PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrFLUDARABINE PHOSPHATE FOR INJECTION

Solution, 25 mg/mL (2 mL per vial), Intravenous

Teva Standard

Antineoplastic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

Date of Initial Authorization:
FEB 07, 2014

Date of Revision:
MAY 23, 2025

Submission Control Number: 294245

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECATIONS, Reproductive Health: Female and Male Potential	05/2025
7 WARNINGS AND PRECAUTIONS, 7.1.1 PREGNANT WOMEN	05/2025
7 WARNINGS AND PRECAUTIONS, 7.1.2 BREAST-FEEDING	05/2025

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLUDARABINE PHOSPHATE FOR INJECTION (fludarabine phosphate) 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.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

2 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 6 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 7 WARNINGS AND PRECAUTIONS - Hematologic)** • **Irreversible CNS effects, including fatal cases (see 7 WARNINGS AND PRECAUTIONS - Neurologic)** • **Auto-immune hemolytic anemia, including fatal cases (see 7 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.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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 treatment is contraindicated if creatinine clearance is <30 mL/min. (See 7 WARNINGS AND PRECAUTIONS)

Incompatibilities:

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

4.2 Recommended Dose and Dosage Adjustment

The usual starting dose of FLUDARABINE PHOSPHATE FOR INJECTION 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. Health Canada has not authorized an indication for pediatric use

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.

4.4 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.

5 OVERDOSAGE

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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada’s toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous	Solution/ 25 mg/mL	Mannitol and sodium hydroxide

FLUDARABINE PHOSPHATE FOR INJECTION is supplied as a 2 mL single use vial containing 50 mg of fludarabine phosphate, 50 mg of mannitol, and 6.6 mg of sodium hydroxide. Packaged in a single vial carton. The stopper is not made with natural rubber latex.

pH

6.0-7.1

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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 7 WARNINGS AND PRECAUTIONS - Skin).

Driving and Operating Machinery

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.

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 8 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 (eg, 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.

Monitoring and Laboratory Tests

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

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.

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 postmarketing 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 (≥ 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 4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential

Preclinical toxicology studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. The possible adverse effects on fertility in males and females in humans have not been adequately evaluated. Therefore, it is recommended that females of child-bearing potential take contraceptive measures during FLUDARABINE PHOSPHATE FOR INJECTION therapy and for at least 6 months after the cessation of FLUDARABINE PHOSPHATE FOR INJECTION therapy. Sexually active male patients must use effective methods of contraception and be advised to not father a child while receiving FLUDARABINE PHOSPHATE FOR INJECTION, and for at least 6 months following completion of treatment. Male patients taking FLUDARABINE PHOSPHATE FOR INJECTION should inform their female sexual partners of FLUDARABINE PHOSPHATE FOR INJECTION use and the potential serious risks to a developing fetus if pregnancy occurs during the treatment period. Prior to FLUDARABINE PHOSPHATE FOR INJECTION treatment, patients must seek advice on fertility preservation options. After FLUDARABINE PHOSPHATE FOR INJECTION treatment, patients planning pregnancy are advised to seek genetic counselling. [1]

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.

Teratogenic Risk:

Fludarabine phosphate may increase the risk of genetic defects or fetal malformations. Consequently, fludarabine phosphate must not be used during pregnancy.

7.1 Special Populations

7.1.1 Pregnant Women

Fludarabine phosphate has been shown to be genotoxic. Fludarabine phosphate has also been shown to be both embryotoxic, fetotoxic and teratogenic in rabbits and rats (see 16 NON-CLINICAL TOXICOLOGY). FLUDARABINE PHOSPHATE FOR INJECTION may cause fetal harm when administered to pregnant females. Therefore, FLUDARABINE PHOSPHATE FOR INJECTION must not be used during pregnancy.

Females of childbearing potential receiving FLUDARABINE PHOSPHATE FOR INJECTION should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.[1] (see 16 NON-CLINICAL TOXICOLOGY)

Due to the genotoxic risk of fludarabine phosphate, women of childbearing potential must take effective contraceptive measures during and at least for 6 months after cessation of therapy. If the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus. Male patients must use effective methods of contraception and be advised to not father a child while receiving FLUDARABINE PHOSPHATE FOR INJECTION, and for 6 months following completion of treatment.

---

[1]Safety evaluation report fludarabine and pregnancy/lactation exposure with associated adverse outcomes, Prashant Kathuria, MD, Date: 08-Jun-2022

7.1.2 Breast-feeding

It is not known whether fludarabine phosphate is excreted in human milk. Breastfeeding must not be initiated during FLUDARABINE PHOSPHATE FOR INJECTION treatment. Because of the potential for adverse reactions in nursing infants, breast feeding must be discontinued for the duration of FLUDARABINE PHOSPHATE FOR INJECTION therapy.

There is evidence from preclinical data that after intravenous administration to rats that fludarabine phosphate and/or metabolites transfer from maternal blood to milk.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 (incl. 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,	

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
			metabolic acidosis, hematuria, urate crystalluria, hyperuricemia, hyperphosphatemia, hypocalcemia)	
Nervous system disorders		Neuropathy peripheral	Confusion	Agitation, seizures, coma
Eye disorders		Visual disturbance		Optic neuritis, optic 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		

8.5 Post-Market Adverse Reactions

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, trilineage 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 7 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

9 DRUG INTERACTIONS

9.1 Serious 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.

9.2 Drug Interactions Overview

Interactions with drugs have not been established.

