, a decreased weaning index and a reduced body weight gain. The skeletal maturation was delayed (reduced ossification of phalanges and vertebrae) in pups of the high dose group sacrificed on day 4 post partum. In postnatal behavioural and learning tests, no drug related effects were observed. No relevant changes in the incidence of external and internal malformations in F2 fetuses were observed. The general toxicological no-effect dose level in this peri-/postnatal reproduction toxicity study was estimated to be 10 mg/kg/d.

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PART III: CONSUMER INFORMATION

[Pr]FLUDARABINE PHOSPHATE FOR INJECTION
(Fludarabine Phosphate)
Sterile Solution for Injection
25 mg/mL
(2 mL per vial)

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

Please read this leaflet carefully before you start using FLUDARABINE PHOSPHATE FOR INJECTION. Keep this leaflet. You may need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:
FLUDARABINE PHOSPHATE FOR INJECTION is an anticancer drug. It can be given by slow infusion (with a drip) into the veins (intravenously).

FLUDARABINE PHOSPHATE FOR INJECTION is used as a second line treatment in patients with chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin's lymphoma (Lg-NHL) who have failed other conventional treatments.

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. FLUDARABINE PHOSPHATE FOR INJECTION works by hindering the production of new DNA. Therefore, when the cells take up FLUDARABINE PHOSPHATE FOR INJECTION, it stops the growth of new 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 FLUDARABINE PHOSPHATE FOR INJECTION if any of the following apply to you:

- Allergy (hypersensitivity) to any of the ingredients of this medication
- Kidney function is severely reduced
- Low red blood cell count because of a certain type of anemia (hemolytic anemia). Your doctor will have told you if you have this condition.

FLUDARABINE PHOSPHATE FOR INJECTION 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.

What dosage forms it comes in:
FLUDARABINE PHOSPHATE FOR INJECTION 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

FLUDARABINE PHOSPHATE FOR INJECTION should be prescribed by a doctor experienced with the use of anticancer drugs.

The following are possible serious side effects:

- Decreased production of the blood cells by the bone marrow (bone marrow suppression). The protection against infections, the ability of blood cells to carry oxygen, or blood clotting can be affected. It may result in death.
- Central nervous system problems including blindness, coma, and death at doses four times greater than the recommended dose for CLL. This has been rarely reported at the recommended dose for CLL.
- Low red blood cell count due to a breakdown of red blood cells (hemolytic anemia) may result in death.
- Lung toxicity resulting in death when used in combination with pentostatin (deoxycoformycin).

BEFORE you use FLUDARABINE PHOSPHATE FOR INJECTION talk to your doctor if you:

- have a low red blood cell count
- are not feeling very well
- have kidney problems
- have liver problems

- are over 75 years old
- have herpes zoster (shingles)
- need a blood transfusion
- are pregnant or intend to become pregnant. FLUDARABINE PHOSPHATE FOR INJECTION may harm an unborn child
- are breast feeding
- need any vaccinations. Live vaccine should be avoided during and after treatment with FLUDARABINE PHOSPHATE FOR INJECTION
- have had a skin cancer. The worsening or flare-up of pre-existing skin cancer lesions, as well as new onset of skin cancer, has been reported in patients during or after FLUDARABINE PHOSPHATE FOR INJECTION therapy
- have a disease associated with decreased immune function.

FLUDARABINE PHOSPHATE FOR INJECTION can harm an unborn baby. FLUDARABINE PHOSPHATE FOR INJECTION should not be used during pregnancy unless clearly necessary. If you are pregnant, it is important to discuss with your doctor prior to starting FLUDARABINE PHOSPHATE FOR INJECTION 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. Women should avoid becoming pregnant while on FLUDARABINE PHOSPHATE FOR INJECTION therapy.

When cancer cells are destroyed they release waste products into the blood. In some cases, FLUDARABINE PHOSPHATE FOR INJECTION may cause a rapid breakdown of cancer cells making it difficult for your body to get rid of these waste products. This may cause nausea and vomiting, joint pain, kidney failure, and heart problems. Your physician may give you medications to stop this from happening.

Encephalopathy is a disease of the brain. It can occur during treatment or up to 4 or more years after FLUDARABINE PHOSPHATE FOR INJECTION has been stopped. It can be irreversible, life-threatening, or cause death.

When you take FLUDARABINE PHOSPHATE FOR INJECTION, encephalopathy can occur:

- At the recommended dose. It happens most commonly,
  - o when given with other drugs known to cause encephalopathy
  - o When you have:
    - Head or total body radiation therapy
    - Hematopoietic Stem Cell transplantation
    - Graft versus host disease
    - Kidney disease
- At higher than recommended doses.

FLUDARABINE PHOSPHATE FOR INJECTION may reduce the ability to drive or use machines, since e.g., fatigue, weakness, visual disturbances, confusion, agitation and seizures have been observed. Do not drive or operate machinery if FLUDARABINE PHOSPHATE FOR INJECTION affects your alertness and your vision.

