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.

USES:

Primary uses:
*Leukemia, chronic lymphocytic
Leukemia, prolymphocytic[3]
*Lymphoma, non-Hodgkin's

Other uses:
Conditioning regimen pre-allogeneic bone marrow transplant[2]
Leukemia, acute myeloid[5]
Leukemia, hairy cell[3,7]
Lymphoma, cutaneous T-cell[3,7]
Waldenstrom's macroglobulinemia[3,7]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients who have a history of hypersensitivity reactions to fludarabine or any components of the formulation, in renally impaired patients with a creatinine clearance less than 30 mL/minute, and in patients with decompensated hemolytic anemia.[1]

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[7,11]; the combination should be avoided.[3]
- High doses of fludarabine ($\geq$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[1,12]; severe neurotoxicity has rarely occurred at recommended doses.[1]

Hepatitis B (HBV) reactivation: All lymphoma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and HBV DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.[13,14]

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: no information found[3]

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: No long term studies have been performed in men or women to determine the effect on fertility. Patients of reproductive potential should use effective contraceptive methods during treatment and for a minimum of 6 months following fludarabine therapy.[1]

Pregnancy: FDA Pregnancy Category D.[2] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[1]

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.[15] When placebo-controlled trials are available, adverse events are 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%)[4,16,17] ***autoimmune hemolytic anemia (<1-23%)***[4,5,17]; has occurred after initial or subsequent dosing,[3,7] see paragraph following the **Side Effects** table
	immunosuppression[11]***; lymphopenia, leukopenia (severe 28%)***[16] ***neutropenia (15-75%, severe 19-54%)***[3,11,17,18]; 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%)[16,17]; 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[19]
constitutional symptoms	chills (1%- >10%)[2]
	fatigue (1%-38%)[2,3]
	fever (>10%)[2]; with iv,[15] unrelated to infection
	sweating (≤13%)[3]
	sleep disorder (≤3%)[3]
dermatology/skin	*extravasation hazard: none*[20]
	alopecia (1-10%, severe ≤1%)[2,16,17,21]
	pruritis (<5%)[3,16]
	rash (≤15%)[2,3,16]
	reversible worsening or flare of pre-existing skin cancer lesions[22]
	seborrhea (<5%)[3]
	Stevens-Johnson syndrome, toxic epidermal necrolysis (<0.1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential: rare*[23]
	anorexia (≤34%)[3]
	constipation (<5%)[3]
	dysphagia (<5%)[3]
	diarrhea (5%-38%, severe 1-5%)[3,16,17]; more frequent with oral formulation[16]
	intestinal pseudo-obstruction[5]
	mucositis (<5%)[3], stomatitis (≤9%)[3], esophagitis (<5%)[3]
	nausea and vomiting (≤39%, severe ≤1%)[3,16,17,21]; generally mild,[3] more frequent with oral formulation[16]
	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%)***[3,11]; 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]
	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,[11] onset typically 4-8 months after treatment[5]
	neurotoxicity (16%)[21]; onset typically 21-60 days after treatment,[3,11] see paragraph following the **Side Effects** table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	sensory neuropathy (≤12%, severe <1%)[2,3,17]
	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, paralysis, vision changes, and coma.[1,3] At regular doses, neurotoxicity is generally mild and may be reversible,[21] 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.[15]

Immunosuppression / opportunistic infections: Patients are at risk for opportunistic infections due to the T-cell lymphopenia, particularly of CD4 cells, induced by fludarabine.[1,11] Lymphopenia develops within 2-3 months and the decrease in CD4 cells may persist for years following treatment.[11] In patients treated with fludarabine, up to 67% of infections are caused by opportunistic organisms.[11] Delayed and/or severe opportunistic infections may occur, particularly after repeated cycles of fludarabine.[11] 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.[11] Infections with gram-negative bacilli, *Listeria,* and

rarely *Mycobacteria* infections have been reported.[3,11] Invasive fungal infections have been caused by several species including *Pneumocystis, Candida*, *Aspergillus*, and *Cryptococcus.*[3,11] Infections by viral pathogens include influenza, herpes, and hepatitis A and B viruses.[3,5,11,24] Herpes virus infections have occurred in up to 57% of patients receiving fludarabine.[5] Herpes simplex reactivation is the most common early viral infection.[11] Varicella zoster virus (VZV) infections typically occur 7-8 months after fludarabine initiation.[5,11] 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.[25-27] 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.[28] 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[29]:

- 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.[30] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[31]

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[1,3,32,33]	severe or fatal pulmonary toxicity (e.g., pneumonitis)	unknown	avoid concomitant therapy

AGENT	EFFECT	MECHANISM	MANAGEMENT
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.[1,34] Consider avoiding concomitant therapy.