9.3 Drug-Behavioural Interactions

Interactions with behaviours have not been established.

9.4 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 ε, 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.

10.3 Pharmacokinetics

Table 3 - Summary of Fludarabine phosphate Pharmacokinetic Parameters in cancer patients

Single dose mean	C_{max}	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$	CL	Vss
25 mg 2F-ara-AMP/m²	3.5 – 3.7 mcM	0.5	20	----	79 mL/min/m²	83 L/m²

Cellular Pharmacokinetics of Fludarabine Triphosphate

Maximum 2F-ara-ATP levels in leukemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited considerable variation with a median peak concentration of approximately 20 µM. 2F-ara-ATP levels in leukemic cells were always considerably higher than maximum 2F-ara-A levels in the plasma, indicating an accumulation at the target sites. *In vitro* incubation of leukemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and duration of incubation) and intracellular 2F-ara-A enrichment. Two independent investigations respectively reported median half-life values of 15 and 23 hours for the elimination of 2F-ara-ATP from target cells.

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

Plasma and Urinary Pharmacokinetics of Fludarabine (2F-ara-A)

Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2F-ara-A, within minutes after intravenous infusion. Consequently, clinical pharmacology studies have focused on 2F-ara-A pharmacokinetics. After single doses of 25 mg 2F-ara-AMP/m^2 to cancer patients infused over 30 minutes, 2F-ara-A reached mean maximum concentrations in the plasma of 3.5 - 3.7 µM at the end of infusion. Corresponding 2F-ara-A levels after the fifth dose showed a moderate accumulation with mean maximum levels of 4.4 - 4.8 µM at the end of infusion. During a 5-day treatment cycle, 2F-ara-A plasma trough levels increased by a factor of about 2. Accumulation of 2F-ara-A over several treatment cycles does not occur. Post maximum levels decayed in three disposition phases with an initial half-life of approximately 5 minutes, an intermediate half-life of 1-2 hours and a terminal half-life of approximately 20 hours.

An interstudy comparison of 2F-ara-A pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 mL/min/m^2 (2.2 mL/min/kg) and a mean volume of distribution (V_{ss}) of 83 L/m^2 (2.4 L/kg). The data showed a high interindividual variability. After IV 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.

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 IV 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.

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 in 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 ($t_{½γ}$) of 8 to 10 hours. However, when the sampling duration is increased to 72 hours, the additional time points give a calculated $t_{½γ}$ 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 4.

Table 4 - 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/m²	mg	Day 1	Day 5	Day 1	Day 5	Plasma	Tissue	Vd_{ss}	Vd	α	β
1	1.57	18	27	32	30	0.285	0.285	13.43	28.3	115.4	48.6	0.59	7.0
2[a]	1.74	18	31	25	30	0.199	0.377	1.51	28.1	1629.9	75.3	1.69	787.5
3	1.62	18	29	38	30	0.693	0.856	4.35	19.8	59.8	16.1	0.37	10.7
4	1.90	25	48	30	30	0.876	0.611[b]	10.38	23.8	91.9	22.9	0.39	7.8
5	1.94	25	48	35	30	0.509	0.550	8.30	5.1	86.4	46.8	1.99	10.6
6	1.74	25	43	33	30	0.550	--[c]	5.28	9.9	88.6	37.0	1.26	13.9
7	2.06	25	51	30	30	0.336	0.458[b]	12.71	33.8	135.2	55.2	0.59	8.44
Mean								9.1	20.01	96.2	37.8	0.60[d]	9.24[d]
SD								3.8	10.9	26.0	15.4	-	-

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

The mean central compartment volume of distribution (Vd) was 37.8 L/m² with a mean steady-state volume of distribution (Vd_{ss}) of 96.2 L/m². The mean tissue clearance was 20.1 L/h/m² and the mean plasma clearance was 9.1 L/h/m². Plasma concentrations declined bi-exponentially with a harmonic mean initial half-life ($t_{½α}$) of 0.6 hours and a harmonic mean terminal half-life ($t_{½β}$) of 9.2 hours. As presented in Table 5, approximately 24% of the parent compound, fludarabine phosphate, was excreted in the urine as 2F-ara-A during the 5-day treatment period.

Table 5 - Urinary Excretion of 2F-ara-A

Patient	% Dose in Urine						Creatinine Clearance (mL/min.)
	Day 1	Day 2	Day 3	Day 4	Day 5	5-Day Average	

1	14	25	31	7	53	26	76
2	72	16	19	14	9	25	73
3	28	29	29	24	7	24	37
4	25	12	20	38	-	24	77
5	20	20	14	20	13	17	59
6	14	23	27	18	35	23	50
7	17	25	35	45	8	26	73
Mean	27	21	25	24	21	24	63
SD	21	6	7	13	19	3	15

Correlation of Pharmacokinetic Parameters with Clinical Parameters

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

Table 6 - Comparison of AUC with Absolute Granulocyte Nadir and Creatinine Clearance

Patient	Dose (mg/m² 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/m²/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/m² and the mean tissue clearance was 20.1 L/h/m². The mean Vd_{ss} was 96.2 L/m², 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 ($t_{½α}$) of 1.41 hours and a median terminal half-life ($t_{½β}$) of approximately 8 hours. Plasma pharmacokinetic parameters for patients with relapsed leukemia (N=8, patient nos. 5-12) are presented in Table 7.

