DRUG NAME: Fludarabine

SYNONYM(S): *9-B-D*-arabinofuranosyl-2-fluoroadenine 5'-monophosphate,[1] FAMP,[2,3] 2-fluoro-ara-A Monophosphate,[3] 2-fluoro-ara-AMP,[1,3] fludarabine phosphate,[1] NSC-312887[1]

COMMON TRADE NAME(S): FLUDARA®

CLASSIFICATION: antimetabolite[1]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Fludarabine phosphate is a synthetic fluorinated analog of the purine nucleoside antiviral agent vidarabine (ara-A).[1,4] Unlike vidarabine, fludarabine phosphate is resistant to deamination by adenosine deaminase.[1] Fludarabine phosphate is a water-soluble prodrug that is rapidly dephosphorylated to 2-fluoro-vidarabine (2F-ara-A). 2F-ara-A is actively transported into cells and is then rephosphorylated via deoxycytidine kinase to the active triphosphate derivative 2F-ara-ATP.[1] 2F-ara-ATP competitively inhibits DNA synthesis via inhibition of DNA polymerase, ribonucleotide reductase, DNA primase, and DNA ligase.[1,5] 2F-ara-ATP prevents elongation of DNA strands through direct incorporation into DNA as a false nucleotide.[1,2] Partial inhibition of RNA polymerase II and resultant reduction in protein synthesis may also occur.[1] Cytotoxicity occurs primarily in the S-phase of cell division[4]; fludarabine is also active against non-proliferating cells.[4] Fludarabine has been shown to induce apoptosis *in vitro*.[1,6]

PHARMACOKINETICS:

IV and oral dosing provide similar systemic exposure[6]

Oral Absorption	50-75%[2,6,7]; dose-independant,[6] unaffected by food[8]	
Distribution	widely distributed[3]	
	cross blood brain barrier?	no information found
	volume of distribution[3]	83-98 L/m^2; suggests significant degree of tissue binding
	plasma protein binding	no *in vivo* information found
Metabolism	rapidly and completely dephosphorylated in plasma to 2-F-ara-A; pharmacokinetic data is based on 2F-ara-A	
	active metabolite(s)	2F-ara-ATP
	inactive metabolite(s)[2,9]	2F-ara-A, 2-F-ara-adenosinediphosphate minor: 2F-ara-hypoxanthine, 2-fluoro-vidarabine
Excretion	urine[2]	40-60%, 23% as 2-fluoro-vidarabine within 24 hours; renal elimination is dose-related: 24% at 25mg/m^2/d, 40-60% at higher doses[3,10]
	feces	no information found
	terminal half life[3]	15-23 h children[3,10]: 10.5-19 h
	clearance	79 mL/min/m^2; directly correlates with creatinine clearance

Adapted from standard reference[1] unless specified otherwise.

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USES:

Primary uses:

*Leukemia, chronic lymphocytic

Leukemia, prolymphocytic[11]

*Lymphoma, non-Hodgkin

Other uses:

Conditioning regimen pre-allogeneic bone marrow transplant[11]

Leukemia, acute myeloid[11]

Waldenstrom's macroglobulinemia[11]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to fludarabine[12,13]
- patients with decompensated hemolytic anemia[12,13]

Caution:

- use fludarabine with caution in patients with severe impairment of bone marrow function, immunodeficiency, or a history of opportunistic infections[1]
- potentially life-threatening transfusion-related graft-versus-host-disease can occur in patients with severe lymphopenia; patients receiving fludarabine should receive irradiated blood products, effectively eliminating this risk[1]
- concomitant therapy with corticosteroids and fludarabine increases the risk of infections with opportunistic pathogens such as *Pneumocystis, Listeria*, and cytomegalovirus[7,14]; the combination should be avoided[3]
- high doses of fludarabine (≥96 mg/m^2/day for 5-7 days) have been associated with severe irreversible central nervous system toxicity characterized by delayed progressive encephalopathy with seizures, blindness, paralysis, coma, and death[1,15]; severe neurotoxicity has rarely occurred at recommended doses[1]
- renal excretion is very important for fludarabine elimination; patients with reduced kidney function demonstrate increased exposure to fludarabine and may require dose modification[12]
- all lymphoma patients should be screened for ***Hepatitis B (HBV) reactivation***[16-19]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***[20]

