

**Oncaspar: Sustained Asparagine Depletion
With Enhanced Patient Benefits**

Helping Patients Gain the Full Benefits of Asparaginase Therapy

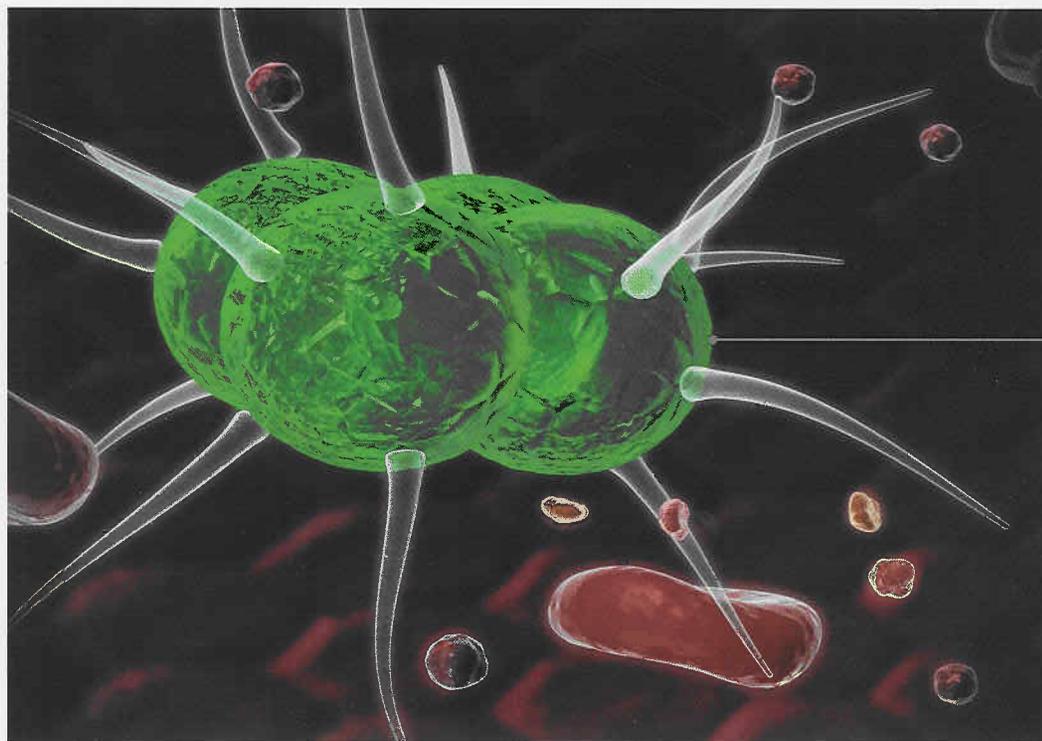


Oncaspar® is indicated as a component of a multiagent chemotherapeutic regimen for the first-line treatment of patients with acute lymphoblastic leukemia and for the treatment of patients with acute lymphoblastic leukemia and hypersensitivity to native forms of L-asparaginase.

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Sustained Activity. Proven Results.

Asparaginase Therapy Is an Essential Component in the Treatment of Acute Lymphoblastic Leukemia (ALL)¹