Table 7 - Pharmacological Characteristics for 2F-Ara-A in the Plasma of Patients with Relapsed Leukemia

Patient		Fludarabine Phosphate Dose (mg/m^2)	2F-ara-A Parameters		
			$t_{½α}$[a] (h)	$t_{½β}$[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 $t_{½β}$

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/m², 50 mg/m², and 100 or 125 mg/m²), a clear dose-dependence emerged (Table 8). Cellular elimination was not dose-dependent, with a half-life of approximately 15 hours at all dose levels. There was a strong correlation between the 2F-ara-ATP levels in leukemic cells obtained from peripheral blood and those found in bone marrow (r=0.84, *P*=0.01), suggesting that there were no pharmacological barriers in the bone marrow. Those patients with bone marrow involvement had the highest 2F-ara-ATP levels. In addition, intracellular 2F-ara-ATP levels in circulating leukemic cells at 12-14 hours after fludarabine phosphate infusion were inversely related to the DNA synthetic capacity of the cells relative to pretreatment. DNA synthesis remained maximally inhibited (>80%) until cellular concentrations of 2F-ara-ATP fell below 90 µM.

Table 8 - Pharmacological Characteristics of 2F-ara-ATP in Circulating Leukemic Cells

Patient	Diagnosis	Fludarabine Phosphate Dose (mg/m²)	2F-ara-ATP Parameters		
			Peak (mcM)	t½[a](h)	AUC[b](mcM·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 IV 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 9. This metabolite exhibited a very short initial half-life (mean $t_{½α}$) of 5.42 minutes, followed by an intermediate half-life (mean $t_{½β}$) of 1.38 hours and a terminal half-life (mean $t_{½γ}$) 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}/Cl_T) was 10.4 hours and total body clearance (Cl_T) ranged from 26.5 to 120.4 mL/min/m^2 with a mean of 68.98 mL/min/m^2.

Table 9 - 2F-ara-A Harmonic Mean Half-lives, Mean Residence Time, and Total Body Clearance in Patients

Dose (mg/m^2)	No. of Patients	$t_{½α}$ (min)	$t_{½β}$ (hour)	$t_{½γ}$ (hour)	MRT (hour)	Cl_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**
CV (%)	-	-	-	-	-	33.7

MRT: mean residence time
CV: coefficient of variation

Table 10 - 2F-ara-A Mean Volume Pharmacokinetic Parameters

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

The mean volume parameters for each dosage level are shown in Table 10. The central compartment volume of distribution was approximately 20% of body weight (V_1 = 7.30 L/m^2). The steady-state volume of distribution indicated significant binding of the drug to tissue components (Vd_{ss} = 44.22 L/m^2). The smallest of the microscopic rate constants was k_{31}, indicating release of the drug from the deep tissue compartment to be the rate-determining step in the elimination of 2F-ara-A from the body. Table 11 lists the microscopic rate constants for the first 9 patients studied.

Table 11 - 2F-ara-A Microscopic Rate Constants (N=9)

Patient	Dose (mg/m^2)	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{13} (min^{-1})	k_{31} (min^{-1})	k_{10} (min^{-1})
W.Y.	260	0.0402	0.0341	0.00650	0.00333	0.00786
R.E.	260	0.0940	0.0418	0.00375	0.00176	0.01644
H.W.	260	0.0470	0.0360	0.00588	0.00268	0.00632
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**
CV (%)		45.6	18.9	43.7	25.4	47.6

Correlation of Pharmacokinetic Parameters with Clinical Parameters

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

Table 12 - Correlation of 2F-ara-A Pharmacokinetic Parameters with Creatinine Clearance and Serum Creatinine

	Pharmacokinetic Parameter	Correlation Coefficient (*r*)[a]	*P* Value	N
Creatinine	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 13 - Correlation of 2F-ara-A Pharmacokinetic Parameters with Other Clinical Parameters

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

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

A rank ordering of the areas under the plasma concentration-time curve (AUC) for the first 9 patients enrolled in the study showed good agreement with the corresponding severity of neutropenia developed by each patient (Table 14). Thus, the capacity of the compound to depress hematopoiesis appears to be dose-related.

Table 14 - Areas Under the Plasma Concentration-Time Curve and Neutropenia Grade

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

11 STORAGE, STABILITY AND DISPOSAL

Store FLUDARABINE PHOSPHATE FOR INJECTION under refrigeration between 2°C and 8°C. 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.

12 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

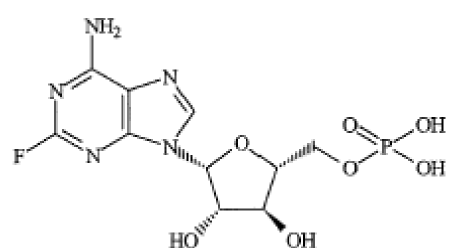
Drug Substance

Proper name: Fludarabine Phosphate

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

Molecular formula & Molecular mass: $C_{10}H_{13}FN_5O_7P$; 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, pH value of 2.0 (9mg/mL in water) and melts with decomposition at 195°C -202°C.

