

DRUG NAME: (a) Asparaginase
(b) Erwinia asparaginase
(c) Pegaspargase

SYNONYMS: (a) A-ase,¹ ASN-ase, Colaspase, Crasnitin,² Elspar,³ L-asparagine amidohydrolase¹
(b) Crisantaspasum,² Krisantaspasasi, Krisantaspas
(c) PEG-L-asparaginase,² Pegaspargasa, Pegaspargasum

COMMON TRADE NAMES: (a) KIDROLASE®
(b) ERWINASE®
(c) ONCASPAR®

CLASSIFICATION: antitumour antibiotic, cytotoxic⁴

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

MECHANISM OF ACTION:

Asparaginase hydrolyzes the amino acid L-asparagine to L-aspartic acid and ammonia.^{1,5} Asparagine is required for DNA synthesis and cell survival; however, most cells are capable of synthesizing asparagine from glutamine. Acute lymphoblastic leukemia (ALL) cells lack adequate levels of the required enzyme, asparagine synthetase, and cannot survive asparagine depletion. Asparaginase is cycle-specific for the G1 phase.⁶

There are three formulations of asparaginase available. These will be identified in the text as:

- Asparaginase (L-asparaginase isolated from *E.coli*)
- Erwinia asparaginase (L-asparaginase isolated from *Erwinia chrysanthemi*, previously called *Erwinia carotova*)⁷⁸
- Pegaspargase (L-asparaginase isolated from *E.coli* and attached to polyethylene glycol)

Erwinia asparaginase is serologically and biochemically distinct from asparaginase, although the antineoplastic activity and toxicity is similar. Pegaspargase has a longer half-life and decreased toxicity.

PHARMACOKINETICS:

Oral Absorption	denaturation and peptidase digestion within GI tract ^{1,9}	
Distribution	diffuses poorly from the capillaries; approximately 80% of the dose remains within the intravascular space ¹ ; IM injection yields a much larger volume of distribution	
	cross blood brain barrier?	not detectable in cerebrospinal fluid (CSF), but CSF asparagine is depleted with systemic administration of any formulation ¹⁰
	volume of distribution	asparaginase ¹⁰ : 3 L/m ²
		Erwinia asparaginase ¹⁰ : 5 L/m ²
	pegaspargase ¹⁰ : 2 L/m ²	
	plasma protein binding	no information found
Metabolism	unknown ¹¹	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	unknown, possibly using reticuloendothelial system ¹¹	
	urine	asparaginase, ⁶ pegaspargase ¹² : trace amounts
	feces	no information found
	terminal half life	asparaginase IM ¹³ : 26-60 h

	clearance	Erwinia asparaginase IM ¹³ : 16 h
		pegaspargase IM ¹³ : 5.5-7 d
		asparaginase ¹⁰ : 1.4 mL/min/m ²
		Erwinia asparaginase ¹⁰ : 3.4 mL/min/m ²
		pegaspargase ¹⁰ : 0.15 mL/min/m ²

USES:**Primary uses:**

- *Leukemia, acute lymphoblastic^{a b c}
- *Leukemia, acute lymphoblastic and hypersensitivity to asparaginase^{b c}
- *Leukemia, acute myeloid^a
- *Leukemia, chronic lymphocytic^a
- *Lymphoma, Hodgkin's^a
- Lymphoma, non-Hodgkin's^{14 a}
- *Health Canada approved indication

^a asparaginase^b Erwinia asparaginase^c pegaspargase**Other uses:****SPECIAL PRECAUTIONS:****Contraindications:**

- Asparaginase is contraindicated in patients with a history of an allergy to asparaginase, or past or present pancreatitis.⁶
- Erwinia asparaginase is contraindicated in patients with a history of allergy to Erwinia asparaginase, or past or present pancreatitis.¹⁵
- Pegaspargase is contraindicated in patients with a history of allergy to pegaspargase, or past or present pancreatitis, or in patients who have experienced significant hemorrhagic or thrombotic side effects previously with other formulations of asparaginase.¹⁶

