Drug Monograph

A - Drug Name

Erwinia asparaginase

COMMON TRADE NAME(S): Erwinase®

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B - Mechanism of Action and Pharmacokinetics

Erwinia asparaginase is an enzyme purified from *Erwinia chrysanthemi*. 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. Erwinia asparaginase is serologically distinct from asparaginase derived from E. coli, although their antineoplastic activity and toxicity are similar.

Distribution	Mostly confined to blood compartment.	
	Cross blood brain barrier?	Minimal
Metabolism	The metabolism pathway for asparaginase is unknown; it may occur via degradation within the reticuloendothelial system and by serum proteases.	
	Active metabolites	None known
	Inactive metabolites	Yes
Elimination	Erwinia asparaginase is absent from blood 7 days after a single 25000 u/m^2 IM dose.	
	Half-life	IM: 16 hours

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C - Indications and Status

Health Canada Approvals:

- Acute lymphoblastic leukemia (ALL); primarily in combination with other antineoplastic agents to induce remission
- For patients who developed hypersensitivity (not anaphylaxis) to E-coli derived L-asparaginase

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The adverse effects in the following table were mainly observed in 2 pediatric ALL Erwinia asparaginase clinical trials. The list also includes severe or life-threatening events reported with other asparaginase formulations.

^ Incidences reported in Erwinia asparaginase

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial/venous thromboembolism (2%) (including CNS)^	E
Gastrointestinal	Abdominal pain (1%) ^	E
	Anorexia, weight loss (>20% weight loss: 1%)^	E
	Diarrhea (3%) ^	E
	GI perforation (rare)	E
	Nausea, vomiting (5%) (usually mild, rarely severe)^	I E
General	Fever (3%) (drug or disease-related; may be severe)^	I
Hematological	Fibrinogen decreased (1%) (also ↑ PT, aPTT ± bleeding; may be severe)^	E
	Hemorrhage (3%) (including CNS)^	E
	Myelosuppression (rare, usually mild ± infection)	E

Hepatobiliary	↑ LFTs (1%) (may be severe)^	E D
	Pancreatitis (2%) ^	E D
Hypersensitivity	Hypersensitivity (14%) (anaphylaxis <1%)^	I
Immune	Antibody response	E D
Metabolic / Endocrine	Hyperglycemia (diabetes <1%; may be severe)^	E
	Hyperuricemia (during periods of active cell lysis)	I
	Other (↑ or ↓ in lipids)	E
Nervous System	Cognitive disturbance (2%) (coma ± seizures)^	E D
	Headache (usually mild)	E
	RPLS / PRES (rare)	E
	Tremor (rare)	E
Renal	Nephrotoxicity (rare)	E
Reproductive and breast disorders	Infertility	E D L

* "*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 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.

Hepatotoxicity is frequent, usually mild but may be severe especially in debilitated patients or when used in combination with other hepatotoxic drugs. 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. Replacement therapy should be given if fibrinogen is less than 1g/L or ATIII less than 60%. Increased fibrinolytic activity has also been observed

Hemorrhagic and thrombotic cardiovascular or neurologic events occur in approximately 1-2% of patients receiving asparaginase. These events 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. Rare cases of posterior

reversible encephalopathy syndrome (PRES / RPLS) have been reported.

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.

Hypersensitivity reactions to l-asparaginase have occurred in the absence of a positive skin test. A lower incidence of anaphylaxis has been reported with IM use, although there was a higher incidence of mild hypersensitivity than with the IV route. Risk of anaphylaxis to Erwinia l-asparaginase may be greater in patients who have reacted to E. coli l-asparaginase (or pegaspargase) and is related to the number of doses given.

Anti-drug antibodies were detected in up to 13% of patients in 2 clinical trials. 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

Patients who are rechallenged after prior hypersensitivity reactions should be pretreated with steroids.

When substituting one asparaginase formulation for the other, modifications in dose and schedule are required. Refer to specific regimen for details.

Adults:

May be given either by intramuscular (preferable), subcutaneous or IV (bolus) injection.

Numerous dosing schedules exist. Refer to protocol by which patient is being treated. Usually used in combination with other cytotoxic drugs.

Example: Induction, in combination: 10000 u/m^2 SC 3 times weekly starting on week 4 for 4 weeks

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
Suspected pancreatitis	Hold, investigate and if confirmed, discontinue.
Grade 2 bilirubin ± grade 3 AST/ALT	Hold; restart if resolved to ≤ grade 1 within 7 days; otherwise discontinue
Severe hypersensitivity reactions, anaphylaxis	Discontinue
RPLS / PRES	
Grade ≥3 bilirubin ± grade 4 AST/ALT	
Other grade 4 organ/ non-hematologic	

Dosage with Hepatic Impairment:

May increase pre-existing liver impairment. The following recommendations are based on literature.

