

DRUG NAME: Calaspargase pegol

SYNONYM(S): SC-PEG¹, EZN-2285¹, Succinimidyl Carbonate-PEG E. coli L-asparaginase¹

COMMON TRADE NAME(S): ASPARLAS®

CLASSIFICATION: antitumour antibiotic

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

MECHANISM OF ACTION:

Calaspargase pegol is a pegylated conjugate of L-asparaginase (*E. coli*-derived asparaginase), an enzyme that catalyzes the conversion of L-asparagine into aspartic acid and ammonia. L-asparagine is an amino acid that is essential for the synthesis of protein, RNA, and DNA. Leukemia cells are unable to synthesize adequate amounts of L-asparagine on their own and rely on extracellular sources for DNA synthesis and survival. The sustained depletion of plasma asparagine results in the death of leukemic cells and is thought to be the basis of the pharmacologic effect of asparaginase. L-asparaginase is cell-cycle specific for the G1 phase.¹⁻³ Calaspargase pegol is an immunosuppressive agent.

Although calaspargase pegol contains the identical enzyme and polyethylene glycol moiety present in pegaspargase, it has a more hydrolytically stable succinimidyl carbonate linker which gives calaspargase pegol a longer half-life. Asparaginase derived from *Erwinia chrysanthemi* is immunologically distinct from *E-coli* derived asparaginase and lacks immunologic cross-reactivity.¹⁻³ See comparison table below.

Comparison table of asparaginase products by source and availability

<i>E. coli</i>-derived Asparaginase	
Asparaginase (KIDROLASE)	withdrawn from CAN market
Pegaspargase (ONCASPARG)	pegylated conjugate of <i>E. coli</i> -derived asparaginase (attached to polyethylene glycol)
Calaspargase pegol (ASPARLAS)	pegylated conjugate of <i>E. coli</i> -derived asparaginase (attached to monomethoxy-polyethylene glycol)
<i>Erwinia chrysanthemi</i>-derived Asparaginase	
Asparaginase-erwinia (ERWINASE)	withdrawn from CAN market
Crisantaspase recombinant (RYLAZE)	recombinant asparaginase (identical to <i>Erwinia chrysanthemi</i> -derived asparaginase)

PHARMACOKINETICS:

Absorption	time to peak = 1.17 h; steady state concentrations achieved around fourth dose	
Distribution	rapidly depletes plasma asparagine; high levels of plasma asparaginase activity observed 5 minutes after infusion ⁴	
	cross blood brain barrier?	does not appear to cross the blood brain barrier; CSF asparagine depletion has been demonstrated as a result of plasma asparaginase depletion ⁵
	volume of distribution	2.96 L
	plasma protein binding	no information found

Metabolism	not metabolized by hepatic enzymes but expected to undergo proteolytic degradation	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	time-dependent elimination	
	urine	no information found
	feces	no information found
	terminal half life	16.1 d
	clearance	0.147 L/d

Adapted from standard reference^{1-3,6} unless specified otherwise.

USES:

Primary uses:

*Leukemia, acute lymphoblastic

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:

- history of anaphylaxis or severe hypersensitivity reaction to pegylated L-asparaginase therapy^{2,3}
- history of pancreatitis, serious hemorrhagic events, or serious thrombosis with previous L-asparaginase therapy^{2,3}

Caution:

- calaspargase pegol is **not interchangeable** with pegaspargase or other asparaginase formulations²
- calaspargase pegol is associated with increased hepatotoxicity and should be avoided in patients with **severe hepatic impairment**^{2,3}
- **sinusoidal obstruction syndrome (SOS) (aka hepatic veno-occlusive disease)** has been reported; use caution in patients with pre-existing liver disease or history of SOS²
- **premedication** with acetaminophen, H1-blocker, and H2-blocker +/- corticosteroid prior to administration may decrease the risk and severity of infusion and hypersensitivity reactions; if using premedications, consider monitoring asparaginase activity levels^{2,3,7,8}
- potential for **immunogenicity** exists; consider monitoring for asparaginase activity²
- **tumour lysis syndrome** may result in uric acid nephropathy with asparaginase products; closely monitor uric acid levels, particularly during induction therapy²
- concurrent administration of **live vaccines** may increase the risk of severe infections; administer live vaccines at least 3 months following termination of treatment²

Special populations: The risk of hepatic adverse effects from asparaginase (e.g., increased transaminases and bilirubin, hypofibrinogenemia) is increased in patients over 18 years of age.²

Carcinogenicity: No studies have been conducted.

