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

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

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

CLASSIFICATION: antitumour antibiotic

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.[1,4] 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.[5]

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*[6])[7]
- 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[1,8]	
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[9]
	volume of distribution	asparaginase[9]: 3 L/m^2
		Erwinia asparaginase[9]: 5 L/m^2
		pegaspargase[9]: 2 L/m^2
	plasma protein binding	no information found
Metabolism	unknown[10]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	unknown, possibly using reticuloendothelial system[10]	
	urine	asparaginase,[5] pegaspargase[11]: trace amounts
	feces	no information found

	terminal half life	asparaginase IM[12]: 26-60 h
		Erwinia asparaginase IM[12]: 16 h
		pegaspargase IM[12]: 5.5-7 d
	clearance	asparaginase[9]: 1.4 mL/min/m^2
		Erwinia asparaginase[9]: 3.4 mL/min/m^2
		pegaspargase[9]: 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[13] [a]

Other uses:

*Health Canada approved indication

[a] asparaginase
[b] Erwinia asparaginase
[c] pegaspargase

SPECIAL PRECAUTIONS:

Contraindications:
- Asparaginase is contraindicated in patients with a history of an allergy to asparaginase, or past or present pancreatitis.[5]
- Erwinia asparaginase is contraindicated in patients with a history of allergy to Erwinia asparaginase, or past or present pancreatitis.[14]
- 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.[15]

Cautions:

Significant hypersensitivity reactions may occur with all three formulations. During administration, resuscitation equipment and emergency drugs should be readily available.[15,16] 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.[1,14,17]
- Asparaginase has the highest frequency at 15-35%.[5] 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.[16] Risk factors include IV administration (decreased in IM or SC administration), prolonged therapy, high dose (> 6,000-12,000 units/m^2), previous asparaginase therapy, and intermittent dosing.[16]
- Erwinia asparaginase may be used in patients who had an allergic reaction to asparaginase (see dosing guidelines).[7] Up to 33% of patients who had an allergic reaction to asparaginase will also react to Erwinia asparaginase.[7]

- Pegaspargase is the least immunogenic, and may be used in patients who had an allergic reaction to asparaginase or Erwinia asparaginase (see dosing guidelines).[16] 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.[18]

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.[11]

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test.[15] Not known if asparaginase, Erwinia asparaginase or pegaspargase are clastogenic.

Fertility: No information found.

Pregnancy: FDA Pregnancy Category C.[19] 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.[5]

Special populations: Adults experience a higher incidence of toxicities, other than hypersensitivity reactions, compared to ***children.***[5] Patients can form ***asparaginase antibodies***, which at least partially explains the high interpatient variability in asparaginase pharmacokinetics.[10] 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.[20] When placebo-controlled trials are available, adverse events are included if the incidence is ≥ 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.[21] Pegaspargase toxicities have a later onset than comparable toxicities of asparaginase.[11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***hypersensitivity reactions (anaphylaxis 15-35%,[5] pegaspargase 1-5%[11])***
blood/bone marrow/ febrile neutropenia	anemia (<1%, nadir 14 days, recovery 21 days,[5] pegaspargase (1-5%) nadir 14 days, recovery 21 days[11])
	leucopenia (<1%, nadir 14 days, recovery 21 days,[5] pegaspargase (1-5%) nadir 14 days, recovery 21 days[11])
	thrombocytopenia (<1%, nadir 14 days, recovery 21 days,[5] pegaspargase (1-5%) nadir 14 days, recovery 21 days[11])
cardiovascular (arrhythmia)	tachycardia (pegaspargase: 1-5%)[11]
coagulation	antithrombin III decreased (may be dose-limiting or fatal >10%)[5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	clotting factors V, VII, VIII, IX decreased (>10%)[5]
	coagulation abnormalities (30%,[21] Erwinia asparaginase 12%,[18] pegaspargase 1-5%[11])
	fibrinogen decreased (>10%,[5] pegaspargase 1-5%[11])[20]
	protein C severe decrease (>10%)[5]
	thromboplastin increased (pegaspargase 1-5%)[11]
constitutional symptoms	fatigue (>10%,[5] pegaspargase >5%[11])
	night sweats (pegaspargase 1-5%)[11]
	weight loss (0.1-1%)[16]
dermatology/skin	*extravasation hazard: nonvesicant*[22]
	injection site reaction, pain, itching, erythema, inflammation (pegaspargase 1-5%)[11]
gastrointestinal	*emetogenic potential: rare,*[23] pegaspargase *rare*[11,18,23]
	abdominal cramps (70%,[5] pegaspargase 1-5%[11])
	anorexia (>10%,[5] pegaspargase 1-5%[11])
	diarrhea (0.1-1%,[16] pegaspargase 1-5%[11])
	stomatitis (1-10%)[5]
	vomiting (<10%,[23] pegaspargase > 5%[11,18])
hepatic	***hepatotoxicity (>0.01% and <0.1%,[16] pegaspargase 1-5%[11])***
hepatobiliary/pancreas	***pancreatitis acute (15%,[5] pegaspargase ≥2%[15])***
infection	upper respiratory infection (pegaspargase 1-5%)[18]
	sepsis[5]
metabolic/laboratory	albumin decrease possibly with peripheral edema (<1%,[1,5] pegaspargase[18])
	alkaline phosphatase, transient increase (>10%,[5] pegaspargase 1-5%[11])
	azotemia (>10%)[5]
	bilirubin, transient increase (>10%,[5] pegaspargase 1-5%[11])
	hyperglycemia requiring insulin (1.4%,[21] pegaspargase 3%[11])
	hyperuricemia (1-10%,[5] pegaspargase 1-5%[11])
	hypocholesterolemia (<1%)[16]
	hypoglycemia (pegaspargase 1-5%)[11]
	hypoproteinemia (pegaspargase 1-5%)[11]
	transaminase, transient increase (>10%,[5] pegaspargase 1-5%[11])
musculoskeletal	arthralgia, myalgia (pegaspargase 1-5%)[11]
neurology	coma (>25%)[5]
	convulsions (10-60%,[5] pegaspargase seizure (1-5%[11])
	neurotoxicity (>10%,[5] pegaspargase 1-5%[11]); generally reversible
	paresthesia (pegaspargase 1-5%)[11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
pain	headache (pegaspargase 1-5%)[11]
pulmonary	cough (>1%,[5] pegaspargase 1-5%[18])
	respiratory distress (>0.1% and <1%,[16] pegaspargase 1-5%[11])
renal/genitourinary	hematuria (pegaspargase 1-5%)[18]
	renal dysfunction (pegaspargase 1-5%)[18]
	renal failure, acute (<1%,[5] pegaspargase[18])
	urinary frequency (pegaspargase 1-5%)[18]
vascular	***thrombosis (<1%),[11,18] pegaspargase (4%)[11]***