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

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 15 - Summary of patient demographics for clinical trials in Second-line treatment in patients with chronic lymphocytic leukemia (CLL) who have failed other conventional therapies

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
1 (MDACC)	single-arm open- label	22-40 mg/m^2 daily for 5 days every 28 days	48 patients	NA	NA
2 (SWOG)	single-arm open- label	15-25 mg/m^2 for 5 days every 28 days	31 patients	NA	NA

Two single-arm open-label studies of fludarabine phosphate have been conducted in patients with CLL refractory to at least 1 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.

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.

14.2 Study Results

Table 16 - Results of study for clinical trials in Second-line treatment in patients with chronic lymphocytic leukemia (CLL) who have failed other conventional therapies

STUDY	MDACC	SWOG
Primary End Points	Results	
Overall objective response rates	48%	32%

Complete Response Rate	13%	13%
Partial Response Rate	35%	19%
Median Time to Response	7 weeks (1 - 68 weeks)	21 weeks (1 - 53 weeks)
Median duration of disease control	91 weeks	65 weeks
Median survival of all refractory CLL patients treated with fludarabine phosphate	43 weeks	52 weeks
Normalized lymphocyte count, one measure of disease regression, occurred at a median of 2 weeks (complete responders), 2 weeks (partial responders) and 22 weeks (nonresponders).		
Rai stage improvement	58% (to stage II or better in 7 of 12 MDACC responders)	71% 5 of 7 SWOG responders who were stage III or IV at baseline
Associated value and statistical significance for Drug at specific dosages	NA	
Associated value and statistical significance for Placebo or active control	NA	

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 pretreated 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 (nonresponders).

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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL 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 is associated with a relevant risk of teratogenic effects in humans (see 7 WARNINGS AND PRECAUTIONS).

Table 17 – Acute Toxicity Studies – Mouse

Study Type/ Route of Administration	Animal Information	Number 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 Study No. 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	Dose-related decrease in motor activity (reversible in survivors) and death. Lethal dose estimates (mg/kg/day) were: LD_{10} / LD_{50} / LD_{90}

Study Type/ Route of Administration	Animal Information	Number of Animals	Dosage (mg/kg/day)	Results
			1,070 1,358 No treatment	M 404.6 593.3 870.0 F 355.4 496.8 694.5 M & F 372.5 542.7 790.7
Single dose toxicity Intravenous injection Study No. SIB 6101.7	Mouse (CD2F1) 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 (CD2F1) 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	Number 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 (10 males, 10 females)	13.1[a] 131.2[b] 262.4[c] 393.6[d] 524.8[e]	Dose-dependent signs of toxicity included changes in clinical status and adverse effects on the hematopoietic, gastrointestinal, renal and hepatic systems. In addition, male dogs receiving 4 x $MELD_{10}$ had pancreatic and reproductive toxicity and were sacrificed moribund. The 1/10 $MELD_{10}$ and $MELD_{10}$ doses were considered safe, as effects seen were minimal and readily reversible.
Five daily dose toxicity Intravenous injection Study Nos. SIB 6101.6 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.

Study Type/ Route of Administration	Animal Information	No. of Animals	Dosage (mg/kg/day)	Results
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 nonactivated assays: 0.0015; 0.005; 0.015; 0.05; 0.15; 0.5 mg/plate	Nonactivated 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 nonmutagenic to *S. typhimurium* strains tested, under both activated and nonactivated conditions.
Sister chromatid exchange assay Study No. TBT03-010	Chinese hamster ovary cells (CHO)	Nonactivated 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	Nonactivated 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 nonactivated assay conditions.

Study Type	System Used	Concentration Range	Results
CHO/HGPRT Mammalian cell mutagenesis assay Study No. TBT03-012	Chinese hamster ovary cells (CHO)	<u>Nonactivated assay</u>: 0.3; 1; 3; 10; 30; 100; 300; 500 mcg/mL <u>Activated assay</u>: 3;10; 30; 100; 300; 1,000; 1,500; 2,000; 2,500 mcg/mL	<u>Nonactivated assay</u> At concentrations of 1 to 300 mcg/mL, fludarabine phosphate was nonmutagenic 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. <u>Activated assay</u> 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 nonmutagenic under both nonactivated and activated conditions in the CHO/HGPRT system.
Chromosome aberration assay Study No. TBT03-011	Chinese hamster ovary cells (CHO)	<u>Nonactivated assay</u>: 2.6, 4.5, 9, 13, 26, 45, 90, 130, 260 mcg/mL <u>Activated assay</u>: 30, 50, 100, 150, 300, 500, 1000, 1500, 2000 mcg/mL	<u>Nonactivated assay</u> 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. <u>Activated assay</u> 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 nonactivated conditions in this assay.

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. Postimplantation 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).

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. Postimplantation 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. Postimplantation 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)

Study Type/ Route of Administration	Animal Information	No. of Animals	Dosage (mg/kg/day)	Results
				for maternal toxicity but equivocal for fetal developmental toxicity because of the appearance of a single fetus with diaphragmatic hernia at this dose level.
Reproduction Toxicity (Peri-/Postnatal Study) Intravenous injection (gestation day 15 to day 21 post partum)	Rat (Jcl:Sprague Dawley)	96 female s	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.

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 nontoxic 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 IV, 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 nontoxic 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 IV treatment on day 1 produced a maximum ILS of 28%.