**Oncaspar® (pegaspargase):
The Pegylated Formulation
of Native L-asparaginase**

Asparagine is an essential
amino acid for leukemic cells,
not for normal cells²

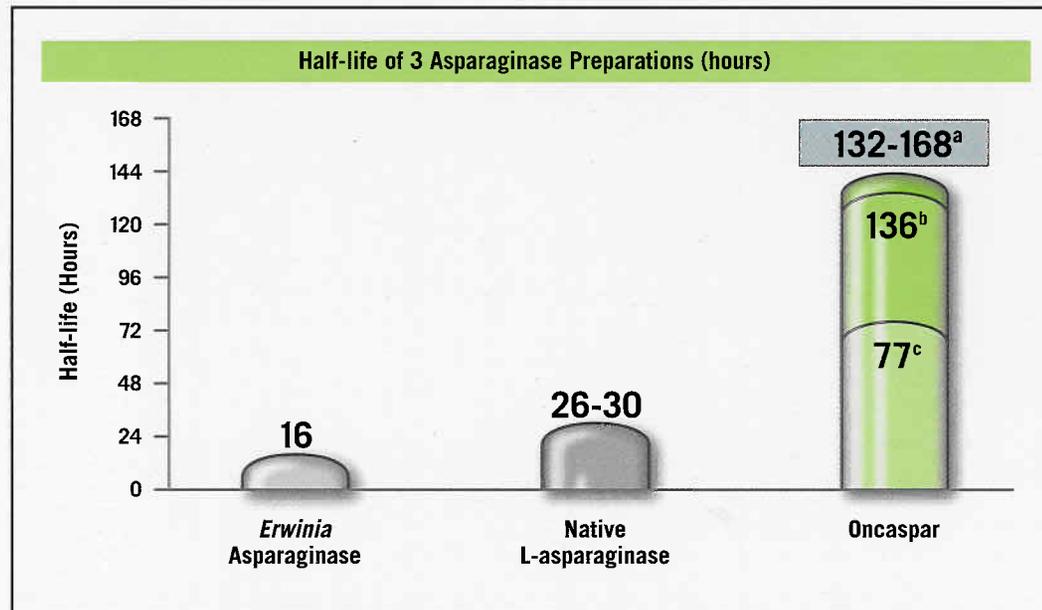
L-asparaginase metabolizes
asparagine to aspartic acid
and ammonia¹

L-asparaginase depletes
circulating asparagine, leading
to the death of leukemic cells²

Please see enclosed full Prescribing Information before prescribing Oncaspar.

Oncaspar®: The Power of Pegylation

Pegylation significantly increases the half-life of asparaginase^{1,3,4}



^aHalf-life of Oncaspar in newly diagnosed ALL patients with no prior exposure to either native L-asparaginase or Oncaspar was 5.5-7 days.

^bHalf-life of Oncaspar in 28 patients with relapsed ALL previously treated with native L-asparaginase and not considered to be hypersensitive to native L-asparaginase was 5.7 ± 3.2 days.

^cHalf-life of Oncaspar in 9 patients who were previously treated with native L-asparaginase and considered to be hypersensitive to native L-asparaginase was 3.2 ± 1.8 days.

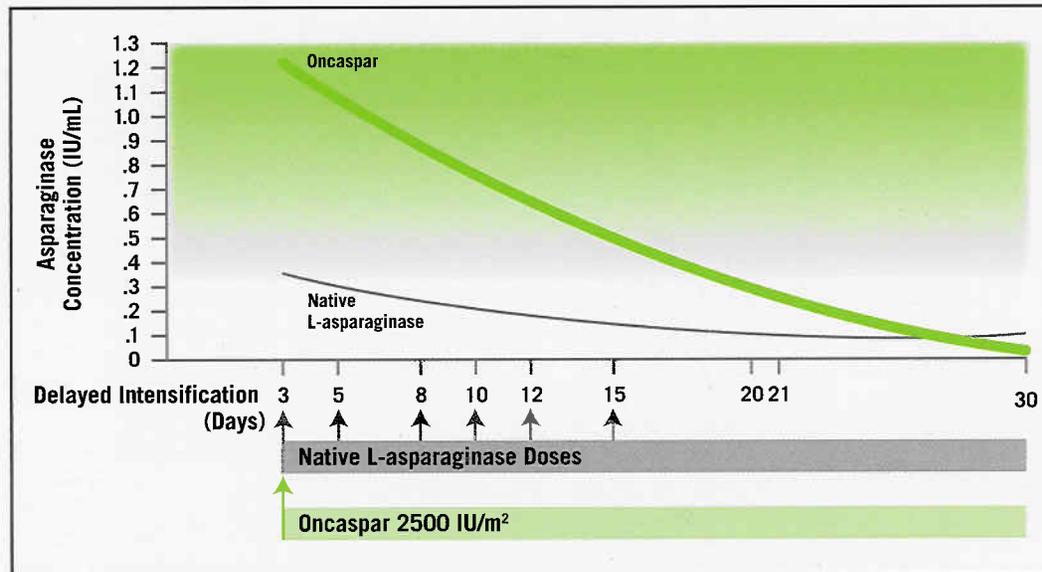
Pegylation can alter the pharmacokinetics; therefore, the pharmacodynamics of a therapeutic molecule⁵

Pegylation protects L-asparaginase from enzyme degradation, allowing for sustained plasma concentrations⁵

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Oncaspar®: Sustained Asparaginase Activity With a Single Dose^{1-3,6-8*,†}



One dose of Oncaspar results in therapeutic asparaginase concentrations for more than 2 weeks^{1-3,6-8}

Adapted from Avramis et al 2002.