Hepatic Impairment	LFTs	Action
Mild		Use with caution; no information found.
Moderate		
Severe	Grade ≥3 bilirubin ± AST/ALT > 10 x ULN	Do not use

Dosage with Renal Impairment:

No adjustment required.

Dosage in the elderly:

Limited data are available in patients ≥ 65 years.

Children:

Refer to protocol being used. Asparaginase toxicity is reported to be greater in adults than in children.

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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.

- Reconstitute with Normal Saline. Do not use Sterile Water for injection as the reconstituted product is not isotonic and may cause painful injections.
- Minimize drug contact with the rubber stopper of the vial as it may denature the reconstituted drug and form transiently insoluble filaments.
- Avoid vigorous shaking as a loss of enzymatic potency may result.
- IM or SC administration routes are recommended due to lower incidence of anaphylaxis than other routes (e.g. IV).
- Use multiple injection sites if an IM/SC dose greater than 2 mL is to be given.
- Refrigerate unopened vials (2 to 8ºC).

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G - Special Precautions

Contraindications:

- patients who a history of hypersensitivity reactions to Erwinia asparaginase or any of its components
- patients who have or had pancreatitis (including hemorrhagic)
- patients with known serious thrombosis or serious hemorrhagic events with previous l-asparaginase therapy
- patients who have recently been vaccinated against yellow fever

Other Warnings/Precautions:

- Avoid live and attenuated live vaccines.
- L-asparaginase 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.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: Unknown
- Embryotoxicity: Yes
- Teratogenicity: Yes
  L-asparaginase is contraindicated in pregnancy. Adequate contraception should be used by both sexes, during asparaginase treatment and for at least 6 months after treatment cessation.
- Breastfeeding: Contraindicated
- Fertility effects:
  Azoospermia and amenorrhea have been reported in l-asparaginase.

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H - Interactions

The following also includes interactions reported in other formulations of asparaginase.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Hepatotoxic drugs	↑ hepatotoxicity	Additive	Monitor liver function; 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 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	↑ vincristine toxicity when vincristine given concurrently or immediately after asparaginase	Unknown	Refer to protocol by which patient is treated
Anticoagulants, including NSAIDs,	↑ risk of bleeding	Changes in coagulation by	Use with caution

ASA		asparaginase	
Serum thyroxine-binding globulin	↓ total serum thyroxine-binding globulin 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	↑ 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 and serum amylase levels	Baseline and as clinically indicated
Clotting profile (aPTT, fibrinogen, AT III, KPTT)	Baseline and before each dose
Blood glucose especially in patients known to be diabetic	Baseline and as clinically indicated
Clinical toxicity assessment for tumour lysis syndrome, pancreatitis, GI, infection, hypersensitivity reactions, 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
Albumin levels	As clinically indicated
Urinary glucose	Baseline and as clinically indicated
CBC	Baseline and as clinically indicated

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Erwinia Asparaginase - Newly Diagnosed Pediatric ALL Lymphoblastic Lymphoma or Mixed_Biphenotypic Leukemia
- Erwinia Asparaginase - Relapsed or Refractory Pediatric ALL Lymphoblastic Lymphoma or Mixed_Biphenotypic Leukemia

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K - References

Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations. Clin Pharmacokinet 2005; 44(4): 367-93.

Feinberg WM and Swensen FR. Cerebrovascular complications of l-asparaginase therapy. Neurology 1988; 38: 127-33.

Ho DH, Yap HY, Brown N, et al. Clinical pharmacology of intramuscularly administered L-asparaginase. J Clin Pharmacol 1981 Feb-Mar;21(2):72-8.

Kingsley CD. Hypersensitivity reactions. In: Perry MC, editor. The Chemotherapy Source Book. 4th ed. Philadelphia: Lippincourt Williams & Wilkins; 2008. p. 153.

L-asparaginase drug monograph, Cancer Care Ontario. September 2019.

McEvoy GK, editor. AHFS Drug Information 2013. Bethesda: American Society of Health-System Pharmacists.

Product Monograph: Kidrolase® (asparaginase). Jazz Pharmaceuticals, December 2017.

Product Monograph: Erwinase® (Erwinia asparaginase). Jazz Pharmaceuticals. July 2016.

Product Monograph: Oncaspar® (pegaspargase) . Shire Pharma Canada Corp. April 20, 2018.

Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma 2011;52(12):2237-53.

January 2020 Added NDFP forms

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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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