The intraperitoneally (IP) implanted L1210 leukemia was less sensitive to fludarabine phosphate when the drug was given either intravenously (IV) or orally compared to IP administration. A maximal ILS value of 122% was produced following IP administration of 266 mg/kg on days 1-5. This same dose given by IV administration on days 1-5 produced an ILS value of 95%. However, with both IP and IV 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 IP 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 (IP) implanted murine L1210 leukemia and the human LX-1 lung tumor xenograft. The drug has shown moderate activity against the murine subcutaneously (SC) implanted CD8F1 mammary epithelioma and the IP implanted P388 lymphocytic leukemia. Fludarabine phosphate was not active against the IP implanted B16 melanoma, the SC implanted colon tumor or the intravenously (IV) 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 LD63 of
0.51 mcg/mL for normal human granulocyte-macrophage colony-forming units in culture (GM-CFUC). In the tumor sensitivity assay, fludarabine phosphate demonstrated an LD40 and LD78 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.

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 mcM 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 bicompartmental 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 22 and

Table 23, 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 16 NON-CLINICAL TOXICOLOGY).

The metabolism, distribution and excretion information is presented in Table 24 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 22 – Pharmacokinetic Parameters of Fludarabine Phosphate and 2F-ARA-A

Study Details				Results					
Species	**Dose of Test Article (mg/m^2)**		**Route of Admin.**	**Metabolite**	$t_{1/2\alpha}$	$t_{1/2\beta}$	**Vd (mL)**	**Clearance mL/min**	**Comments**
Mouse (BDF1) 18-25 g	40 500	2F-ara-AMP 2F-ara-AMP	IV IV	2F-ara-AMP 2F-ara-A 2F-ara-AMP 2F-ara-A	0.7 min 31.1 min 2.5 min 35.7 min	21.2 min 113.9 min 26.9 min 184.9 min	73.4 60.6 309.1 88.0	2.40 0.37 7.97 0.33	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.
Dog (Beagle) 7.8-10.8 kg	40 500	2F-ara-AMP 2F-ara-AMP	IV IV	2F-ara-AMP 2F-ara-A 2F-ara-HX 2F-ara-AMP 2F-ara-A 2F-ara-HX	5.3 min 15.7 min 113.5 min 9.2 min 4.6 min 112.5 min	30.5 min 96.6 min ---- 51.5 min 90.3 min ----	142,960.0 9,552.7 ---- 196,520.0 7,243.5 ----	3,254.0 68.5 115.5 2,646.0 55.6 111.2	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.
Dog (Beagle) 2 dogs	260	2F-ara-AMP	IV	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.

Study Details				Results					
Species	Dose of Test Article (mg/m²)		Route of Admin.	Metabolite	$t_{½\alpha}$	$t_{½\beta}$	Vd (mL)	Clearance mL/min	Comments
Monkey (3 animals)	20	2F-ara-AMP	IV	2F-ara-AMP (plasma) 2F-ara-A (plasma) 2F-ara-A (CSF)	56 min 2.5-3.1 h 1.1-1.8 h	---- 21.3-35.6 h 20.4-29.8 h	---- ---- ----	---- ---- ----	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 (BDF1) 25-31 g	30	2F-ara-A	IV	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	IV IV	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	IV IV	2F-ara-A Phosphate Metabolites 2F-ara-A	26 min 131 min 15 min	125 min ---- 6.7 h	---- ---- ----	---- ---- ----	12-14% of 2F-ara-A became serum protein bound.

HPLC: high performance liquid chromatography
TLC: thin layer chromatography

Table 23 – Pharmacokinetic Parameters of Fludarabine Phosphate and Metabolites

Study Data			Results				
Species/Test Model	**Test Article Dose**	**Route of Admin.**	**Metabolite**	**t½**	**Time to C_{max}**	**C_{max}**	**Comment**
Mouse (BD2F1) P388 tumor cell model	1,485 mg/kg 2F-ara-AMP	IP	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)	---- ---- > 1 mM ≈0.4 mM ----	After separation of nucleotides by HPLC, metabolites were quantified by UV or radioactivity.
Mouse (BD2F1) P388 tumor cell model	1,485 mg/kg 2F-ara-AMP	IP	---- 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 mcM 27 mcM	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/m² 2F-ara-AMP	IP	2F-ara-A	----	5-140 min (peritoneal fluid) 120-240 min (plasma)	7.7-18 mcg/mL (peritoneal fluid) 0.15-0.46 mcg/mL (plasma)	HPLC was used.

C_{max}: maximal concentration
IP: intraperitoneal

Table 24 – Metabolism, Distribution and Excretion of Fludarabine Phosphate

Species	Design	Compound Administered	Dose (mg/m^2)	Metabolism and Distribution	Elimination	Metabolites
Mouse (BDF_1)	IV 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	IV administration	2F-ara-AMP	40 500	2F-ara-AMP underwent dephosphorylation to 2F-ara-A in mice.	Elimination of 2F-ara-A from tissue occured 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	IP administration	2F-ara-AMP	1,485 (mg/kg)	Peak 2F-ara-A ascites conc. occurred at 4 h Peak 2F-ara-HX ascites conc. occurred at 4 h Peak 2F-ara-A plasma conc. (≥1mM) occurred at 1-6 h Peak 2F-ara-HX plasma conc. (≈0.4mM) occurred at 4 h	2F-ara-A t½ = 2.1 h (ascites) ---- 2F-ara-A t½ = 3.8 h (plasma) 2F-ara-HX t½ = 3 h (plasma)	2F-ara-A (ascites & plasma) 2F-ara-HX (ascites & plasma) 2F-ara-ATP (intracellular) 2F-ara-AMP (intracellular)