Cautions:

Significant hypersensitivity reactions may occur with all three formulations. During administration, resuscitation equipment and emergency drugs should be readily available.^{16,17} Reactions include rash, urticaria, edema, hypotension, respiratory distress, chills, fever and anaphylaxis, which may result in sudden death.¹ An intradermal test dose is recommended for asparaginase but not for Erwinia asparaginase or pegaspargase.^{1,15,18}

- Asparaginase has the highest frequency at 15-35%.⁶ Although skin testing is not completely reliable in predicting asparaginase hypersensitivity, an intradermal test dose is generally recommended prior to the first dose, or before restarting therapy after several days.¹ While a positive skin test is often considered a contraindication to asparaginase treatment, some clinicians choose to use a desensitization procedure in positive reactors or before restarting therapy after several days. Anaphylactic reactions can occur within one-half to one hour following the first injection, including during skin testing, but occur mainly between the fifth and ninth injection.¹⁷ Risk factors include IV administration (decreased in IM or SC administration), prolonged therapy, high dose (> 6,000-12,000 units/m²), previous asparaginase therapy, and intermittent dosing.¹⁷
- Erwinia asparaginase may be used in patients who had an allergic reaction to asparaginase (see dosing guidelines).⁸ Up to 33% of patients who had an allergic reaction to asparaginase will also react to Erwinia asparaginase.⁸
- Pegaspargase is the least immunogenic, and may be used in patients who had an allergic reaction to asparaginase or Erwinia asparaginase (see dosing guidelines).¹⁷ Treatment-limiting reactions occurred in 9% of all

patients, 14% of patients who had an allergic reaction to asparaginase, and 26% of patients who had an allergic reaction to both asparaginase and Erwinia asparaginase.¹⁹

Administration: Toxicity, other than hypersensitivity reactions, may be more severe when the drug is administered daily rather than weekly.¹ For pegaspargase, IM administration is preferred over IV administration due to a lower incidence of hepatotoxicity, coagulopathy, gastrointestinal, and renal disorders.¹²

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test.¹⁶ Not known if asparaginase, Erwinia asparaginase or pegaspargase are clastogenic.

Fertility: No information found.

Pregnancy: FDA Pregnancy Category C.²⁰ Animal studies have shown fetal risks and there are no controlled studies in women. Asparaginase, Erwinia asparaginase and pegaspargase should be given only if potential benefit justifies the potential risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk.⁶

Special populations: **Adults** experience a higher incidence of toxicities, other than hypersensitivity reactions, compared to **children**.⁶ Patients can form **asparaginase antibodies**, which at least partially explains the high interpatient variability in asparaginase pharmacokinetics.¹¹ Clinically, the formation of these antibodies may result in hypersensitivity reactions or may lead to a faster decrease in asparaginase activity.

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.²¹ When placebo-controlled trials are available, adverse events are included if the incidence is \geq 5% higher in the treatment group.

The table refers to asparaginase unless otherwise noted. Generally, the toxicities seen with Erwinia asparaginase are very similar to asparaginase.²² Pegaspargase toxicities have a later onset than comparable toxicities of asparaginase.¹²

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	<i>hypersensitivity reactions (anaphylaxis 15-35%,⁶ pegaspargase 1-5%¹²)</i>
blood/bone marrow/ febrile neutropenia	anemia (<1%, nadir 14 days, recovery 21 days, ⁶ pegaspargase (1-5%) nadir 14 days, recovery 21 days ¹²)
	leucopenia (<1%, nadir 14 days, recovery 21 days, ⁶ pegaspargase (1-5%) nadir 14 days, recovery 21 days ¹²)
	thrombocytopenia (<1%, nadir 14 days, recovery 21 days, ⁶ pegaspargase (1-5%) nadir 14 days, recovery 21 days ¹²)
cardiovascular (arrhythmia)	tachycardia (pegaspargase: 1-5%) ¹²
coagulation	antithrombin III decreased (may be dose-limiting or fatal >10%) ⁶
	clotting factors V, VII, VIII, IX decreased (>10%) ⁶