INTERACTIONS WITH THIS MEDICATION

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

The effectiveness of FLUDARABINE PHOSPHATE FOR INJECTION may be reduced by medications containing dipyridamole and similar substances.

Tell your doctor if you are taking cytarabine.

If you are taking any other medicines regularly, tell your doctor.

PROPER USE OF THIS MEDICATION

Usual dose:

FLUDARABINE PHOSPHATE FOR INJECTION should be administered by a qualified physician experienced in the use of anticancer 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 once a day for 5 consecutive days.

This five day course of treatment will normally be repeated every 28 days. Usually six 28-day cycles are required.

Overdose:

If you take more FLUDARABINE PHOSPHATE FOR INJECTION than you should, talk to your doctor, nurse, pharmacist, or call your local poison control centre right away.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, ask your doctor how to continue with the treatment. Do not take a double dose**.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects have been reported very commonly:

- decreased production of the blood cells by the bone marrow (bone marrow suppression) which may cause:
  - -increased risk of serious infections such as pneumonia or viral infections (like latent viral reactivation, e.g., Herpes zoster virus, Epstein-Barr-virus, Progressive multifocal leucoencephalopathy)
  - -anemia (reduced number of red blood cells)
  - -abnormal bleeding or bruising
- fever
- feeling tired
- feeling weak
- cough
- nausea
- vomiting
- diarrhea

The following side effects have been reported commonly:

- loss of appetite
- numb or weak limbs
- visual problems (blurred vision)
- inflammation or sores of the mouth, lips and digestive track
- skin rash
- generally feeling unwell
- chills
- build-up of fluid in the body (edema)

Prolonged vomiting, diarrhea, or mouth sores may limit your fluid intake. This can make you prone to dehydration.

Contact your doctor if these symptoms persist for 24 hours.

The following side effects have been reported uncommonly:

- bleeding in the digestive system
- confusion
- pulmonary injury, with symptoms such as difficulty breathing and shortness of breath
- pain in your side, blood in your urine, or a reduced amount of urine
- red or purple discolourations on the skin caused by bleeding underneath the skin

The following side effects have been reported rarely:

- coma
- seizures
- agitation
- blindness
- pain in the eye
- heart failure
- irregular heartbeat
- inflammation of the bladder
- skin and/or mucous membrane reaction with redness, inflammation, blistering and erosion (e.g. Stevens-Johnson syndrome, Lyell's syndrome or toxic epidermal necrosis)
- skin cancer
- Epstein-Barr virus associated lymphoproliferative disorder (disorders of the lymph system due to a viral infection)

The following side effects for which frequency is unknown:

- bleeding (hemorrhage) including the following:
  - bleeding from a ruptured blood vessel in the brain (cerebral hemorrhage),
  - lung bleeding (pulmonary hemorrhage),
  - eye bleeding (includes retinal hemorrhage)

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 call your doctor or pharmacist
		Only if severe	In all cases	
Common	Vomiting, diarrhea (24 hours)/ dehydration		T	
	Cough, trouble breathing, fever/ pneumonia		T	
	Fever, chills, feeling unwell, pain/ infection		T	
	Numb or weak limbs/ motor disturbances		T	
	Blurred vision/ changes in vision		T	

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
Uncommon	Difficulty breathing, rash, itching/ allergic reaction			T
	Pain in your side, blood in your urine/ infection		T	
	Tar-coloured or bloody stool/ bleeding in the digestive system		T	
	Chest pain/ heart failure, irregular heartbeat		T	
	Extreme fatigue, unusual bruising, excessive bleeding after injury/ reduction in blood cell production by the bone marrow		T	
	Yellowing of the skin or eyes and/or red-brown urine/ rapid breakdown of red blood cells (also called hemolytic anemia)		T	
	Confusion/ severe central nervous system effects		T	
	Loss of hearing		T	
Rare	Coma, seizures, agitation/ severe central nervous system effects		T	
	Red and flaky skin/ severe skin disorder			T
	Pain in your eyes, blindness		T	

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
Unknown frequency	Headache with nausea and vomiting, seizure, visual disturbances (vision loss), confusion, muscle spasm, drowsiness			T

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

HOW TO STORE IT

Store all drugs properly. Keep out of the reach and sight of children and pets.

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

Store FLUDARABINE PHOSPHATE FOR INJECTION under refrigeration between 2°C and 8°C. Do not freeze. Discard unused portion.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Report online at MedEffect (www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labelsand the Consumer Side Effect Reporting Form are available at MedEffect™ (www.healthcanada.gc.ca/medeffect).

NOTE:Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited:
at: 1-800-268-4127 ext. 1255005 (**English**)
or 1-877-777-9117 (**French**)
or druginfo@tevacanadacom

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Last revised: March 1, 2016