DRUG NAME: Pegaspargase

SYNONYM(S)[1]**:** pegylated asparaginase *E. coli*, PEG-asparaginase, PEG-L-asparaginase, polyethylene glycol-L-asparaginase, L-asparaginase with polyethylene glycol, PEG-ASP, PEGLA

COMMON TRADE NAME(S): ONCASPAR®

CLASSIFICATION: antitumour antibiotic

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

MECHANISM OF ACTION:

Pegaspargase is a pegylated conjugate of L-asparaginase (*E. coli*-derived asparaginase, asparaginase *E. coli*). It is comprised of a polyethylene glycol (PEG) moiety conjugated with L-asparaginase,[2] the enzyme that breaks down L-asparagine to L-aspartic acid and ammonia by hydrolysis. Asparagine is required for DNA synthesis and cell survival, and most normal cells can synthesize asparagine from glutamine using asparagine synthetase. However, acute lymphoblastic leukemia (ALL) cells lack adequate levels of asparagine and cannot survive its depletion.[2,3] Therefore, the anti-leukemic effect of L-asparaginase is related to sustained depletion of L-asparagine.[3] L-asparaginase is cell cycle-specific for the G1 phase.[1] Pegaspargase offers a longer half-life and more favourable dosing schedule than non-conjugated asparaginase formulations, and is considered less immunogenic.[2] Pegaspargase is an immunosuppressive agent.[4]

Comparison table of asparaginase products by source and availability

***E. coli*-derived Asparaginase**	
Asparaginase (KIDROLASE)	withdrawn from Canadian market
Pegaspargase (ONCASPAR)	pegylated conjugate of E. coli-derived asparaginase (attached to polyethylene glycol)
Calaspargase pegol (ASPARLAS)	pegylated conjugate of E. coli-derived asparaginase (attached to monomethoxy-polyethylene glycol)
***Erwinia chrysanthemi*-derived Asparaginase**	
Asparaginase-erwinia (ERWINASE)	withdrawn from Canadian market
Crisantaspase recombinant (RYLAZE)	recombinant asparaginase (identical to *Erwinia chrysanthemi*-derived asparaginase)

PHARMACOKINETICS:

Oral Absorption	denaturation and peptidase digestion within GI tract[5,6]; therefore, requires parenteral administration[1]	
Distribution	high molecular weight[7]; distributed intravascularly[7]; distribution volume is in the range of the estimated plasma volume[3]	
	cross blood brain barrier?	no; however, CSF asparagine concentrations are reduced proportional to the reduction of blood asparagine[2,7]
	volume of distribution[8,9]	children (IM): 1.86 L/m^2; children (IV): 2 L; adults (IV, asparaginase naive): 2.4 L/m^2
	plasma protein binding	no information found

Developed: 1 April 2022
Revised: 1 January 2025

Metabolism	systemically degraded[8]; possibly by the reticuloendothelial system[7]; the proteolytic enzymes responsible for metabolism are ubiquitously distributed in tissues[9]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	terminal half-life may be longer in asparaginase naïve patients possibly due to the formation of neutralizing antibodies following drug exposure[3,8]	
	urine	not detected[1]
	feces	no information found
	terminal half life[9]	IM: 5.8 days IV: 5.3 days
	clearance[9]	IM: 0.17 L/m^2/day IV: 0.2 L/day

USES:

Primary uses:
*Leukemia, acute lymphoblastic

Other uses:
Lymphoma, Natural Killer/T-cell[10,11]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to pegaspargase[3]
- past or present pancreatitis, serious hemorrhagic events or thrombosis related to previous asparaginase therapy[3]

Caution:
- pegaspargase is ***not interchangeable*** with other asparaginase formulations[1] as formulations differ in concentration, dosing, and indications
- patients with ***known hypersensitivity*** to other forms of L-asparaginase will have a higher risk of serious reactions to pegaspargase compared to non-hypersensitive patients[9]
- ***potential for immunogenicity*** exists (secondary to development of binding or neutralizing antibodies to pegaspargase)[9] and may present as either overt allergy or silent inactivation; consider monitoring for asparaginase activity[12]
- pegaspargase is associated with increased ***hepatotoxicity***, particularly in combination with other hepatotoxic substances, among patients over 18 years of age, and in patients with pre-existing hepatic impairment[4]
- concurrent administration of ***live vaccines*** may increase the risk of severe infections; administer live vaccines at least 3 months following termination of treatment[4]
- pegaspargase may ***impair the ability to drive*** or operate machines[4]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test.[9]