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	<i>coagulation abnormalities (30%,²² Erwinia asparaginase 12%,¹⁹ pegaspargase 1-5%¹²)</i>
	<i>fibrinogen decreased (>10%,⁶ pegaspargase 1-5%¹²)²¹</i>
	protein C severe decrease (>10%) ⁶
	thromboplastin increased (pegaspargase 1-5%) ¹²
constitutional symptoms	fatigue (>10%, ⁶ pegaspargase >5% ¹²)
	night sweats (pegaspargase 1-5%) ¹²
	weight loss (0.1-1%) ¹⁷
dermatology/skin	<i>extravasation hazard: nonvesicant²³</i>
	injection site reaction, pain, itching, erythema, inflammation (pegaspargase 1-5%) ¹²
gastrointestinal	<i>emetogenic potential: rare,²⁴ pegaspargase rare^{12,19,24}</i>
	abdominal cramps (70%, ⁶ pegaspargase 1-5% ¹²)
	anorexia (>10%, ⁶ pegaspargase 1-5% ¹²)
	diarrhea (0.1-1%, ¹⁷ pegaspargase 1-5% ¹²)
	stomatitis (1-10%) ⁶
	vomiting (<10%, ²⁴ pegaspargase > 5% ^{12,19})
hepatic	<i>hepatotoxicity (>0.01% and <0.1%,¹⁷ pegaspargase 1-5%¹²)</i>
hepatobiliary/pancreas	<i>pancreatitis acute (15%,⁶ pegaspargase \geq2%¹⁶)</i>
infection	upper respiratory infection (pegaspargase 1-5%) ¹⁹
	sepsis ⁶
metabolic/laboratory	albumin decrease possibly with peripheral edema (<1%, ^{1,6} pegaspargase ¹⁹)
	alkaline phosphatase, transient increase (>10%, ⁶ pegaspargase 1-5% ¹²)
	azotemia (>10%) ⁶
	<i>bilirubin, transient increase (>10%,⁶ pegaspargase 1-5%¹²)</i>
	hyperglycemia requiring insulin (1.4%, ²² pegaspargase 3% ¹²)
	hyperuricemia (1-10%, ⁶ pegaspargase 1-5% ¹²)
	hypcholesterolemia (<1%) ¹⁷
	hypoglycemia (pegaspargase 1-5%) ¹²
	hypoproteinemia (pegaspargase 1-5%) ¹²
	<i>transaminase, transient increase (>10%,⁶ pegaspargase 1-5%¹²)</i>
musculoskeletal	arthralgia, myalgia (pegaspargase 1-5%) ¹²
neurology	coma (>25%) ⁶
	convulsions (10-60%, ⁶ pegaspargase seizure (1-5%) ¹²)
	<i>neurotoxicity (>10%,⁶ pegaspargase 1-5%¹²); generally reversible</i>
	paresthesia (pegaspargase 1-5%) ¹²
pain	headache (pegaspargase 1-5%) ¹²

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
pulmonary	cough (>1%, ⁶ pegaspargase 1-5% ¹⁹)
	respiratory distress (>0.1% and <1%, ¹⁷ pegaspargase 1-5% ¹²)
renal/genitourinary	hematuria (pegaspargase 1-5%) ¹⁹
	renal dysfunction (pegaspargase 1-5%) ¹⁹
	renal failure, acute (<1%, ⁶ pegaspargase ¹⁹)
	urinary frequency (pegaspargase 1-5%) ¹⁹
vascular	thrombosis (<1%),^{12,19} <i>pegaspargase (4%)¹²</i>

Hypersensitivity reactions: see **Special Precautions**.

