Drug Monograph

A - Drug Name

pegaspargase

COMMON TRADE NAME(S): Oncaspar®

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B - Mechanism of Action and Pharmacokinetics

Pegaspargase is a pegylated form of L-asparaginase. It hydrolyzes extracellular L-asparagine, an amino acid that appears to be essential for protein synthesis by some tumour cells, which are unable to synthesize asparagine. Pegylation does not change L-asparaginase's enzymatic properties, but affects its pharmacokinetics and immunogenicity. Pegaspargase is less immunogenic than asparaginase derived from *E. coli* or *Erwinia chrysanthemi*; however, cross-hypersensitivity (including anaphylaxis) can occur. Pegaspargase has immunosuppressive activity.

Absorption	Bioavailability	82% (after first IM dose), 98% (after repeat IM dosing)
	T max	5 days (single IM dose); 1.25 h (single IV dose)
Distribution	Cross blood brain barrier?	Distribution in to the CSF is reported to be similar to L-asparaginase (minimal).
Metabolism	Degraded by enzymes distributed ubiquitously in tissues.	
	Active metabolites	None known
	Inactive metabolites	Yes

Elimination	Half-life appeared to be unaffected by dose, age, sex, BSA, renal or hepatic function. Pegaspargase is not excreted renally. Terminal half-life was shorter in hypersensitive patients than in non-hypersensitive patients, which may be due to the formation of high levels of anti-drug antibodies	
	Half-life	IM: 5.8 days; IV: 5.3 days

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C - Indications and Status

Health Canada Approvals:

- Acute lymphoblastic leukemia

Refer to the product monograph for a full list of approved indications.

Other Uses:

- Extranodal natural killer/T-cell lymphoma (ENKTL)

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following adverse events were reported from clinical trials (including pediatric patients) with pegaspargase and post-marketing reports. The list also includes severe or life-threatening events reported with other asparaginase formulations.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (1 to <10%)	E
	Hypotension (3%) (severe)	I
	Venous thromboembolism (3%) (including CNS)	E
Dermatological	Rash (5%) (severe skin disorders)	E

Gastrointestinal	Abdominal pain (≥10%)	E
	Diarrhea (≥10%)	E
	GI perforation (rare)	E
	Mucositis (1 to <10%)	E
	Nausea, vomiting (1 to <10%)	I
General	Fever (may be severe)	I
Hematological	Fibrinogen decreased (1 to <10%; also ↑ PT, aPTT ± bleeding; may be severe, including CNS)	E
	Myelosuppression (1 to <10%; ± infection)	E
Hepatobiliary	↑ LFTs (≥10%) (may be severe with hepatic failure)	E
	Pancreatitis (≥10%) (2% severe, including hemorrhagic or necrotizing)	E D
Hypersensitivity	Hypersensitivity (10%) (in asparaginase-naive patients; may be severe)	I
Immune	Antibody response (antibody formation; 2-11%)	E D
Metabolic / Endocrine	Hyperglycemia (≥10%) (5% severe)	E
	Hyperlipidemia (1 to <10%)	E
	Hyperuricemia (during periods of active cell lysis)	I
Musculoskeletal	Musculoskeletal pain (1 to <10%)	E
Nervous System	Cognitive disturbance (1 to <10%)	E
	Peripheral neuropathy (7%) (severe)	E
	Posterior reversible leukoencephalopathy syndrome (PRES) (rare)	E
	Seizure (1 to <10%)	E
	Tremor (rare)	E
Renal	Nephrotoxicity (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g. some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by

addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

Severe hepatotoxicity has been described when used in combination with other hepatotoxic agents and in debilitated patients . Asparaginase treatment may increase pre-existing liver impairment from underlying liver disease or caused by prior therapy. Liver abnormalities usually resolve after the end of therapy and some reversal may occur during the course of treatment.

Asparaginase or hepatic impairment may produce decreased levels of factors V, VII, VIII, IX, X and fibrinogen, and possibly contribute to **coagulation** disorders. Increased fibrinolytic activity has also been observed.

Hemorrhagic and thrombotic cardiovascular or neurologic events occur in approximately 1-2% of patients receiving asparaginase. These generally occur after a few weeks of l-asparaginase therapy, and may occur after therapy is completed.

Cognitive dysfunction may include mild to severe lethargy, drowsiness, depression, confusion, hallucination, agitation, seizures or personality changes. They are seen during the first day of therapy and resolve within a few days to a week after drug discontinuation.

Pancreatitis can occur during or after therapy, and can be fatal. It may be present despite normal serum amylase concentrations.

Hyperglycemia has been observed, which appears to be potentiated by prednisone. Transient diabetes mellitus may develop. Insulin may be required for severe hyperglycemia, but it is usually reversible when the drug is discontinued. Glucose intolerance may be irreversible.

Severe **hypersensitivity** reactions may occur with pegaspargase. There is a higher risk in patients with known hypersensitivity to other forms of L-asparaginase.