Hypersensitivity reactions*:* see **Special Precautions**.

Coagulation abnormalities: Asparaginase may cause hemorrhagic and/or thrombotic events.[24] 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.[25] Venous thrombosis may be caused by decreased antithrombin III, proteins C and S, and increased thrombin.[25] The majority of thromboses occur in the CNS.[26] Hemostatic function should be monitored periodically during therapy.[1] If coagulation abnormalities occur, the risk of recurrence with further asparaginase therapy is very low.[24] 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.[25] 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.[20]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cytarabine[9]	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[20]

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[20]
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[20]

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.[27] 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,[28,29] or 1 mL to give 10,000 u/mL.[29] 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.[30]

PARENTERAL ADMINISTRATION:

The table refers to asparaginase unless otherwise noted.

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

Intradermal[28]	****test dose only***
Subcutaneous	has been used, not generally recommended
	Erwinia asparaginase[7]: can be used
Intramuscular (asparaginase, Erwinia asparaginase and pegaspargase)	***commonly used:*** it is recommended that dose volumes greater than 2 mL be administered in two sites if possible to reduce pain of injection, although a single site can be used if necessary.[31-33]
	Erwinia asparaginase: maximum volume of 2 mL to be injected at a single site; two injection sites should be used for volumes greater than 2 mL.[34]
	pegaspargase: maximum volume of 2 mL to be injected at a single site; multiple injection sites should be used for volumes greater than 2 mL.[35]
Direct intravenous	into the tubing of a running infusion of preservative-free D5W or NS over ≥ 30 minutes[15,28]
	Erwinia asparaginase[7]: can be used
	pegaspargase: not given direct IV[11]
Intermittent infusion	***over ≥ 30 minutes[28]***
	Erwinia asparaginase[7]: can be used
	pegaspargase: over 1-2 h[15]

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

Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	has been used[36]
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.[20] 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:	
Intravenous/intramuscular asparaginase:	n/a[37]:	***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)***
	n/a[13]:	***test dose: 2 units intradermally and observe for 1 h then: 10,000 units/m^2 IV daily on days 15, 17, 19, 22, 25, 28 (total dose 60,000 units/m^2)***
	n/a[33]:	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[33]:	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[5]:	6,000-12,000 units/m^2 IM daily on day 1 (total dose 6,000-12,000 units/m^2)
	2-3 weeks[5]:	10,000-40,000 units IV daily on day 1 (total dose per cycle 10,000-40,000 units)
	3 weeks[5]:	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.[5]

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

	Cycle Length:	
Intravenous/intramuscular Erwinia asparaginase:	1 week[7]:	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.[14] Generally, each dose of asparaginase should be replaced with a single dose of 20,000 units/m^2 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.[7]

Intravenous/intramuscular pegaspargase:	2 weeks[15]:	2,500 units/m^2 IV or IM for one dose on day 1 Note: pegaspargase is **not** to be given direct IV.

Concurrent radiation:	not given[20]
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:	no adjustment required
Dosage in hepatic failure:	discontinue[16]
Dosage in dialysis:	no information found

Children:

	Cycle Length:	
Intravenous/intramuscular L-asparaginase or Erwinia L-asparaginase:	1 week[9]:	6,000-10,000 units/m^2 IV or IM for one dose on days 1, 3, and 5
Intravenous pegaspargase:	1-4 weeks[9]:	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.[38] Note: pegaspargase is **not** to be given direct IV.

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