Species	Design	Compound Administered	Dose (mg/m^2)	Metabolism and Distribution	Elimination	Metabolites
Mouse ($BD2F_1$) P388 tumor cell implant model	IP administration	2F-ara-AMP	1,485 (mg/kg)	The peak concentration (1,036 mcM) 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 t½ = 4.1 h (in P388 cells) 2F-ara-ATP t½ = 2 h (in host tissue)	---- ----
Mouse P388 tumor cell implant model	IP administration	2F-ara-AMP	1,485 (mg/kg)	930 mcM 2F-ara-ATP was the peak intracellular concentration observed in P388 cells. Peak 2F-ara-ATP concentrations of 34 nmol/mcmol of DNA accumulated in bone marrow. Peak 2F-ara-ATP concentrations of 23 nmol/mcmol 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
Dog (Beagle)	IV 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

Species	Design	Compound Administered	Dose (mg/m2)	Metabolism and Distribution	Elimination	Metabolites
Dog (Beagle)	IV administration	2F-ara-AMP	40 500	2F-ara-AMP underwent dephosphorylation to 2F- ara-A in dogs.	----	2F-ara-A
Dog (Beagle)	IV 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 was metabolized by dephosphorylation to 2F-ara- A with subsequent deamination to 2F-ara-HX	2F-ara-A 2F-ara-HX
Miniature swine	IP infusion	2F-ara-AMP	10 16 25	Peak IP 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	IV 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

Species	Design	Compound Administered	Dose (mg/m²)	Metabolism and Distribution	Elimination	Metabolites
Mouse (BDF_1)	IV administration	2F-ara-A	30	42% of radioactivity found in the liver, 20% in the spleen, pancreas, and colon, and 15% in the lung and small intestine was a phosphorylated derivative of 2F-ara-A.	≥59% of the drug was excreted in urine as 2F-ara-A at 24 hr. 12% of dose was excreted as a metabolite at 24 h	2F-ara-AMP 2F-ara-ADP 2F-ara-ATP
Mouse P388 tumor cell implant model	IP administration	2F-ara-A	234 (mg/kg)	560 mcM of 2F-ara-ATP was the peak intracellular concentration observed. 2F-ara- A passed rapidly from ascites to blood in concentrations proportional to the dose.	2F-ara-ATP disappeared with an intracellular half-life of 2.9 h. 2F-ara-A exhibited a plasma half-life of 2.2 h.	2F-ara-ATP
Dog (Beagle)	IV 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 the urine at 24 h. 53% of the drug was excreted as metabolites in urine at 24 h.	----
Dog (Beagle)	IV 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 h. 70% of the drug was excreted as metabolites in the urine at 24 h.	----

Species	Design	Compound Administered	Dose (mg/m^2)	Metabolism and Distribution	Elimination	Metabolites
Monkey (Rhesus)	IV administration	2F-ara-A	30	----	50% of the drug was excreted unchanged in 24 h. 26% of the drug was excreted as metabolites at 24 h.	----
Monkey (Rhesus)	IV administration	2F-ara-A	400	----	58% of the drug was excreted unchanged at 24 h. 25% of the drug was excreted as metabolites at 24 h.	----
Rat (Sprague Dawley)	IV administration	^3H-2F-ara-AMP	60 (10mg/kg)	After intravenous administration of ^3H-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)	IV administration	^3H-2F-ara-AMP	60 (10mg/kg)	^3H-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 ^3H-labelled substances could be observed in fetus and in maternal tissues examined.	----

17 SUPPORTING PRODUCT MONOGRAPHS

1. FLUDARA® (powder for solution, 50 mg / vial; tablets, 10 mg), submission control 143857, Product Monograph, Genzyme Canada Inc. (APR 9, 2011)
2. FLUDARA® (Tablets; 10 mg), submission control 268846, Product Monograph, sanofi-aventis Canada Inc (SEP 13, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrFLUDARABINE PHOSPHATE FOR INJECTION

Read this carefully before you start taking **FLUDARABINE PHOSPHATE FOR INJECTION** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLUDARABINE PHOSPHATE FOR INJECTION**.

Serious Warnings and Precautions

FLUDARABINE PHOSPHATE FOR INJECTION should be prescribed and administered by a healthcare professional experienced with the use of anticancer drugs.

The following are possible serious side effects:

- **Myelosuppression**: This is a decreased production of the blood cells by the bone marrow. It can affect:
  - your body's ability to protect against infections due to low white blood cells (neutropenia)
  - the ability of blood cells to carry oxygen due to low red blood cells (anemia), or
  - blood clotting due to low platelets (thrombocytopenia)

  Myelosuppression 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.

- **Hemolytic anemia:** This is a low red blood cell count due to a breakdown of red blood cells. It may result in death.

- Lung toxicity resulting in death. This has happened when fludarabine phosphate was used in combination with the medicine pentostatin (deoxycoformycin).

What is FLUDARABINE PHOSPHATE FOR INJECTION used for?

FLUDARABINE PHOSPHATE FOR INJECTION is used to treat adults with chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin's lymphoma (Lg-NHL) when other treatments have not worked.