Mutagenicity: No studies have been conducted.

Fertility: No studies have been conducted.

Pregnancy: In animal studies with calaspargase pegol, adverse developmental outcomes were not observed at exposures 0.2 to 1 times those seen following human clinical exposure. However, maternal toxicity resulted in reductions in gravid uterine and placental weights, with slight reductions in fetal body weights. Published animal studies with L-asparaginase suggest asparagine depletion may cause harm to the animal offspring. In females of childbearing potential, pregnancy tests are recommended prior to starting treatment and contraception is

recommended during treatment and for three months after the last dose. Calaspargase pegol may impair the hepatic clearance of oral contraceptives; alternative contraceptive measures are recommended.^{2,3}

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for three months after the last dose.^{2,3}

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.⁸ **Incidence data in the Side Effects table is mostly based on data from pediatric clinical trials with calaspargase pegol.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
blood and lymphatic system/ febrile neutropenia	anemia (26%, severe 26%)
	<i>coagulopathy</i> (9-14%); see paragraph following Side Effects table
	<i>febrile neutropenia</i> (severe 34-56%)
	leukopenia (severe 37%)
	lymphopenia (severe 9%)
	<i>neutropenia</i> (severe 56%)
	thrombocytopenia (severe 35%)
cardiac	arrhythmia (severe 2%)
	cardiac failure (severe 2%)
gastrointestinal	<i>emetogenic potential: low</i> ^{9,10}
	abdominal pain (33%, severe 21%)
	diarrhea (7%, severe 7-9%)
	nausea (severe 7%)
	neutropenic colitis (severe 7%)
	<i>pancreatitis</i> (12-19%, severe 10-18%); see paragraph following Side Effects table
	stomatitis (severe 14-25%)
	vomiting (12%, severe 9%)
general disorders and administration site conditions	<i>extravasation hazard: none</i> ¹¹
	pyrexia (9%, severe 7%)
hepatobiliary	<i>sinusoidal obstruction syndrome</i> (aka veno-occlusive disease); see paragraph following Side Effects table
immune	<i>antibody development</i> (15%) ¹ ; see paragraph following Side Effects table
infections and infestations	cellulitis (severe 9%)
	fungal infection (severe 3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	pneumonia (severe 3%)
	sepsis (severe 5%)
	staphylococcal infection (severe 6-19%)
injury, poisoning, and procedural complications	hypersensitivity , including anaphylaxis (9-26%, severe 7-21%); see paragraph following Side Effects table
investigations	activated partial thromboplastin time prolonged (12-30%, severe 6-7%)
	alkaline phosphatase increase (9%, severe 3%)
	ALT increase (35-79%, severe 33-49%)
	amylase increase (9-18%, severe 5-11%)
	AST increase (23-53%, severe 21-26%)
	bilirubin increase (46-63%, severe 18-23%)
	bilirubin (conjugated) increase (22%, severe 9%)
	cholesterol increase (9%, severe 5%)
	fibrinogen decrease (14-22%, severe 9-13%)
	gamma glutamyl transferase increase (16%, severe 16%)
	hyperammonemia ¹² ; see paragraph following Side Effects table
	international normalized ratio increase (12-16%, severe 3-7%)
	lipase increase (17-23%, severe 15-21%)
	weight loss (16%, severe 14%)
metabolism and nutrition	acidosis (severe 12%)
	appetite decrease (23%, severe 21%)
	dehydration (severe 14%)
	hyperkalemia (8%, severe <1%)
	hyperglycemia (34-79%, severe 24-37%); see paragraph following Side Effects table
	hypertriglyceridemia (16-28%, severe 12-21%)
	hypoalbuminemia (28-81%, severe 26-27%)
	hypoglycemia (31%, severe 7%)
	hypokalemia (28-46%, severe 28-43%)
	hyponatremia (19-22%, severe 19-20%)
hypophosphatemia (severe 7%)	
musculoskeletal and connective tissue	back pain (7%, severe 5%)
	pain in extremity (severe 9%)
nervous system	confusional state
	encephalopathy (severe 7%)
	headache (12%, severe 9%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
	peripheral motor neuropathy (28%, severe 9%)
	peripheral sensory neuropathy (19%, severe 9%)
	reversible posterior leukoencephalopathy syndrome
	seizure (5%)
	somnolence
	syncope (7%, severe 7%)
psychiatric	depression (7%, severe 5%)
respiratory, thoracic, and mediastinal	cough (7%)
	dyspnea (severe 4%)
	hypoxia (severe 7%)
vascular (see paragraph following Side Effects table)	<i>hemorrhage</i> (severe 4%)
	hypertension (5%, severe 3%)
	hypotension (severe 14%)
	<i>thrombosis, thromboembolic complications</i> (9-12%, severe 8%)

