Drug Monograph

A - Drug Name

fludarabine

COMMON TRADE NAME(S): Fludara®

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B - Mechanism of Action and Pharmacokinetics

The pyrimidine analogue, cytarabine, has been used effectively against a wide variety of acute leukemias. The success of cytarabine prompted a search for other potentially useful analogues. Fludarabine is a fluorinated analogue of adenine which is relatively resistant to deamination by adenosine deaminase. It is rapidly metabolized by deoxycytidine kinase to 2F-ara-ATP which inhibits DNA synthesis by inhibition of DNA polymerases, and prevention of elongation of DNA strands through direct incorporation into the DNA molecule. Fludarabine also inhibits RNA polymerase and protein synthesis

Absorption	Bioavailability	oral: 50-65% bioavailable (2F-ara-A)
Distribution	Pharmacokinetics are dose dependent and linear, widely distributed, Vd suggests significant degree of tissue binding. Some accumulation occurs during a 5 day treatment cycle, but does not occur over several cycles.	
	Cross blood brain barrier?	yes
	PPB	minor
Metabolism	Uptake, rapidly dephosphorylated in plasma to 2F-ara-ATP, which is necessary for cellular uptake.	
	Active metabolites	2F-ara-ATP
	Inactive metabolites	yes

Elimination	Predominantly excreted by kidneys; clearance is inversely correlated with serum creatinine and creatinine clearance.	
	Urine	40 - 60%.
	Half-life	15 - 23 hours (2F-Ara-ATP).

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C - Indications and Status

Health Canada Approvals:

- Chronic lymphocytic leukemia (second-line therapy after failure of other conventional therapies) (intravenous or oral)
- Low grade non-Hodgkin's lymphoma (second-line therapy after failure of other conventional therapies) (for intravenous only).

Other Uses:

- Acute Lymphoblastic Leukemia
- Acute Myeloid Leukemia

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended (PO)
Minimal (IV)

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Heart failure (rare)	E
	Pericardial effusion (rare)	E
Dermatological	Rash (<10%; may be severe including TEN and SJS)	I
Gastrointestinal	Anorexia (1-10%)	E

	Diarrhea (≥10%)	E
	GI hemorrhage (<1%)	E
	Mucositis (1-10%)	E
	Nausea (or vomiting - ≥10%, mostly mild to moderate)	I
General	Chills	I
	Edema (1-10%)	E
	Fatigue (≥10%)	E
	Fever (>10%)	I
Hematological	Anemia (≥10%)	E
	Hemolysis	E
	Myelosuppression ± infection, bleeding (≥10%) (including opportunistic infection)	E
	Other (transfusion associated GVHD)	E D
Hepatobiliary	↑ Amylase , lipase (may be severe)	E D
	↑ LFTs (<1%)	E
Immune	Autoimmune disorder (hemolytic anemia, TTP, pemphigus, etc. < 1%)	D
Metabolic / Endocrine	Hyperuricemia (<1%)	I
	Tumor lysis syndrome (<1%)	I
Neoplastic	MDS , AML (1-10%)	D
	Other (flare in skin cancer lesions)	E
Nervous System	Agitation (rare)	E
	Confusion (<1%)	E
	Encephalopathy (36% with high doses)	E D L
	Peripheral neuropathy (1-10%)	D
	Seizure (rare)	E
Ophthalmic	Blurred vision (visual changes - common)	E
	Optic nerve disorder (optic neuritis - rare)	E
Renal	Renal failure (rare)	E
Respiratory	Cough , dyspnea (>10%)	E
	Pneumonitis (rare)	D
	Pulmonary fibrosis (rare)	D
Urinary	Hemorrhagic Cystitis (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Myelosuppression may be cumulative, is often reversible but may persist for up to a year.

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g., some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

In a dose-finding study, severe irreversible **central nervous system** effects, including blindness, demyelination, coma and death, were seen in 36% of patients receiving four times the recommended dose for chronic lymphocytic leukemia (i.e., ≥96 mg/m^2/day x 5-7 days). Symptoms appeared from 21 to 60 days post dosing. These effects are rare (0.2%) at the recommended dose

Risk of leukoencephalopathy (including PRES/RPLS) increases when fludarabine is given at high doses or following, or in combination with, medications known to be associated with encephalopathy, in patients with cranial or total body irradiation, Graft versus Host Disease, renal impairment, or following Hematopoietic Stem Cell Transplantation. Late onset encephalopathy has been reported up to 4.8 years after fludarabine treatment.

Life-threatening and sometimes fatal autoimmune hemolytic anemia has been reported to occur during or after treatment with fludarabine in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test. Steroids may be beneficial. Re-challenge with fludarabine should be avoided. It is recommended that patients receive irradiated blood (or white cell-depleted red cells using a leuco-filter) to minimize the chances of hemolytic anemia and transfusion-induced graft-versus-host disease. Other autoimmune phenomena have been reported including ITP, TTP, Evans syndrome and pemphigus.

Fludarabine in combination with pentostatin (deoxycoformycin) results in an unacceptably high incidence of **fatal pulmonary toxicity**, and concomitant use is contraindicated.

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy. In general, fludarabine should be discontinued when the maximal response has been obtained.