Antibodies to pegaspargase have been observed. Patients with hypersensitivity reactions to asparaginase were more likely to have antibodies than those who did not have reactions. Hypersensitivity reactions are associated with increased asparaginase clearance, and higher antibody levels may lead to decreased asparaginase activity.

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E - Dosing

May be given either by intravenous or intramuscular injection.

Numerous dosing schedules exist. Refer to protocol by which the patient is being treated.

Usually used in combination with other cytotoxic drugs.

Thromboprophylaxis may be considered.

Premedications (prophylaxis for infusion reaction)

Give 30-60 minutes before administration:

- Acetaminophen (e.g. 500 mg PO)
- H1-receptor blocker (e.g. diphenhydramine 50 mg PO)
- H2-receptor blocker (e.g. famotidine 20 mg IV)
- Corticosteroid (e.g. hydrocortisone 100 mg IV)

Adults:

- 2000 units/m² q14-21 days
- 2500 units/m^2 q21 days (SMILE or DDGP)

Consider monitoring trough serum L-asparaginase activity measured before the next pegaspargase administration. A switch to a different L-asparaginase preparation could be considered if L-asparaginase activity failed to reach target levels. Consult with a hematology expert.

Dosage with Toxicity:

Dosage with Myelosuppression: No dose adjustment required.

- Myelosuppression is not increased when used with other antileukemic drugs.

Dosage with Other Toxicity:

Toxicity	Action
Thrombotic or hemorrhagic events	Hold; restart when resolved if appropriate . Discontinue for severe events.
Suspected pancreatitis	Hold, investigate and if confirmed, discontinue.
Bilirubin 2.5-4 x ULN and/or AST/ALT 5-20 x ULN*	Hold; restart if resolved to bilirubin ≤1.5 x ULN and LFTs ≤3 x ULN
Bilirubin >4 x ULN and/or AST/ALT >20 x ULN*	Discontinue

Severe hypersensitivity reactions, anaphylaxis	Discontinue
RPLS / PRES	
Other grade 4 organ/ non-hematologic	

*Adapted from Stock et al, 2011.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

IV Pegaspargase:

Grade	Management	Re-challenge
1	• Reduce the infusion rate by 50%	No specific recommendations available
2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** After symptom resolution, restart by reducing the infusion rate by 50%.	
3 or 4	• Stop treatment. • Aggressively manage symptoms.	Permanently discontinue. (Do not re-challenge.)

Dosage with Hepatic Impairment:

Not formally studied in patients with hepatic impairment. May increase pre-existing liver impairment. There is an increased risk of hepatic effects (e.g. ↑ LFTs or bilirubin) among patients > 18 years of age.

Hepatic Impairment	LFTs	Starting dose
Mild	bilirubin ≤ 3 x ULN ± AST/ALT ≤ 10 x ULN	No information found
Moderate		
Severe	bilirubin > 3 x ULN ± AST/ALT > 10 x ULN	Contraindicated

Dosage with Renal Impairment:

Not formally studied in patients with renal impairment. Pegaspargase is not excreted renally; no dose adjustment is required.

Dosage in the elderly:

There are limited data available for patients > 65 years.

Children:

Refer to protocol by which the patient is being treated. There is very limited information on safety and efficacy of pegaspargase in children < 1 year of age.

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F - Administration Guidelines

Risk of medication error: The 3 asparaginase formulations (pegaspargase, E. coli asparaginase, Erwinia asparaginase) **are not Interchangeable**. Confirm the formulation carefully against the regimen used before prescribing, dispensing and administration.

- May be given either IV or IM
- For IV administration, dilute the dose in 100 NS or D5W and infuse over 1 to 2 hours.

- The IM injection volume should not exceed 3 mL in adults (or 2 mL in children/adolescents) per injection site; divide the dose and give at several injection sites for higher injection volumes.
- Refrigerate unused vials (2 to 8ºC). Do not freeze or shake. Protect from light.

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G - Special Precautions

Contraindications:

- anaphylactic or severe hypersensitivity reactions to the active substance or to any of the excipients
- known serious allergic reactions to pegaspargase
- patients with known serious thrombosis or serious hemorrhagic events with previous L-asparaginase therapy
- patients who have or had pancreatitis (including hemorrhagic)
- severe hepatic impairment (bilirubin > 3 times upper limit of normal [ULN]; transaminases > 10 times ULN).

Other Warnings/Precautions:

- Avoid live and attenuated live vaccines.
- Pegaspargase may worsen pre-existing liver impairment.
- Use with caution in diabetic patients.
- Risk of severe hypersensitivity reactions is higher in patients with known hypersensitivity to other forms of asparaginase.
- Patients should use caution when driving or using machinery as fatigue, drowsiness or confusion have been reported with treatment.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: Unknown
- Embryotoxicity: Yes
- Teratogenicity: Yes
  Pegaspargase is contraindicated in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose. Since an indirect interaction between oral contraceptives and pegaspargase cannot be excluded, females should use a method other than oral contraceptives.
- Breastfeeding: Contraindicated
  L-asparaginase is found in animal milk.
- Fertility effects: Unknown

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H - Interactions

Formal interaction studies have not been conducted with pegaspargase. Pegaspargase may interfere with enzymatic metabolism of other medications, especially in the liver.