Fertility: no information found

Pregnancy: Multiple malformations and embryolethal effects were observed in animals studies using therapeutic doses of L-asparaginase.[9]

Breastfeeding is not recommended due to the potential secretion into breast milk.[9]

Special populations: Compared to children, ***adults*** experience a higher incidence of many toxicities, namely elevated liver enzymes, hyperbilirubinemia, hypofibrinogenemia, pancreatitis and thrombosis, but a lower incidence of hypersensitivity and bleeding.[13,14]

Developed: 1 April 2022
Revised: 1 January 2025

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.[15,16] 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***	
blood and lymphatic system/ febrile neutropenia	anemia (1-10%)
	coagulopathy (1-10%; severe 2-7%)[8,9]; see paragraph following **Side Effects** table
	febrile neutropenia (≥5%)
	neutropenia (1-10%)
	thrombocytopenia (1-10%)
endocrine	diabetic ketoacidosis
	hyperosmolar hyperglycemia
gastrointestinal	*emetogenic potential:* minimal (rare)[17]
	abdominal pain (≥10%)
	ascites (1-10%)
	diarrhea (3%)
	pancreatitis (1%; severe 2%)[8]; see paragraph following **Side Effects** table
	stomatitis (1-10%)
	vomiting (1-10%)
general disorders and administration site conditions	*extravasation hazard:* none[18]
	pyrexia after injection; usually subsides spontaneously
hepatobiliary	***hepatotoxicity*** (1-10%); see paragraph following **Side Effects** table
immune system	anaphylactic reactions (1%)[8]
	antibody formation (2-11%)[13]; see paragraph following **Side Effects** table
	hypersensitivity (32% with prior asparaginase hypersensitivity;10% with no prior hypersensitivity)[8]; see paragraph following **Side Effects** table
	rash (≥10%)
	urticaria (≥10%)
infections and infestations	infection (5%)
	sepsis (3%)
investigations	activated partial thromboplastin time (APTT) prolongation (≥10%)
	ALT/AST increase (3-11%, severe 3%)[8]; independent of dose
	amylase increase (≥10%)
	hyperammonemia[19-21]; see paragraph following **Side Effects** table

Developed: 1 April 2022
Revised: 1 January 2025

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyperbilirubinemia (≥10%; severe 1-2%)[8,9]; independent of dose
	fibrinogen (blood) increase (≥10%)
	international normalized ratio (INR) increase (≥10%)
	lipase increase (≥10%)
metabolism and nutrition	appetite decrease (1-10%)
	hypercholesterolemia (1-10%)
	hyperglycemia (3%; severe 5%)[8]; may require insulin, glucose intolerance may be irreversible
	hyperlipidemia (1-10%)
	hypertriglyceridemia (≥10%); may require triglyceride-lowering therapy[15]
	hypoalbuminemia (≥10%); dose dependent
	hypokalemia (1-10%)
musculoskeletal and connective tissue	extremity pain (1-10%)
nervous system	***cerebral thrombosis*** (2%; severe 3%)[8]; see paragraph following **Side Effects** table
	convulsion (1-10%)
	peripheral motor neuropathy (1-10%)
	reversible posterior leukoencephalopathy syndrome (<1%)
	syncope (1-10%)
respiratory, thoracic and mediastinal	hypoxia (1-10%)
skin and subcutaneous tissue	toxic epidermal necrolysis
vascular	embolism (≥10%); see paragraph following **Side Effects** table
	hypotension (3%)
	thrombosis (4%); see paragraph following **Side Effects** table

Adapted from standard reference[9] unless specified otherwise.