How does FLUDARABINE PHOSPHATE FOR INJECTION work?

FLUDARABINE PHOSPHATE FOR INJECTION slows or stops the growth of cancer cells. It does this by interfering with the production of the cell's genetic material called DNA.

What are the ingredients in FLUDARABINE PHOSPHATE FOR INJECTION?

Medicinal ingredient: fludarabine phosphate

Non-medicinal ingredients: Mannitol and sodium hydroxide.

FLUDARABINE PHOSPHATE FOR INJECTION comes in the following dosage forms:

Solution: 25 mg/mL fludarabine phosphate

Do not use FLUDARABINE PHOSPHATE FOR INJECTION if:

- you are allergic to fludarabine or any of the ingredients of this medication
- you have severe kidney problems
- you have hemolytic anemia (when red blood cells are broken down rapidly)
- you are also using a medicine called pentostatin (deoxycoformycin)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLUDARABINE PHOSPHATE FOR INJECTION. Talk about any health conditions or problems you may have, including if you:

- have problems with your immune system
- are not feeling very well
- have kidney problems
- have liver problems
- are over 75 years old
- need any vaccinations. Live vaccine should be avoided during and after treatment with FLUDARABINE PHOSPHATE FOR INJECTION.
- have skin cancer. FLUDARABINE PHOSPHATE FOR INJECTION may worsen skin cancer lesions or cause them to flare-up. New skin cancers have also been reported in patients during or after FLUDARABINE PHOSPHATE FOR INJECTION therapy.
- have an infection associated with decreased immune function.

Other warnings you should know about:

Pregnancy and breastfeeding:

Female patients:

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- Do not use FLUDARABINE PHOSPHATE FOR INJECTION if you are pregnant. It may harm your unborn baby or make you lose the pregnancy. If you are able to become pregnant:
  - Avoid becoming pregnant while you are receiving FLUDARABINE PHOSPHATE FOR INJECTION. Use birth control during your treatment with FLUDARABINE PHOSPHATE FOR INJECTION. Continue using this birth control for at least 6 months after stopping treatment.
  - Tell your healthcare professional right away if you become pregnant during your treatment.
  - Do not breastfeed while you are receiving FLUDARABINE PHOSPHATE FOR INJECTION.

Male patients while taking FLUDARABINE PHOSPHATE FOR INJECTION and for at least 6 months after stopping treatment:

- Do not father a child.
- Use effective birth control each time you have sex with a woman who could get pregnant. Be sure to tell her you are taking FLUDARABINE PHOSPHATE FOR INJECTION and that there are risks to an unborn baby should she get pregnant.
- If your sexual partner gets pregnant during your treatment, tell your healthcare professional right away.

Fertility: FLUDARABINE PHOSPHATE FOR INJECTION might affect your ability to have a child in the future. Before you start FLUDARABINE PHOSPHATE FOR INJECTION, you should speak with your healthcare professional about ways to protect your eggs or sperm.

If you are planning a pregnancy after your FLUDARABINE PHOSPHATE FOR INJECTION treatments, you should speak with a Genetic Counselor.

Tumour Lysis Syndrome: 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 is called Tumour Lysis Syndrome. It may cause nausea and vomiting, joint pain, kidney failure, and heart problems. Your healthcare professional may give you medications to stop this from happening.

Encephalopathy: This 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 permanent, life-threatening, or cause death. Your healthcare professional will do assessments of your nervous system to monitor for encephalopathy. This might include scans like a MRI.

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

- At the recommended dose. It happens most commonly;

- when given with other drugs known to cause encephalopathy
- when you have:
  - Head or total body radiation therapy
  - Hematopoietic Stem Cell transplantation
  - Graft versus host disease
  - Kidney disease
- At higher than recommended doses

Driving and using machines: FLUDARABINE PHOSPHATE FOR INJECTION can cause fatigue, weakness, vision problem, confusion, agitation and seizures. This may reduce your ability to drive or use machines. Do not drive or operate machinery if FLUDARABINE PHOSPHATE FOR INJECTION affects your alertness or your vision.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FLUDARABINE PHOSPHATE FOR INJECTION:

- A medicine used to prevent blood clots called dipyridamole.
- A medicine used in the treatment of cancer called cytarabine.

How to take FLUDARABINE PHOSPHATE FOR INJECTION:

- FLUDARABINE PHOSPHATE FOR INJECTION will be given to you by a healthcare professional in a healthcare setting. It will be given into your vein (intravenously) as an infusion over 30 minutes.

Usual dose: Your dose of FLUDARABINE PHOSPHATE FOR INJECTION will be based on your height and weight. Your healthcare professional will decide how much FLUDARABINE PHOSPHATE FOR INJECTION you will receive. You may receive a lower dose if you have kidney problems.

FLUDARABINE PHOSPHATE FOR INJECTION is given in treatment cycles.

- Each cycle is 28 days long.
- You will be given FLUDARABINE PHOSPHATE FOR INJECTION once a day for the first 5 days of each 28-day cycle.
- The number of cycles you will receive depends on how you respond and tolerate the treatment. Usually, six 28-day cycles are required.

Overdose:

If you think you, or a person you are caring for, have been given too much FLUDARABINE PHOSPHATE FOR INJECTION, contact a healthcare professional, hospital emergency

department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

FLUDARABINE PHOSPHATE FOR INJECTION should be given on a fixed schedule. If you miss an appointment, call your doctor for instructions.