SUPPLY AND STORAGE:

Tablets: Berlex Canada supplies fludarabine phosphate as a 10 mg film-coated tablet. Selected non-medicinal ingredients: lactose and red and yellow iron oxide. Store at room temperature in original packaging until use.[1]

Injection: Berlex Canada supplies fludarabine as a 6 mL vial of sterile lyophilized solid cake or powder containing fludarabine phosphate sodium equivalent to 50 mg of fludarabine phosphate.[1]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Compatibility of selected drugs: The following are compatible via Y-site injection[35]: allopurinol, amifostine, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, amsacrine, aztreonam, bleomycin, butorphanol, carboplatin, carmustine, cefazolin, cefepime, cefoperazone, cefotaxime, cefotetan, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, cisplatin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dexamethasone sodium phosphate, diphenhydramine, doxorubicin, doxycycline, droperidol, etoposide, etoposide phosphate, famotidine, filgrastim, floxuridine, fluconazole, fluorouracil, furosemide, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, ifosfamide, imipenem/cilastatin, lorazepam, magnesium sulfate, mannitol, mechlorethamine, melphalan, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, minocycline, mitoxantrone, morphine, multivitamins, nalbuphine, netilmicin, ondansetron, pentostatin, piperacillin, piperacillin/tazobactam, potassium chloride, promethazine, ranitidine, sodium bicarbonate, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine.

Incompatibility of selected drugs: The following are incompatible via Y-site injection[3,35]: acyclovir, amphotericin B, chlorpromazine, daunorubicin, ganciclovir, hydroxyzine, prochlorperazine edisylate.

PARENTERAL ADMINISTRATION:

BCCA 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:

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Oral:	***4 weeks***[1,13,14]	***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***[1,3,13,14]:	***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[2,36]:	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]	
Dosage in myelosuppression:	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[1,13,14]:

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 = $\frac{N^* \times (140 - \text{Age}) \times \text{weight (kg)}}{\text{Serum Creatinine in } \mu\text{mol/L}}$

* 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[37]

Children:

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

Intravenous: 25 mg/m^2 IV once daily for 5 consecutive days[38,39]

REFERENCES:

1. Berlex Canada. FLUDARA® product monograph. Pointe-Claire, Quebec; December 2003.
2. Rose BD editor. Fludarabine. UpToDate 14.2 ed. Waltham, Massachusetts: UpToDate®; 2006.
3. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1046-1052.
4. USP DI® Drug Information for the Health Care Professional [database on the Internet]. Fludarabine (Systemic). Thompson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 7 September 2006.
5. DRUGDEX® Evaluations (database on the Internet). Fludarabine. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 7 September 2006.
6. Foran JM, Oscier D, Orchard J, et al. Pharmacokinetic study of single doses of oral fludarabine phosphate in patients with 'low-grade' non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia. Journal of Clinical Oncology 1999;17(5):1574-1579.
7. MARTINDALE - The Complete Drug Reference (database on the Internet). Fludarabine. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 7 September 2006.
8. Oscier D, Orchard JA, Culligan D, et al. The bioavailability of oral fludarabine phosphate is unaffected by food. Hematol J 2001;2(5):316-21.
9. Gandhi V, Plunkett W. Cellular and clinical pharmacology of fludarabine. Clinical Pharmacokinetics 2002;41(2):93-103.
10. Rose BD editor. Fludarabine: Pediatric drug information. UpToDate 14.2 ed. Waltham, Massachusetts: UpToDate®; 2006.
11. Anaissie E, Kiwan E. Overview of infectious complications following purine analog therapy. UpToDate®, 2006. Available at: www.uptodate.com. Accessed 7 September 2006, UpToDate 14.2.
12. Wen P, Plotkin S. Neurological complications of cancer therapy. UpToDate®, 2006. Available at: www.uptodate.com. Accessed 7 September 2006, UpToDate 14.2.
13. BC Cancer Agency Lymphoma Tumour Group. (LYFLU) BCCA Protocol Summary for the Treatment of Low Grade Lymphoma or Chronic Lymphocytic Leukemia with Fludarabine. Vancouver, British Columbia: BC Cancer Agency; September 2006.
14. BC Cancer Agency Lymphoma Tumour Group. (LYFLUDR) BCCA Protocol Summary for Treatment of Chronic Lymphocytic Leukemia or Prolymphocytic Leukemia with Fludarabine and Rituxumab. Vancouver, British Columbia: BC Cancer Agency; September 2006.
15. Adrian Yee MD. Personal communication. BC Cancer Agency Lymphoma Tumour Group; 1 November 2006.
16. Boogaerts MA, Van Hoof A, Catovsky D, et al. Activity of oral fludarabine phosphate in previously treated chronic lymphocytic leukemia. Journal of Clinical Oncology 2001;19(22):4252-4258.