Adapted from standard reference² unless specified otherwise.

Elevated **ammonia** levels are an expected side effect of asparaginase treatment based on the mechanism of action of the enzyme. Asparaginase catabolizes asparagine to aspartic acid and ammonia, and secondarily converts glutamine to glutamate and ammonia. Many patients with reported asparaginase-induced hyperammonemia are asymptomatic. Severe complications and fatal outcomes have occurred. Consider monitoring ammonia levels in the presence of symptoms such as nausea, vomiting, lethargy, and irritation.^{2,12}

As with all therapeutic proteins, there is the potential for immunogenicity. Exposure to asparaginase can trigger the development of **anti-asparaginase antibodies**, which have been associated 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. Consider monitoring asparaginase activity levels in the setting of hypersensitivity and for the detection of silent inactivation.^{2,13,14} Consider switching to an *Erwinia*-derived asparaginase product if asparaginase activity levels fall below reference range.^{7,8}

Glucose intolerance can occur in patients receiving asparaginase products when alterations in endocrine pancreatic function become expressed as abnormal glucose metabolism. Glucose intolerance may be irreversible. Diabetic ketoacidosis, hyperosmolar hyperglycemia, and clinical hyperglycemia have been reported. Treatment with insulin may be required. Monitor patients for signs and symptoms of hyperglycemia regularly throughout treatment.²

Hemorrhage, serious **thrombotic events**, and an increased risk of bleeding have been reported. As calaspargase pegol can cause fluctuations in coagulation factors, regular monitoring of the coagulation profile is recommended throughout treatment. Coagulation parameters such as PT, PTT, and fibrinogen should be evaluated in patients with signs and symptoms of hemorrhage. Replacement therapy may be required. Permanently discontinue calaspargase pegol if serious or life-threatening thrombotic events occur.^{2,3}

Asparaginase products may worsen pre-existing **hepatic impairment** and the toxicity of other hepatically metabolized medications may be increased if administered concurrently with asparaginase. Hepatotoxicity, including

severe and life-threatening **sinusoidal obstruction syndrome (SOS)** (aka veno-occlusive disease) has been reported in patients treated with calaspargase pegol in combination with standard chemotherapy. Calaspargase pegol is not recommended in patients with severe hepatic impairment. Signs and symptoms of SOS may include rapid weight gain, fluid retention with ascites, hepatomegaly, and rapid increase of bilirubin. Monitor bilirubin and transaminases throughout treatment. Discontinue treatment if total bilirubin >10 x ULN or other signs of serious liver toxicity, including SOS, are present.

Hypersensitivity reactions observed with other asparaginase products include a range of reactions such as angioedema, lip swelling, eye swelling, erythema, decreased blood pressure, bronchospasm, dyspnea, pruritus, and rash. Grade 3 or 4 hypersensitivity reactions are reported in 7-21% of patients receiving calaspargase pegol, including life-threatening anaphylaxis and other serious allergic reactions.^{2,3} **Premedication** with acetaminophen, H1-blocker, and H2-blocker +/- corticosteroid prior to administration may decrease the risk and severity of infusion and hypersensitivity reactions. If using premedications, consider monitoring asparaginase activity levels.^{2,3,7,8} Be prepared to treat anaphylaxis with each administration and manage reactions according to the severity of the symptoms. Permanently discontinue calaspargase pegol for grade 3 or 4 hypersensitivity reactions.^{2,3}