Special populations: Because ***geriatric patients*** may have decreased renal function, and patients with renal impairment may be at increased risk of fludarabine-induced toxicity, these patients should be monitored and dosage adjusted accordingly.[1] Geriatric patients with advanced Rai stage chronic lymphocytic leukemia may require substantial dosage reductions.[3]

Carcinogenicity: Animal studies have not been conducted.[21] Disease progression and transformation (e.g., Richter's Syndrome) have been commonly reported in CLL patients. Acute myelocytic leukemia, myelodysplastic syndrome, and lymphoproliferative disorders (Epstein Barr virus associated) have been reported in post-marketing. New onset skin cancer and worsening or flare-up of pre-existing skin cancer lesions has been reported to occur in patients during or after intravenous fludarabine phosphate therapy.[12,13]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Fludarabine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1,3]

Fertility: Possible effects on fertility have not been evaluated in humans. In animal studies, dose related adverse effects on the male reproductive system have been reported, including degeneration and necrosis of the spermatogenic epithelium of the testes and decreased mean testicular weights.[12]

Pregnancy: Data in pregnant women is very limited. Early pregnancy loss has been reported in fludarabine monotherapy and combination therapy. Premature delivery has been reported. After first trimester use of fludarabine, one newborn was reported to have absent bilateral radii and normal thumbs, thrombocytopenia, fossa ovalis aneurysm, and patent ductus arteriosus. In animal studies, fludarabine was shown to have embryolethal and teratogenic potential which manifested as omphalocele and skeletal malformations (tail, craniofacial, limb, and digit

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effects), fetal weight loss, and postimplantation losses. Male and female patients of reproductive potential should use contraception during treatment with fludarabine and for at least 6 months after cessation of therapy.[12]