17. Johnson S, Smith AG, Loffler H, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. Lancet 1996;347(9013):1432-1438.
18. Boogaerts MA. Oral fludarabine therapy in chronic lymphocytic leukemia - Increased convenience. Hematology Journal 2004;5(SUPPL. 1):S31-S37.
19. Margaret Gagnon. Personal communication. Medical Services Associate, Berlex Canada.; 7 November 2006.
20. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 September 2006.
21. Leporrier M. Role of fludarabine as monotherapy in the treatment of chronic lymphocytic leukemia. Hematology Journal 2004;5(SUPPL. 1):S10-S19.
22. Rashid K, Ng R, Mastan A, et al. Accelerated growth of skin carcinoma following fludarabine therapy for chronic lymphocytic leukemia. Leukemia & Lymphoma 2005;46(7):1051-1055.
23. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 November 2005.
24. Picardi M, Pane F, Quintarelli C, et al. Hepatitis B virus reactivation after fludarabine-based regimens for indolent non-Hodgkin's lymphomas: high prevalence of acquired viral genomic mutations. Haematologica 2003;88(11):1296-1303.
25. Hegde UP, Wilson WH, White T, et al. Rituximab treatment of refractory fludarabine-associated immune thrombocytopenia in chronic lymphocytic leukemia. Blood 2002;100(6):2260-2262.
26. Swords R, Nolan A, Fay M, et al. Treatment of refractory fludarabine induced autoimmune haemolytic with the anti-cd20 monoclonal antibody rituximab. Clinical & Laboratory Haematology 2006;28(1):57-59.
27. Nishida H, Murase T, Ueno H, et al. Fludarabine-associated autoimmune hemolytic anemia occurring in B-cell chronic lymphocytic leukemia. Leukemia Research 2006;30(12):1589-1590.
28. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 2640.
29. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. 4th ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2003. p. 27.
30. Sanofi-Synthelabo. FASTURTEC® product information. Markham, Ontario; 2004.
31. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. E-Edition ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2010. p. 93-94.
32. Facts and Comparisons® Drug Interactions (database on the Internet). Fludarabine Phosphate. Wolters Kluwer Health Inc. Facts and Comparisons® 4.0, updated periodically. Available at: http://online.factsandcomparisons.com. Accessed 12 September 2006.
33. Rose BD. Lexi-Interact™ Online. UpToDate® 14.2, 2006. Available at: www.uptodate.com.
34. Margaret Gagnon. Personal communication. Medical Services Associate, Berlex Canada; 10 October 2006.
35. Trissel L. Handbook on injectable drugs. 13th ed. Bethesda, Maryland: American Society of Health-System Pharmacists; 2005. p. 666-670.
36. Russell JA, Tran HT, Quinlan D, et al. Once-daily intravenous busulfan given with fludarabine as conditioning for allogeneic stem cell transplantation: Study of pharmacokinetics and early clinical outcomes. Biology of Blood & Marrow Transplantation 2002;8(9):468-476.
37. Kielstein JT, Stadler M, Czock D, et al. Dialysate concentration and pharmacokinetics of 2F-Ara-A in a patient with acute renal failure. European Journal of Haematology 2005;74(6):533-534.
38. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott - Raven; 2006. p. 300-303.
39. McCarthy AJ, Pitcher LA, Hann IM, et al. FLAG (fludarabine, high-dose cytarabine, and G-CSF) for refractory and high-risk relapsed acute leukemia in children. Medical & Pediatric Oncology 1999;32(6):411-415.