Coagulation abnormalities: Asparaginase may cause hemorrhagic and/or thrombotic events.²⁵ These may occur after several weeks of therapy or after completion of therapy, and may be dose-related. Bleeding may be caused by a reduction in vitamin K-dependent clotting factors, a fall in fibrinogen levels, or decreased platelet aggregation to collagen.²⁶ Venous thrombosis may be caused by decreased antithrombin III, proteins C and S, and increased thrombin.²⁶ The majority of thromboses occur in the CNS.²⁷ Hemostatic function should be monitored periodically during therapy.¹ If coagulation abnormalities occur, the risk of recurrence with further asparaginase therapy is very low.²⁵ Patients who require further asparaginase treatment may be treated prophylactically with fresh frozen plasma plus low dose heparin, or low dose heparin 3 to 4 days after therapy, or fresh frozen plasma plus antithrombin III concentrate.

Pancreatic effects: Impairment of pancreatic function occurs frequently and may be caused by decreased insulin synthesis or necrosis and inflammation of the cells of the pancreas.¹ Pancreatitis can occur despite normal serum amylase, and can be fatal. Pancreatic function, including blood glucose, should be determined prior to and regularly monitored during therapy.¹

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.²⁶ 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. Follow the local institutional treatment guidelines for hyperuricemia and tumour lysis syndrome.²¹

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cytarabine ¹⁰	decreased effect of cytarabine when asparaginase is given immediately prior to or with cytarabine; enhanced effect of cytarabine when asparaginase is given after cytarabine	suppression of asparagine concentrations	refer to protocol by which patient is being treated ²¹

AGENT	EFFECT	MECHANISM	MANAGEMENT
methotrexate ¹	decreased effect of methotrexate when asparaginase is given immediately prior to or with methotrexate; enhanced effect of methotrexate when asparaginase is given after methotrexate	suppression of asparagine concentrations	refer to protocol by which patient is being treated ²¹
serum thyroxine-binding globulin ¹	decreased total serum thyroxine concentration	decreased synthesis of thyroxine-binding globulin in liver	delay measurement until 4 weeks after asparaginase therapy
vincristine ¹	increased vincristine neurotoxicity	unknown	refer to protocol by which patient is being treated ²¹

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.

Additional information: Potential overfill in KIDROLASE® vials has been a cause of concern when calculating final concentration. The manufacturer states that, when reconstituted with 4 mL SWI, the final concentration is 2,500 IU/mL ± 250 IU/mL.²⁸ The BC Cancer Agency considers the final concentration to be 2,500 IU/mL. For IM injection, asparaginase may be reconstituted with 2 mL NS to give a final concentration of 5,000 IU/mL,^{29,30} or 1 mL to give 10,000 u/mL.³⁰ For high-dose therapy, the practice of reconstituting the 10,000 IU vial with 0.5 mL or 1 mL of NS has been used, but this is not supported by the literature and not recommended by the manufacturer.³¹

Compatibility of selected drugs with L-asparaginase²⁹: The following are compatible via Y-site injection: methotrexate, sodium bicarbonate.

PARENTERAL ADMINISTRATION:

The table refers to asparaginase unless otherwise noted.

BCCA administration guideline noted in **bold, italics**

Intradermal ²⁹	<i>*test dose only</i>
Subcutaneous	has been used, not generally recommended Erwinia asparaginase ⁸ : can be used
Intramuscular (asparaginase, Erwinia asparaginase and pegaspargase) ^{8,16,29}	<i>commonly used</i>
Direct intravenous	into the tubing of a running infusion of preservative-free D5W or NS over <i>≥ 30 minutes</i> ^{16,29} Erwinia asparaginase ⁸ : can be used pegaspargase: not given direct IV ¹²
Intermittent infusion	<i>over ≥ 30 minutes</i> ²⁹ Erwinia asparaginase ⁸ : can be used pegaspargase: over 1-2 h ¹⁶
Continuous infusion	no information found

BCCA administration guideline noted in ***bold, italics***

Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	has been used ³²
Intra-arterial	no information found
Intravesical	no information found

*MD or RN to administer test dose as per institutional policy.