Breastfeeding is not recommended due to the potential secretion into breast milk.[1] There is evidence in animals that fludarabine phosphate and its metabolites can transfer from maternal blood to milk following intravenous administration of fludarabine.[12]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[22] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥ 5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylaxis (≤6%)[3,4]
	autoimmune reactions; Evans' syndrome, pemphigus[5]
auditory/hearing	hearing disturbances (≤6%)[3]; loss, auditory hallucinations
blood/bone marrow/ febrile neutropenia	anemia (35%, severe 7-24%)[4,23,24]
	autoimmune hemolytic anemia (<23%)[4,5,24]; has occurred after initial or subsequent dosing,[3,7] see paragraph following the **Side Effects** table
	lymphopenia, leukopenia (severe 28%)[23]
	neutropenia (15-75%, severe 19-54%)[3,14,24,25]; dose-related, nadir day 13 (range 3-25), complete recovery typically occurs 5-7 weeks after treatment[2,3]
	autoimmune neutropenia[5]
	myelodysplastic syndrome (<0.1%); duration may be prolonged, up to 1 year[2]
	pancytopenia[3,5]; durations of 2 months to 1 year have been reported[3]
	thrombocytopenia (32%, severe 14-26%)[23,24]; nadir day 16 (range 2-32), complete recovery typically occurs 5-7 weeks after treatment[2,3]
	autoimmune thrombocytopenia[5]
cardiovascular (arrhythmia)	arrhythmia (<0.1%)
cardiovascular (general)	angina (≤6%)[3]
	heart failure (<0.1%)
	pericardial effusion
coagulation	thrombocytopenic purpura; idiopathic and thrombotic[26]
constitutional symptoms	chills (1%-10%)[2]
	fatigue (1%-38%)[2,3]
	fever (>10%)[2]; with iv,[22] unrelated to infection
	sweating (≤13%)[3]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	sleep disorder (≤3%)[3]
dermatology/skin	*extravasation hazard:* none[27]
	alopecia (1-10%, severe ≤1%)[2,23,24,28]
	pruritis (<5%)[3,23]
	rash (≤15%)[2,3,23]
	reversible worsening or flare of pre-existing skin cancer lesions[29]
	seborrhea (<5%)[3]
	Stevens-Johnson syndrome, toxic epidermal necrolysis (<0.1%)
gastrointestinal	*emetogenic potential:* minimal (rare)[30,31]
	anorexia (≤34%)[3]
	constipation (<5%)[3]
	dysphagia (<5%)[3]
	diarrhea (5%-38%, severe 1-5%)[3,23,24]; more frequent with oral formulation[23]
	intestinal pseudo-obstruction[5]
	mucositis (<5%)[3], stomatitis (≤9%)[3], esophagitis (<5%)[3]
	nausea and vomiting (≤39%, severe ≤1%)[3,23,24,28]; generally mild,[3] more frequent with oral formulation[23]
	taste alterations[3] (<1%)[2]
hemorrhage	epistaxis (≤5%)[3]
	gastrointestinal bleed (≤13%)
	hemoptysis (≤6%)[3]
	hemorrhage (≤6%)[3]
hepatobiliary/pancreas	liver dysfunction (≤6%)[3]
	pancreatitis[3]
infection	***infections*** (≤77%, severe <35%)[3,14]; see paragraph following the **Side Effects** table
	pneumonia (9-22%)[2,3]
	upper respiratory infections (2%-16%)[5]
	urinary tract infection (≤15%)[3]
lymphatics	edema (≤19%)[2,3]
metabolic/laboratory	abnormal liver function tests (≤≤6%)[3,4]
	abnormal renal function tests (1%)[4]
	hyperglycemia (≤6%)[3]
	hyperuricemia[3]; see syndromes
	pancreatic enzyme level changes (<1%)
musculoskeletal	osteoporosis (≤6%)[3]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	weakness (≤65%)[2,3]
neurology	cerebellar syndrome[3]
	cognitive disturbances[3]; agitation (<1%), confusion (<1%)
	coma (<0.1%)
	dizziness[3]
	depression[3]
	leukoencephalopathy (<0.2%); higher incidence (36%) associated with high-dose,[14] onset typically 4-8 months after treatment[5]
	neurotoxicity (16%)[28]; onset typically 21-60 days after treatment,[3,14] see paragraph following the **Side Effects** table
	sensory neuropathy (≤12%, severe <1%)[2,3,24]
	seizure (<0.1%)
	wrist drop[3]
ocular/visual	blindness (<0.1%)
	optic neuropathy (<0.1%), optic neuritis (<0.1%)
	photophobia (<1%); primarily at higher doses[2]
	visual disturbances (≤15%)[3]; blurred vision, diplopia (<1%)[2]
pain	dysuria
	headache (1-10%)[2,3]
	myalgia (≤16%),[2,3] arthralgia (≤6%)[3]
	pain not otherwise specified (≤44%)[2,3]
pulmonary	cough (≤44%)[3]
	dyspnea (≤22%)[3]
	pharyngitis (≤9%),[3] bronchitis and sinusitis (≤5%)[3]
	pulmonary hypersensitivity reactions; pneumonitis, pulmonary infiltrates, fibrosis (≤5%)[3]; onset typically 3-28 days after the third or later treatment,[3] see paragraph following the **Side Effects** table
renal/genitourinary	hemorrhagic cystitis (<0.1%)
	renal failure (<1%)[2]
	urinary hesitancy (<5%)[3]
syndromes	hemophagocytic syndrome[5]
	tumour lysis syndrome[3] (0.3%-10%)[2,5]

Adapted from standard reference[1] unless specified otherwise.