Pegaspargase has similar efficacy and toxicity to non-conjugated L-asparaginase. Most adverse effects are attributed to asparagine and glutamine depletion.[22]

Elevated ***ammonia*** levels are an expected side effect of asparaginase treatment based on the mechanism of action of the enzyme. Asparaginase releases ammonia through the hydrolysis of asparagine to aspartate and glutamine to glutamate. Transient hyperammonemia has been reported in all age groups and occurs irrespective of which asparaginase product is used. The prolonged half-life of pegaspargase may contribute to the accumulation of ammonia over time as elevated levels may not have time to return to baseline before the next dose is given. Patients with elevated ammonia are at risk of encephalopathic hyperammonemia. However, despite high ammonia levels, some patients do not develop symptoms of acute encephalopathy and may remain completely asymptomatic. Monitor ammonia levels in the presence of symptoms such as nausea, vomiting, lethargy, and irritation. Ammonia detoxification may be required.[4,19-21]

Developed: 1 April 2022
Revised: 1 January 2025

Pegaspargase is associated with ***hepatotoxicity*** such as hepatic steatosis (fatty liver), cholestasis, icterus, hepatic cell necrosis and hepatic failure with fatal outcome. The risk of hepatic effects may be increased in patients over 18 years of age. Pegaspargase may worsen pre-existing liver impairment and increase the toxicity of concomitant medication that is also hepatically metabolized. Monitor liver function throughout treatment and, in the presence of symptoms of hyperammonemia, monitor ammonia levels as well.[9]

Hypersensitivity reactions remain the most frequent adverse effect of pegaspargase treatment even though pegaspargase is considered less immunogenic than non-conjugated asparaginase.[22] Hypersensitivity reactions may include a range of reactions from local erythema, swelling, systemic rash, and urticaria to serious and life-threatening reactions, including anaphylaxis. Risk of hypersensitivity to pegaspargase is affected by prior exposures to asparaginase, the type of asparaginase product used, and concomitant immunosuppressive therapy. Be prepared to treat anaphylaxis with each administration of pegaspargase and monitor patients following each dose. Reactions are managed depending on the severity of the symptoms and may require administration of antihistamines, corticosteroids, and possibly inotropes, vasopressors and/or other countermeasures as indicated. Pegaspargase should be permanently discontinued following a life-threatening hypersensitivity reaction.[2,9,13] Switching to another asparaginase preparation may be considered following a reaction to pegaspargase.[12,16]

Exposure to asparaginase can trigger the development of ***anti-asparaginase antibodies***, which have been *a*ssociated with ***reduced asparaginase activity.*** Overt clinical hypersensitivity is considered a strong indicator that a patient has developed anti-asparaginase antibodies. However, the formation of these neutralizing antibodies has also been demonstrated in the absence of overt hypersensitivity and this phenomenon is known as silent inactivation. Continuing treatment with the same asparaginase formulation in the setting of either overt allergy or silent inactivation may be therapeutically ineffective. Measures to continue treatment, such as premedication (e.g., steroids, antihistamines) and decreasing the infusion rate, do not prevent the inactivation of asparaginase. Consider monitoring asparaginase activity levels for the detection of silent inactivation and also in the setting of hypersensitivity to confirm continued activity of the treatment.[12,14,23] Refer to protocol by which patient is being treated.

Impairment of ***pancreatic function*** occurs frequently with pegaspargase treatment. The precise mechanism is unknown but may be caused by decreased insulin synthesis secondary to asparagine depletion or necrosis/inflammation of the cells in the pancreas. Pancreatitis may sometimes be fulminant. Rarely, hemorrhagic or necrotising pancreatitis with fatal outcomes have been reported. Monitor blood glucose, triglycerides, serum amylase, and/or lipase to identify early signs of pancreatic inflammation. Clinician may consider continuing treatment in patients with asymptomatic chemical pancreatitis or radiologic abnormalities. Permanently discontinue pegaspargase if pancreatitis is confirmed.[8,9,13,15]