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) and liver function.²¹ 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***

<i>Intravenous/intramuscular asparaginase:</i>	Cycle Length:	
	n/a ³³ :	<i>test dose: 2 units intradermally and observe for 1 h then: 10,000 units IV daily on days 17-28 inclusive (total dose 120,000 units)</i>
	n/a ¹⁴ :	<i>test dose: 2 units intradermally and observe for 1 h then: 10,000 units/m² IV daily on days 15, 17, 19, 22, 25, 28 (total dose 60,000 units/m²)</i>
	n/a ^{6,17} :	200-1,000 units/kg/day IV or IM daily on days 1-28 inclusive (total dose is 5,600-28,000 units/kg) may be continued for an additional 14 days if complete remission is not obtained (in this case: total dose 8,400-42,000 units/kg)
	n/a ¹⁷ :	400 units/kg IV or IM daily Monday and Wednesday 600 units/kg daily on Friday for 4 weeks (total dose 4,800 units/kg) may be continued for an additional 14 days if complete remission is not obtained (in this case: total dose 5,600 units/kg)
	n/a ⁶ :	6,000-12,000 units/m ² IM daily on day 1 (total dose 6,000-12,000 units/m ²)
	2-3 weeks ⁶ :	10,000-40,000 units IV daily on day 1 (total dose per cycle 10,000-40,000 units)
	3 weeks ⁶ :	5,000-10,000 units/m ² /day IV daily on days 1-7 inclusive (total dose per cycle 35,000-70,000 m ²)

A test dose is often recommended prior to the first dose of asparaginase, or prior to restarting therapy, when there has been an interval of several days since the last dose.⁶

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

<i>Intravenous/intramuscular Erwinia asparaginase:</i>	Cycle Length:	
	1 week ⁸ :	6,000 units/m ² IV or IM for one dose on days 1, 3, and 5 for three weeks (total dose per cycle 54,000 units/m ²) Therapy may be further intensified as per protocol.

When Erwinia asparaginase is used following a hypersensitivity reaction to asparaginase, dosing is different due to the different pharmacokinetic profiles.¹⁵ Generally, each dose of asparaginase should be replaced with a single dose of 20,000 units/m² of Erwinia asparaginase. For intermittent therapy, Erwinia asparaginase treatment should be resumed at a low dose, 10 units/kg/day, and increased to the full dose over five days if tolerated.⁸

<i>Intravenous/intramuscular pegaspargase:</i>	2 weeks ¹⁶ :	2,500 units/m ² IV or IM for one dose on day 1 Note: pegaspargase is not to be given direct IV.
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<i>Concurrent radiation:</i>	not given ²¹
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"
<i>Dosage in renal failure:</i>	no adjustment required
<i>Dosage in hepatic failure:</i>	discontinue ¹⁷
<i>Dosage in dialysis:</i>	no information found

Children:

<i>Intravenous/intramuscular L-asparaginase or Erwinia L-asparaginase:</i>	Cycle Length:	
	1 week ¹⁰ :	6,000-10,000 units/m ² IV or IM for one dose on days 1, 3, and 5
<i>Intravenous pegaspargase:</i>	1-4 weeks ¹⁰ :	2,500 units/m ² IV or IM once daily on day 1 Note: often 2 or 3 syringes are required for a single IM dose. ³⁴ Note: pegaspargase is not to be given direct IV.