Neurotoxicity: Severe and potentially irreversible or fatal neurotoxicity has occurred with fludarabine. While these effects typically occur with doses higher than those recommended, they have occurred at standard doses.[1,3] Neurotoxicity generally occurs 21-60 days following fludarabine and may cause confusion, incontinence, seizures,

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paralysis, vision changes, and coma.[1,3] At regular doses, neurotoxicity is generally mild and may be reversible,[28] causing headache, somnolence, agitation, confusion, and paresthesias. Rarely, coma and seizures have occurred.[1] The mechanism by which fludarabine causes neurotoxicity is unknown.[3] It is not known if the rate of drug administration affects the risk of neurotoxicity; neurotoxicity has been reported with rapid IV injections and slow IV infusions.[3] If vision changes occur, discontinue fludarabine treatment.[22]

Immunosuppression / opportunistic infections: Patients are at risk for opportunistic infections due to the T-cell lymphopenia, particularly of CD4 cells, induced by fludarabine.[1,14] Lymphopenia develops within 2-3 months and the decrease in CD4 cells may persist for years following treatment.[14] In patients treated with fludarabine, up to 67% of infections are caused by opportunistic organisms.[14] Delayed and/or severe opportunistic infections may occur, particularly after repeated cycles of fludarabine.[14] Concomitant therapy with corticosteroids increases the risk of opportunistic infections and the combination should be avoided.[3] Routine anti-infective prophylaxis or immune globulin use is not currently recommended but may be considered for high risk patients.[3] If a serious infection occurs, fludarabine therapy should be interrupted but may be reinitiated following the resolution of the infection.

Fludarabine-associated ***infections*** are caused by bacterial, fungal, and viral pathogens. *Streptococcus* and *Staphylococcus* are the most common bacterial pathogens.[14] Infections with gram-negative bacilli, *Listeria,* and rarely *Mycobacteria* infections have been reported.[3,14] Invasive fungal infections have been caused by several species including *Pneumocystis, Candida*, *Aspergillus*, and *Cryptococcus.*[3,14] Infections by viral pathogens include influenza, herpes, and hepatitis A and B viruses.[3,5,14,32] Herpes virus infections have occurred in up to 57% of patients receiving fludarabine.[5] Herpes simplex reactivation is the most common early viral infection.[14] Varicella zoster virus (VZV) infections typically occur 7-8 months after fludarabine initiation.[5,14] VZV ocular infections have also been reported.[5]

Autoimmune hemolytic anemia: Serious and sometimes fatal autoimmune hemolytic anemia has occurred after initial or subsequent dosing of fludarabine,[3,5] in patients with or without a history of autoimmune hemolytic anemia or a positive Coombs' test,[1] whose disease may or may not be in remission.[3] The risk factor that predisposes patients to the development of hemolytic anemia is not known.[3] Patients undergoing treatment with fludarabine should be monitored and treatment discontinued if hemolysis is detected.[1] The transfusion of irradiated blood products and the administration of corticosteroids are the most common treatment measures[1]; it is not known if corticosteroids are beneficial in the management of fludarabine induced hemolytic anemia.[3] Rituximab may be effective in managing the autoimmune thrombocytopenia and hemolytic anemia that results from fludarabine.[33-35] Rechallenge with fludarabine should be avoided.[3]

Pulmonary toxicities including respiratory distress and failure, pulmonary fibrosis and hemorrhage, and interstitial pneumonitis have been reported with fludarabine.[3] Symptoms of cough, dyspnea, hypoxia, and pulmonary infiltrates may be treated with corticosteroids; symptoms have recurred following cessation of the steroid.[3] Respiratory symptoms may resolve spontaneously.[3] The exact mechanism of pulmonary toxicity is not known, though an underlying disease process or previous exposure to agents that cause pulmonary toxicity may contribute to the incidence.[3] Patients with chronic lymphocytic leukemia may be at greater risk of developing pulmonary toxicity.[5]