Adults:

Single Agent:

Intravenous:

- q4w: 25 mg/m^2/day over 30 minutes x 5 days, q28d

Oral:

- q4w: 40mg/m^2/day x 5 days, q28d

Continue until maximal response (complete or partial remission, usually 6 cycles), and then discontinue the drug.

In combination with other chemotherapeutic agents:

Intravenous: 25 – 30 mg/m^2/day over 30 minutes x 3 days, q28d. Refer to individual regimen for details.

Dosage with Toxicity:

Some centres use the guidelines below:

Toxicity / Grade	**Action**	**Dose next cycle**
Platelet < 100 x 10^9/L and/or ANC < 1.5 x 10^9/L	Hold until recovery	reduce by 25%
Febrile neutropenia, thrombocytopenic bleeding	Hold until recovery	reduce by 25%
Grade 3 non-hematologic toxicity	Hold until recovery	reduce by 25%
Suspected encephalopathy	Hold and investigate (preferablly with MRI)	Discontinue if confirmed
Grade 4 non-hematologic toxicity OR Any grade neurotoxicity, hemolysis OR Suspected/proven pneumonitis/fibrosis	Discontinue	Discontinue

Dosage with Hepatic Impairment:

No data available; use with caution.

Dosage with Renal Impairment:

Creatinine clearance (mL/min)	Dose
30-70	50%
< 30	CONTRAINDICATED

Dosage in the elderly:

Limited data available. Exercise caution and assess creatinine clearance.

Children:

Safety and efficacy not established.

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F - Administration Guidelines

- **Oral**: Self-administration; drug available by outpatient prescription. Tablets should be swallowed whole with water, and should not be broken, crushed or chewed.
- In clinical investigation, pharmacokinetic parameters after oral administration were not significantly affected by concomitant food intake.
- **Intravenous**: Mix in 50mL minibag (Normal Saline or Dextrose 5%); Give over 30 minutes. Do not admix with other drugs.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or its components
- Patients who have severe renal impairment (< 30 mL/min)
- Patients who have decompensated hemolytic anemia
- The use of fludarabine in combination with pentostatin (deoxycoformycin) is contraindicated due to unacceptably high incidence of fatal pulmonary toxicity.

Other Warnings/Precautions:

- Patients with GI toxicity should be monitored carefully as volume depletion may reduce clearance and increase toxicity.
- Usage in high dose is not recommended (see "Adverse Effects" section) because of the risk of severe toxicity.
- Fludarabine is associated with myelosuppression, irreversible CNS effects, and auto-immune anemia, including some fatal cases.
- Use with caution in patients with poor performance status, infections, immunosuppression or myelosuppression.
- Irradiated blood products should be used to minimize the risk of transfusion related Graft versus Host disease.
- Consider prophylaxis in patients at increased risk of developing opportunistic infections.
- Avoid the use of live vaccines.

Pregnancy and Lactation:

- Fludarabine is **clastogenic, teratogenic and embryotoxic**; it **crosses the placenta** and inhibits **spermatogenesis**. It is contraindicated in **pregnancy**.
- Adequate contraception must be used by both sexes, during treatment and for at least 6 months after fludarabine cessation.
- Since fludarabine is secreted into breast milk in animals, **breast feeding** is contraindicated.
- Effects on fertility are unknown.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cytarabine	↓ metabolism of fludarabine, increases intracellular concentration and exposure of cytarabine active metabolite	Competes for deoxycytidine kinase needed to convert both drugs to their active form	Clinical importance is yet unknown

Pentostatin (deoxycoformycin)	This combination may be associated with severe and/or fatal pulmonary toxicity	Unknown	Concurrent therapy is CONTRAINDICATED; avoid.
Dipyridamole and other inhibitors of adenosine uptake	↓ effect of fludarabine	↓ adenosine uptake	Avoid concomitant therapy
Live virus vaccines	May result in severe systemic infection	Immunosuppression	Avoid concourrent use

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recomendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Clinical toxicity assessment of fever, infection, hemolysis, dehydration, pulmonary, GI, CNS	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and regular

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K - References

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA)

Coiffier B, Neidhardt-Berard EM, Tilly H, et al. Fludarabine alone compared to CHVP plus interferon in elderly patients with follicular lymphoma and adverse prognostic parameters: a GELA study. Annals of Oncology 1999; 10: 1191-7.

Foran JM, Rohatiner AZS, Coiffier B, et al. Multicenter phase II study of fludarabine phosphate for patients with newly diagnosed lymphoplasmacytoid lymphoma, waldenstrom's macroglobulinemia, and mantle cell lymphoma. JCO 1999; 17: 546-53.

Product Monograph: Fludara® (fludarabine). Sanofi-Aventis Canada, September 18, 2014.

Product Monograph: Fludarabine Phosphate. Novopharm Limited, July 19, 2006.

Product Monograph: Fludarabine Phosphate: Hospira Healthcare Corp., June 18, 2007.

Solal-Celigny P, Brice P, Brousse N, et al. Phase II trial of fludarabine monophosphate as first-line treatment in patients with advanced follicular lymphoma: a multicenter study by the groupe d'etude des lymphomes de l'adulte. JCO 1996; 14: 514-9.

April 2023 Removed NDFP forms

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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