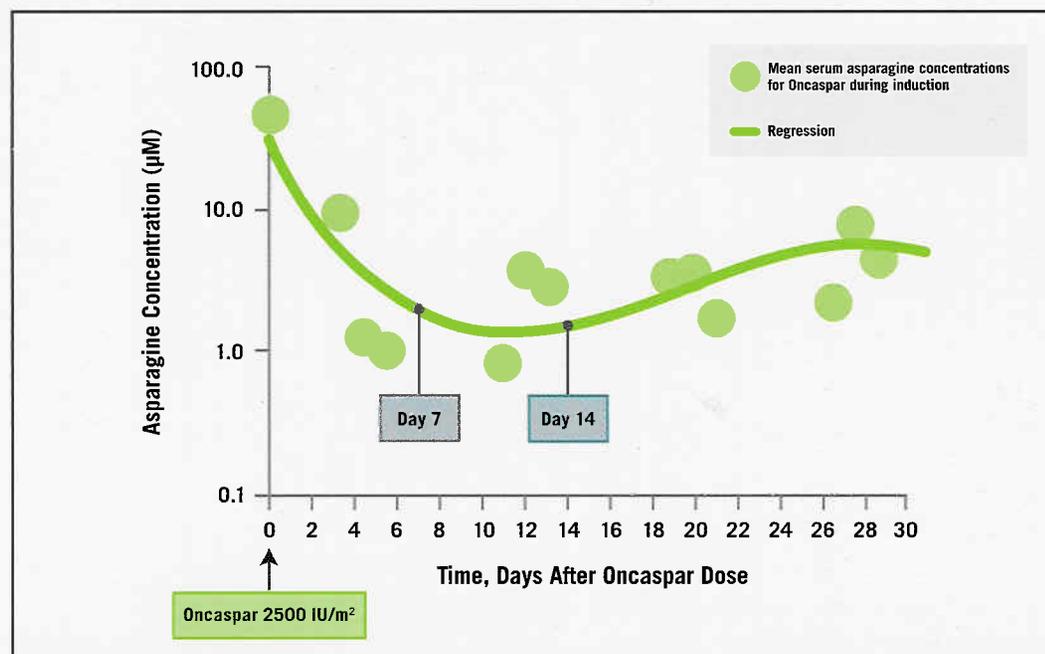
*Asparaginase enzymatic activity in sera over time: Profiles in pediatric patients with acute lymphoblastic leukemia after native asparaginase or pegaspargase administration during delayed intensification no. 1.

†The treatment for Children's Cancer Group 1962: Delayed intensification no. 1 included pegaspargase IM 2500 IU/m² on day 3 or native L-asparaginase IM 6000 IU/m² on days 3, 5, 8, 10, 12, and 15.

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Oncaspar®: Patients Maintain the Benefits of Sustained Asparagine Depletion

A single dose of Oncaspar provides rapid asparagine depletion within 4 days and sustained depletion for 3 weeks^{2,*}



Adapted from Avramis et al 2002.

*In Children's Cancer Group 1962, Oncaspar (2500 IU/m² IM) was administered on day 3 of the 4-week induction phase.

Sustained asparagine depletion correlates with rapid blast clearance

M1 achieved by majority of patients on days 7 and 14⁶

No evidence of M3 bone marrow on day 14⁶

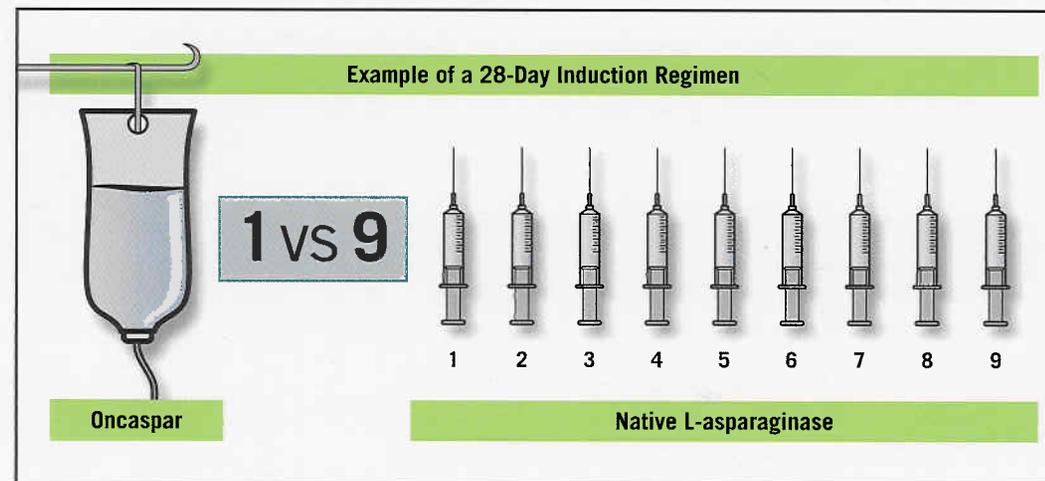
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Oncaspar®: Fewer Doses and Greater Flexibility²