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[36] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[37]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[38] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[39]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cytarabine[3,7]	decreases metabolism of fludarabine to active 2F-ara-ATP; cytarabine given first appears to inhibit the antineoplastic effect of fludarabine; fludarabine given first appears to stimulate rather than inhibit metabolic activation of cytarabine	cytarabine competes for deoxycytidine kinase, needed to convert both drugs to their active triphosphate	clinical importance as yet unknown
pentostatin[1,3,40,41]	severe or fatal pulmonary toxicity (e.g., pneumonitis)	unknown	avoid concomitant therapy
vaccines, killed virus[4]	ability to respond to vaccines following therapy is unknown; duration of decrease response unknown; estimates vary from 3 months - 1 year	fludarabine may decrease the ability to generate a humoral response to vaccines	immunize prior to therapy if possible, potential for decreased benefit of vaccine if administered during or within 1 year after therapy
vaccines, live virus[4,5]	ability to respond to vaccines following therapy is unknown, risk of infection by the live vaccine virus; duration of risk unknown; estimates vary from 3 months - 1 year	fludarabine may potentiate replication of the vaccine virus, decrease the ability to generate a humoral response to the vaccine and enhance the adverse effects of live vaccines	avoid during and within 1 year after therapy

Dipyridamole and other inhibitors of adenosine uptake theoretically may inhibit the cellular uptake of adenine analogs like fludarabine, potentially decreasing their therapeutic effect.[1,42] Consider avoiding concomitant therapy.

SUPPLY AND STORAGE:

Oral: sanofi-aventis Canada Inc. supplies fludarabine phosphate as 10 mg film coated tablets. Tablets contain lactose. Store at room temperature in original package.[43]

Additional information: Tablets are supplied in blister packs of 5 tablets, in units of three or four blister packs.[43]

Injection:
Accord Healthcare Inc. supplies fludarabine phosphate as 50 mg ready-to-use, single-use (preservative free) vials in a concentration of 25 mg/mL. Refrigerate.[12]

Teva Canada Limited supplies fludarabine phosphate as 50 mg ready-to-use, single-use (preservative free) vials in a concentration of 25 mg/mL. Refrigerate.[13]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

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SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	can be used[5]
Intramuscular	no information found
Direct intravenous	can be used[3,9]
Intermittent infusion	***over 20-30 minutes***
Continuous infusion	can be used[2,3,10]
Intraperitoneal	can be used[3]
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

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 absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Oral:	***4 weeks***[1,44,45]	***40 mg/m² PO once daily for 5 consecutive days starting on day 1*** (total dose per cycle 200 mg/m²) Round dose to the nearest 10 mg. Administer with food or on an empty stomach. Swallow whole, do not crush or chew.
Intravenous:	***4 weeks***[1,3,44,45]:	***25 mg/m²*** (range 25-30 mg/m²) ***IV once daily for 5 consecutive days starting on day 1*** (total dose per cycle 125 mg/m² [range 125-150 mg/m²])
	Bone marrow transplant[2,46]:	30-50 mg/m² IV once daily for 4-5 days (total dose 120-250 mg/m²)
Concurrent radiation:	additive bone marrow depression may occur; dose reduction may be required when used concurrently or consecutively[4]	

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BC Cancer usual dose noted in ***bold, italics***

Dosage in myelosuppression:

Cycle Length:
modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure[1,44,45]*:*

Creatinine Clearance (mL/min)	Dose	Actual Dose and Schedule (Note change in number of days)	
		IV	PO
>70	100%	25 mg/m^2/day x 5 days	40 mg/m^2/day x 5 days
30–70	50%	20 mg/m^2/day x **3 days**	32 mg/m^2/day x **3 days**
<30	do not use		

calculated creatinine clearance = $\frac{\text{N* x (140 - Age) x weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

no detailed information found[1]; use with caution if benefit outweighs risk[1]

Dosage in dialysis:

has been used, dose adjusted[47]

Children:

safety and efficacy have not been established in children[1,3]; has been used [2,3,10]

Intravenous:

25 mg/m^2 IV once daily for 5 consecutive days[48,49]

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