What are possible side effects from using FLUDARABINE PHOSPHATE FOR INJECTION?

These are not all the possible side effects you may have when taking FLUDARABINE PHOSPHATE FOR INJECTION. If you experience any side effects not listed here, tell your healthcare professional.

- fever
- feeling tired
- feeling weak
- cough
- nausea
- vomiting
- diarrhea
- loss of appetite
- 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 (swelling)
- bruising

Prolonged vomiting, diarrhea, or mouth sores may limit your fluid intake. This can make you prone to dehydration. Contact your doctor if these symptoms last for 24 hours.

FLUDARABINE PHOSPHATE FOR INJECTION can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment. These will tell your healthcare professional how FLUDARABINE PHOSPHATE FOR INJECTION is affecting your blood.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Myelosuppression (decreased blood cell production including: **neutropenia** (low white blood cell count), **anemia** (low red blood cell count) **thrombocytopenia** (low platelet count)**:** any unusual bruising, more bleeding than usual after injury, frequent infections. This may also lead to an increased risk of (serious) infections, caused by organisms, that usually do not cause disease in healthy persons (opportunistic infections) including a late reactivation of viruses, for example herpes zoster.		✓	
Pneumonia (lung infection): cough, trouble breathing, chest pain with or without fever		✓	
COMMON			
Infection: fever, chills, feeling unwell, pain		✓	
Peripheral neuropathy: pain, numbness or weakness in the arms and / or legs, dropping things from your hands, trouble with tasks like walking, picking up items, or moving your limbs.		✓	
Richter's Syndrome (rare type of lymphoma): Rapid and dramatic increase in the size of the lymph nodes in the neck, abdomen, armpit or groin; night		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
sweats, weight loss, fever, palpitations, fatigue, shortness of breath, dizziness			
UNCOMMON			
Allergic reaction: difficulty breathing, rash, itching			✓
Tumour Lysis Syndrome (the sudden, rapid death of cancer cells due to treatment): pain in your side, blood in your urine, a reduced amount of urine		✓	
Bleeding in the digestive system: tar-coloured or bloody stool		✓	
Hemolytic Anemia (rapid breakdown of red blood cells): yellowing of the skin or eyes and/or red-brown urine		✓	
Confusion: problems with short-term memory, difficulty carrying out tasks, poor attention span, unclear speech and difficulty in following a conversation		✓	
Autoimmune reactions: (when the immune system mistakenly attacks our own cells): can lead to various symptoms depending on the affected part of the body, such as fatigue, dizziness or light-headedness, low grade fever, muscle aches, swelling, skin rash.		✓	
Lung injury: difficulty breathing and shortness of breath			✓
RARE			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Heart Failure: palpitations (you suddenly become aware of your heartbeat), irregular heartbeat, chest pain.		✓	
Epstein Barr Virus-associated lymphoproliferative disorder (disorders of the lymph system due to a viral infection): fever, sore throat, swollen lymph nodes, spleen or liver enlargement, jaundice, high white blood cell count, low red blood cell count, abnormal bleeding or bruising, excessive bleeding, unintentional weight loss, night sweats, loss of appetite, weakness, dizziness, bone pain, rashes, frequent infections, headaches, seizures, confusion, nausea and vomiting		✓	
Coma: prolonged state of unconsciousness		✓	
Seizures: temporary confusion, a staring spell, jerking movements of the arms and legs that can't be controlled, Loss of consciousness or awareness, Cognitive or emotional changes.		✓	
Agitation: feeling of aggravation, annoyance, restlessness, or nervousness		✓	
Lyell's syndrome, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (severe skin reactions): redness, inflammation, blistering, tissue break down			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Pain in your eyes/Blindness (lack of vision)			✓
Cystitis (inflammation of the bladder): feeling the need to urinate more often, sudden desire to pee, pain/ burning with urination, dark or foul-smelling pee		✓	
UNKNOWN FREQUENCY			
Neurological Disorders: headache with nausea and vomiting, seizure, visual disturbances (vision loss), confusion, muscle spasm, drowsiness			✓
Hemorrhage including • **Cerebral hemorrhage** (bleeding in the brain): sudden headache, nausea, loss of consciousness • **Pulmonary hemorrhage:** (bleeding in lung): coughing, which may bring up blood or clots, weakness, dizziness, fainting • **Retinal hemorrhage:** (bleeding in the eye): sudden vision loss, blurry vision, blind spots, flashes or floaters			✓
Transfusion-associated severe allergic reaction: back pain, dark urine, chills, fainting or dizziness, fever, flank pain, skin flushing, shortness of breath or itching.			✓
Skin cancer: a pearly or waxy bump, flesh-colored or brown scar-like lesion, bleeding or scabbing sore that heals and		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
returns, firm and red nodule, flat lesion with a scaly and crusted surface, large brownish spot with darker speckles, a mole that changes in appearance or that bleeds, painful lesion that itches or burns. Usually occurs in sun-exposed areas of your body, such as your neck or face			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

FLUDARABINE PHOSPHATE FOR INJECTION will be stored and managed by your healthcare professional. It will be stored refrigerated between 2°C to 8°C and protected from freezing.

If you want more information about FLUDARABINE PHOSPHATE FOR INJECTION:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited,
Toronto, Ontario M1B 2K9.

Last Revised: MAY 23, 2025