The following also includes interactions reported with other formulations of asparaginase:

AGENT	EFFECT	MECHANISM	MANAGEMENT
Hepatotoxic drugs (e.g. imatinib)	↑ hepatotoxicity	Additive	Monitor liver function, use with caution
Neurotoxic drugs (e.g. vincristine)	↑ risk of neurotoxicity	Additive	Monitor for toxicity, use with caution
Drugs requiring hepatic enzyme metabolism	May ↑ toxicity of these agents	Asparaginase may interfere with enzymatic detoxification	Caution
Methotrexate	↓ effect of both drugs when asparaginase given immediately before or concurrently with methotrexate; Enhanced effect of both drugs when asparaginase given after methotrexate	Suppression of asparagine concentrations or cell replication	refer to protocol by which patient is being treated
Cytarabine	↓ effect of asparaginase when asparaginase given immediately before or concurrently with cytarabine; Enhanced effect of asparaginase when asparaginase given after cytarabine	Suppression of asparagine concentrations or cell replication	Refer to protocol by which patient is treated
Immunosuppressants (i.e., cyclosporine, tacrolimus, sirolimus)	↑immunosuppression, risk of lymphoproliferation	Additive	Caution
Phenytoin	↑ risk of seizures	↓ phenytoin uptake; risk of ↑ toxicity or ↓ efficacy of cytotoxics due to metabolism induction	Use other anticonvulsant alternatives
Prednisone	↑hyperglycemia	Additive	Monitor

Vincristine and/or prednisone	Immediately preceding or simultaneous vincristine and/or prednisone treatment can ↑ pegaspargase toxicity and ↑ risk of anaphylactic reactions	Unknown	refer to protocol by which patient is being treated
Anticoagulants, including NSAIDs, ASA	↑ risk of bleeding	Changes in coagulation by asparaginase	Use with caution
Serum thyroxine-binding globulin	↓ total serum thyroxine concentration	↓ synthesis of thyroxine-binding globulin in liver	Delay measurement until 4 weeks after end of asparaginase therapy
Live and attenuated live vaccines	↑ risk of severe infections	immunosuppressive activity of asparaginase	Avoid. Vaccinations with live vaccines should be given at least 3 months after the end of the entire treatment protocol
Oral contraceptives	May ↓ efficacy of oral contraceptives (reported with pegaspargase)	May impair hepatic clearance of oral contraceptives due to asparaginase's hepatotoxic effects	Use alternative contraception method
Glucocorticoids	Osteonecrosis has been observed in children > 10 years of age, higher incidence in girls	Possible complication from hypercoagulability	Caution
Glucocorticoids	↑ effects on fibrinogen and ATIII decreases (reported with pegaspargase)	Unknown	refer to protocol by which patient is treated
Highly protein-bound drugs	↑ toxicity of these drugs (reported with pegaspargase)	Decreased serum proteins	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests, albumin	Baseline, before each dose, and as clinically indicated
Serum amylase, lipase levels	Baseline, before each dose, and as clinically indicated
Clotting profile (PT, aPTT, fibrinogen, ATIII)	Baseline and as clinically indicated, more frequent if concurrent use of drugs with pro-coagulant/anticoagulant effects
Blood glucose, especially in patients known to be diabetic	Baseline and as clinically indicated
CBC	Baseline and as clinically indicated
Hypersensitivity reactions	For 1 hour after administration
Trough serum L-asparaginase level	Before the next dose (refer to local protocols)
Clinical toxicity assessment for tumour lysis syndrome, infection, hypersensitivity reactions, GI, rash, pancreatitis, thromboembolism/bleeding, neurologic effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Cholesterol and triglycerides	As clinically indicated
Urinary glucose	Baseline and as clinically indicated
Ammonia levels	As clinically indicated

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J - Supplementary Public Funding

High Cost Therapy Funding Program ()

- Pegaspargase (Inpatient) - Adult Acute Lymphoblastic Leukemia (ALL) Lymphoblastic Lymphoma Mixed or Biphenotypic Leukemia

New Drug Funding Program (NDFP Website)

- Pegaspargase - Newly Diagnosed Pediatric ALL Lymphoblastic Lymphoma or Mixed_Biphenotypic Leukemia
- Pegaspargase - Relapsed or Refractory Pediatric ALL Lymphoblastic Lymphoma or Mixed_Biphenotypic Leukemia
- Pegaspargase (Outpatient) - Adult Acute Lymphoblastic Leukemia (ALL) Lymphoblastic Lymphoma Mixed or Biphenotypic Leukemia
- Pegaspargase - Extranodal Natural Killer/T-cell Lymphoma

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K - References

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August 2022 Updated Indications, Adverse Effects, Dosing, Special precautions, Interactions, Monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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