Asparaginase acts as a ***procoagulant***, but can also increase the risk of ***bleeding***. Depletion of asparagine leads to decreased synthesis of fibrinogen, plasminogen, Factor IX, Factor X, antithrombin, protein C, and protein S. Most thromboembolic/hemorrhagic events occur during induction therapy with asparaginase. Thrombosis tends to occur more commonly than bleeding, and incidence may be increased in adults and children receiving higher doses of asparaginase. Use pegaspargase cautiously in patients with an underlying coagulopathy or previous hematologic complications from asparaginase. Monitor coagulation parameters at baseline and regularly throughout treatment, particularly in patients receiving concurrent therapy with coagulation-inhibiting effects (e.g., ASA, NSAIDS). Treat severe or symptomatic coagulopathy with fresh-frozen plasma. Discontinue pegaspargase in patients with serious thrombotic events.[1-3]

INTERACTIONS:

No formal pharmacokinetic drug interaction studies have been conducted. However, pegaspargase may[4]:

- reduce the metabolism/clearance of protein bound drugs and/or increase their toxicity by decreasing serum proteins,
- reduce the metabolism/clearance of other drugs due to its hepatotoxicity,
- negate the action of drugs requiring cell division for their effect by inhibiting protein synthesis and cell division,
- lead to fluctuating coagulation factors and should be used cautiously with drugs having either procoagulant or anticoagulant effects,

Developed: 1 April 2022
Revised: 1 January 2025

- increase the CNS toxicity of other neurotoxic drugs,
- work synergistically with methotrexate and cytarabine if administered subsequent to them,
- be less effective if administered prior to methotrexate or cytarabine due to a weak antagonistic effect,
- be more toxic, and increase the risk of anaphylactic reactions, when it is administered immediately after or simultaneously with vincristine and/or prednisone.

SUPPLY AND STORAGE:

***Injection*:** Servier Canada Inc. supplies pegaspargase as 3750 unit ready-to-use single use (preservative free) vials in a concentration of 750 units/mL. Refrigerate. Store in original packaging to protect from light. Do not shake.[9]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

PARENTERAL ADMINISTRATION:

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

Intradermal	no information found
Subcutaneous[22]	has been used
Intramuscular[4,23-26]	• max volume injected at one site: 3 mL (adults); 2 mL (children and adolescents)[9] If higher volumes are required, divide dose and administer at different injection sites.[9]
Direct intravenous[9]	do NOT use
Intermittent infusion[4,23-26]	***over 1-2 h***
Continuous infusion	no information found
Intraperitoneal	no information found
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.

Developed: 1 April 2022
Revised: 1 January 2025

Adults:

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

Intravenous/intramuscular:	Cycle Length:	
	2 weeks[9]:	2500 units/m^2 (range 2000-2500 units/m^2) IV or IM for one dose on day 1 (total dose per cycle 2500 units/m^2 [range 2000-2500 units/m^2])
	3 weeks[10,11,24,25]:	***2500 units/m^2*** (range 1500-2500 units/m^2) ***IV or IM for one dose on day 1*** or ***day 2*** (total dose per cycle 2500 units/m^2 [range 1500-2500 units/m^2])
	4 weeks[11,26-28]:	***1500-2500 units/m^2 IV or IM for one dose on day 8*** (total dose per cycle range 1500-2500 units/m^2)
	Treatment day and dosing frequency may be based on patient age, treatment phase, and/or length of treatment phase. Refer to protocol by which patient is being treated. IV administration may be preferred over IM due to higher bioavailability after IV. Some dosing strategies have used lower pegaspargase doses (e.g., 1000-2000 units/m^2) and/or capped the dose at 3750 units (1 vial) to minimize the risk of drug-induced toxicities in adults.[14,15]	
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated	
Dosage in renal failure:	no adjustment required[9]	
Dosage in hepatic failure:	no adjustment required[9]	
Dosage in dialysis:	no information found	

Children:

Intravenous/intramuscular:	Cycle Length:	
	2 weeks[9]:	2500 units/m^2 IV or IM for one dose on day 1 (total dose per cycle 2500 units/m^2)

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Developed: 1 April 2022
Revised: 1 January 2025

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Revised: 1 January 2025