Hemorrhagic or necrotizing **pancreatitis**, including cases with fatal outcome, have been reported with other asparaginase products. Pancreatitis has been reported in 12-19% of patients receiving calaspargase pegol, with the majority of cases reported as grade 3 or 4 in severity. Persistent and/or severe abdominal pain that may radiate to the back is the characteristic symptom of pancreatitis and may be fatal if left untreated. Serum amylase and/or lipase can identify early signs of pancreatic inflammation. Glucose and triglyceride levels should be monitored regularly during treatment. Hold calaspargase pegol if pancreatitis is suspected and permanently discontinue if severe pancreatitis is confirmed.^{2,3,7,8}

INTERACTIONS:

No formal pharmacokinetic drug interaction studies have been conducted. However, calaspargase pegol may:²

- 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,
- increase the CNS toxicity of other neurotoxic drugs,
- work synergistically with methotrexate and cytarabine if administered after them,
- be less effective if administered prior to methotrexate or cytarabine due to a weak antagonistic effect,
- increase exposure to glucocorticoids by decreasing glucocorticoid elimination,
- increase the risk of glucocorticoid-induced osteonecrosis in children >10 years of age, with a higher incidence seen in girls.

SUPPLY AND STORAGE:

Injection: Servier Canada Inc. supplies calaspargase pegol 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.²

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.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use ²
Intermittent infusion	over 1-2 h ²
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.

Adults:

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

	Cycle Length:	
<i>Intravenous</i> ^{2,3} :	3 weeks:	2500 units/m² IV for one dose on day 1 (total dose per cycle 2500 units/m ²)
<i>Concurrent radiation:</i>		no information found
<i>Dosage in myelosuppression:</i>		modify according to protocol by which patient is being treated
<i>Dosage in renal failure:</i>		no information found
<i>Dosage in hepatic failure:</i>		mild/moderate impairment: no information found severe impairment: avoid ²
<i>Dosage in dialysis:</i>		no information found

Children:

	Cycle Length:	
<i>Intravenous</i> ^{2,3} :	3 weeks:	≥1 month of age: 2500 units/m² IV for one dose on day 1 (total dose per cycle 2500 units/m ²)

REFERENCES:

1. Lexi-Drugs® - Lexicomp Online (database on the Internet). Calaspargase Pegol. Lexi-Comp Inc., 2024. Available at: <http://online.lexi.com>. Accessed July 2, 2024
2. Servier Canada Inc. ASPARLAS® product monograph. Laval, Quebec; March 8 2024
3. LLC Servier Pharmaceuticals. ASPARLAS® full prescribing information. Boston, MA, USA; December 2023
4. Angiolillo AL, Schore RJ, Devidas M, et al. Pharmacokinetic and Pharmacodynamic Properties of Calaspargase Pegol Escherichia coli L-Asparaginase in the Treatment of Patients with Acute Lymphoblastic Leukemia: Results from Children's Oncology Group Study AALL07P4. J Clin Oncol 2014;32(34):3874-3882
5. Schore, R J, Devidas M, Bleyer A, et al. Plasma asparaginase activity and asparagine depletion in acute lymphoblastic leukemia patients treated with pegaspargase on Children's Oncology Group AALL07P4. Leuk Lymphoma 2019;60(7):1740-1748
6. AHFS Drug Information® (database on the Internet). Calaspargase Pegol-mknl. Lexi-Comp Inc., 2024. Available at: <http://online.lexi.com>. Accessed July 2, 2024
7. COG Pharmacy Steering Committee and COG Pharmacist. Parenteral and Oral Chemotherapy Administration Guidelines Used by the Children's Oncology Group. Version 12. June 11 2024
8. Kendrick, Jennifer. Clinical Pharmacy Specialist, Children's and Women's Health Centre of British Columbia. Personal Communication - calaspargase pegol. October 8, 2024
9. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1 2022
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Antiemesis V.2.2023. National Comprehensive Cancer Network, Inc., 2023. Available at: <http://www.nccn.org>. Accessed December 7, 2023
11. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; March 1 2021
12. Lee A, Eldem I, Altintas B, et al. Treatment and outcomes of symptomatic hyperammonemia following asparaginase therapy in children with acute lymphoblastic leukemia. Molecular Genetics and Metabolism 2023;139(3)
13. van der Sluis, I. M., Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. Haematologica 2016;101(3):279-285
14. Bade NA, Lu C, Patzke CL, et al. Optimizing pegylated asparaginase use: An institutional guideline for dosing, monitoring, and management. J Oncol Pharm Pract 2020;26(1):74-92