REFERENCES:

1. McEvoy GK. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2006. p. 932-934.
2. MARTINDALE - The Complete Drug Reference (database on the Internet). Asparaginase. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 4 October 2006.
3. Merck & Co Inc. Elspar Product Monograph. West Point, Pennsylvania; 2000.
4. National Institute for Occupational Safety and Health (NIOSH). Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. Cincinnati, Ohio: NIOSH - Publications Dissemination; September 2004. p. 31-40.
5. Graham ML. Pegaspargase: a review of clinical studies. Adv Drug Deliv Rev 2003;55(10):1293-302.
6. Rose BD editor. Asparaginase: Drug Information. UpToDate® 14.2 ed. Waltham, Massachusetts: UpToDate®; 2006.
7. Ettinger LJ, Ettinger AG, V A, et al. Acute Lymphoblastic Leukaemia A Guide to Asparaginase and Pegaspargase Therapy. Biopharmaceuticals 1997;1:30-39.
8. OPi SAS. Erwinase Product Monograph. Limonest, France; 2005.
9. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia: Lippincott - Raven; 2002. p. 281-283.
10. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia: Lippincott - Raven; 2002. p. 248.

11. Vieira Pinheiro JP. The best way to use asparaginase in childhood acute lymphatic leukaemia - still to be defined? *bjh* 2004;125:117-127.
12. Rose BD editor. Pegaspargase: Drug Information. UpToDate 14.2 ed. Waltham, Massachusetts: UpToDate®; 2006.
13. Avramis VI, Panosyan EH. Pharmacokinetic/Pharmacodynamic Relationships of Asparaginase Formulations. *Clin Pharmacokinet* 2005;44(4):367-393.
14. Leukemia/Bone Marrow Transplantation Program of British Columbia. (NHL98-01) Treatment of Lymphoblastic Lymphoma. Vancouver, British Columbia: BC Cancer Agency; 10 May 2004.
15. Catherine Lambermont. Pharmacovigilance & Medical Information Manager. OPi SAS; 19 September 2006.
16. Enzon Pharmaceuticals Inc. Oncaspar Product Monograph. Bridgewater, New Jersey; 2003.
17. OPi SAS. Kidrolase Product Monograph. Limonest, France; 2005.
18. Maharaj K. Raina PhD. Director Medical Information, Enzon Pharmaceuticals. Personal communication; 2 October 2006.
19. McEvoy GK. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2006. p. 1166-1168.
20. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 5th ed. Baltimore, Maryland: Williams and Wilkins; 1998.
21. Kevin Song MD. Personal communication. Hematologist, BMT/Leukemia Group Vancouver General Hospital, BC; December 2006.
22. Duval M, Suciu S, Ferster A, et al. Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer---Children's Leukemia Group phase 3 trial. *Blood* 2002;99(8):2734-2739.
23. B.C. 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 February 2004.
24. 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.
25. Feinberg WM, Swenson MR, Feinberg WM, et al. Cerebrovascular complications of L-asparaginase therapy. *Neurology* 1988;38(1):127-33.
26. DeVita VT, Hellman S, Rosenberg SA. *Cancer Principles & Practice of Oncology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 454-455.
27. Pizzo PA, Poplack DG. *Principles and Practice of Pediatric Oncology*. 4th ed. Philadelphia: Lippincott - Raven; 2002. p. 1190.
28. Robert Sarrazin B Pharm. Personal communication. Consultant, OPi Inc; February 2005.
29. Trissel LA. *Handbook on Injectable Drugs*. 13th ed. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc; 2005. p. 159-160.
30. Roberta Esau. Personal Communication. Pharmacist, British Columbia Children's Hospital, Oncology/Hematology Clinic; 11 December 2006.
31. Robert Sarrazin B Pharm. Personal communication. Consultant, OPi Inc; November 2005.
32. Dorr RT, Von-Hoff DD. *Drug monographs. Cancer chemotherapy handbook*. 2nd ed. Norwalk, Connecticut: Appleton and Lange; 1994. p. 201-208.
33. Leukemia/Bone Marrow Transplantation Program of British Columbia. (ALL89-01A) Treatment of Acute Lymphoblastic Leukemia Induction Cycle 1. Vancouver, British Columbia: BC Cancer Agency; 26 November 2004.
34. Roberta Esau. Personal Communication. Pharmacist, British Columbia Children's Hospital, Oncology/Hematology Clinic; 15 October 2006.