When administered via IV, the pain caused by IM injections can be avoided⁶

- Single-dose Oncaspar requires fewer patient visits⁹
 - 6 fewer induction visits
 - 4 fewer delayed intensification visits



IM = intramuscular, IV = intravenous.

*One to six conversion of Oncaspar to native L-asparaginase in other phases of treatment.

One dose of Oncaspar achieves similar levels of asparagine depletion as 9 doses of native L-asparaginase during induction^{2,6,*}

Oncaspar can be administered through IM or IV injection²

1 IV infusion of Oncaspar = 9 IM injections* of native L-asparaginase during induction

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Oncaspar®: No Age Restrictions

No limit on duration of therapy

- The recommended dose of Oncaspar is 2500 IU/m² no more frequently than every 14 days²
- Each single-use vial of Oncaspar contains 3750 IU/5 mL

Overdosage Safety Information

- 3 patients received 10,000 IU/m² of Oncaspar as an IV infusion²
 - 1 patient experienced a slight increase in liver enzymes
 - 1 patient developed a rash 10 minutes after the start of the infusion, which was controlled with the administration of an antihistamine and by slowing down the infusion rate
 - 1 patient did not experience any adverse reactions

Administration of Oncaspar

IM Administration: Limit the volume at a single injection site to 2 mL; if greater than 2 mL, use multiple injection sites.²

IV Administration: Give over a period of 1 to 2 hours in 100 mL of sodium chloride or dextrose injection 5% through an infusion that is already running.²

- Note** Do not administer Oncaspar if drug²:
- Has been frozen
 - Has been stored at room temperature for more than 48 hours
 - Has been shaken or vigorously agitated
 - Is cloudy, discolored, and/or precipitate is present

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Oncaspar[®]: Low Rates of Hypersensitivity May Allow Patients to Remain on Therapy²

3% of first-line Oncaspar patients experienced hypersensitivity of any grade²

**A Comparison of Safety: Oncaspar and Native L-asparaginase
Per-patient Incidence of Selected Grades 3 and 4 Adverse Reactions²**

	Oncaspar (n=58)	Native L-asparaginase (n=59)
Abnormal liver tests	3 (5%)	5 (8%)
Elevated transaminases ^a	2 (3%)	4 (7%)
Hyperbilirubinemia	1 (2%)	1 (2%)
Hyperglycemia	3 (5%)	2 (3%)
Central nervous system thrombosis	2 (3%)	2 (3%)
Coagulopathy ^b	1 (2%)	3 (5%)
Pancreatitis	1 (2%)	1 (2%)
Clinical allergic reactions to asparaginase	1 (2%)	0

^aAspartate aminotransferase, alanine aminotransferase.

^bProlonged prothrombin time or partial thromboplastin time or hypofibrinogenemia.

Low rates of hypersensitivity in patients allergic to native L-asparaginase²

- **68% of relapsed ALL patients with a history of hypersensitivity to native L-asparaginase did not experience a clinical allergic reaction to Oncaspar (n=62)**

Considerations for managing patients treated with Oncaspar²

- **Serious allergic reactions can occur in patients receiving Oncaspar. The risk of serious allergic reactions is higher in patients with known hypersensitivity to other forms of L-asparaginase**
- **Observe patients for 1 hour after administration of Oncaspar in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (for example, epinephrine, oxygen, intravenous steroids, antihistamines)**
- **Discontinue Oncaspar in patients with serious allergic reactions**

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Classification Is Important in the Management of Asparaginase-related Adverse Events

Allergy/Immunology Grades – Common Terminology Criteria for Adverse Events (CTCAE) v3.0 ¹⁰						
Adverse Event	Short Name	1	2	3	4	5
Allergic reaction/hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria ^a ; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria ^a ; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death

Differences exist between grade 2 dermatologic and grade 2 allergic reactions -CTCAE v3.0¹⁰

Local injection-site reactions can be mistaken for clinical allergic reactions

Dermatology/Skin Grades – CTCAE v3.0 ¹⁰						
Adverse Event	Short Name	1	2	3	4	5
Injection-site reaction/extravasation changes	Injection-site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	Not available	Not available

^aUrticaria with manifestations of allergic or hypersensitivity reaction is graded as allergic reaction/hypersensitivity (including drug fever). From National Cancer Institute Web site.

Proper management of asparaginase-related adverse events may:

- Improve patient safety
- Allow patients to maintain the benefits of sustained asparagine depletion

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Oncaspar®: Pegylation Enhances Patient Benefits

Sustained asparaginase activity with a single dose^{1-3,6-8}:

- Fewer patient visits⁹
- Low rates of hypersensitivity that may allow patients to remain on therapy^{2,6}
- Avoidance of IM pain with option of IV administration⁶

IMPORTANT SAFETY INFORMATION

- Oncaspar® is contraindicated in patients with a history of serious allergic reactions to Oncaspar®, and in patients with a history of serious thrombosis, pancreatitis, or serious hemorrhagic events with prior L-asparaginase therapy
- Oncaspar® should be discontinued in the case of anaphylaxis or serious allergic reactions, thrombosis, or pancreatitis. Glucose intolerance, in some cases irreversible, can occur. Coagulopathy can occur. Perform appropriate monitoring
- In study 2 (n=2770), the per-patient incidences for Grades 3 and 4 nonhematologic toxicities were: elevated transaminases (11%), coagulopathy (7%), hyperglycemia (5%), CNS thrombosis/hemorrhage (2%), pancreatitis (2%), clinical allergic reaction (1%), and hyperbilirubinemia (1%). There were 3 deaths due to pancreatitis
- The most common adverse reactions with Oncaspar® (≥2%) are allergic reactions (including anaphylaxis), hyperglycemia, pancreatitis, central nervous system (CNS) thrombosis, coagulopathy, hyperbilirubinemia, and elevated transaminases
- Clinical studies of Oncaspar® did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently than younger subjects

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References: 1. Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future. *Clin Pharmacokinet.* 2005;44(4):367-393. 2. Oncaspar [package insert]. Bridgewater, NJ: Enzo Pharmaceuticals, Inc; 2006. 3. Asselin BL, Whittin JC, Coppola DJ, Rupp IP, Sallan SE, Cohen HJ. Comparative pharmacokinetic studies of three asparaginase preparations. *J Clin Oncol.* 1993;11(9):1780-1786. 4. Asselin BL. The three asparaginases: comparative pharmacology and optimal use in childhood leukemia. In: Kaspers GJL, et al, eds. *Drug Resistance in Leukemia and Lymphoma III.* New York, NY: Kluwer Academic/Plenum Publishers; 1999:621-629. 5. Harris JM, Martin NE, Modi M. Pegylation: a novel process for modifying pharmacokinetics. *Clin Pharmacokinet.* 2001;40(7):539-551. 6. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood.* 2002;99(6):1986-1994. 7. Douer D, Yampolsky H, Cohen LJ, et al. Pharmacodynamics and safety of intravenous pegaspargase during remission induction in adults aged 55 years or younger with newly diagnosed acute lymphoblastic leukemia. *Blood.* 2007;109(7):2744-2750. 8. Dinndorf PA, Gootenberg J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: pegaspargase (Oncaspar®) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). *Oncologist.* 2007;12(8):991-998. 9. Kurre HA, Ettinger AG, Veenstra DL, et al. A pharmacoeconomic analysis of pegaspargase versus native *Escherichia coli* L-asparaginase for the treatment of children with standard-risk, acute lymphoblastic leukemia: the Children's Cancer Group study (CCG-1962). *J Pediatr Hematol Oncol.* 2002;24(3):175-181. 10. National Cancer Institute. Common terminology criteria for adverse events v3.0 (CTCAE). Cancer Therapy Evaluation Program. <http://ctep.cancer.gov/forms/CTCAEv3.pdf>. Published August 9, 2006. Accessed October 9, 2008.