

# Medical Drug Clinical Criteria

**Subject:** Asparagine Specific Enzymes

**Document #:** CC-0096

**Publish Date:** [04/01/202510/01/2025](#)

**Status:** [Reviewed](#)[Revised](#)

**Last Review Date:** [02/21/202508/15/2025](#)

## Table of Contents

[Overview](#)

[Coding](#)

[References](#)

[Clinical criteria](#)

[Document history](#)

## Overview

This document addresses the use of asparagine specific enzymes, Erwinaze (asparaginase [*erwinia chrysanthemi*]), Oncaspar (pegaspargase), Rylaze (asparaginase [*erwinia chrysanthemi*]), and Asparlas (calaspargase pegol-mknl). These products are enzymes that work by depleting blood plasma levels of asparagine. Normal cells create more asparagine; however, some leukemic cells are not able to synthesize this amino acid and subsequently die. Asparagine specific enzymes are primarily used to treat acute lymphoblastic leukemia (ALL).

The native form of asparaginase, marketed as Elspar, is no longer commercially available in the US. Oncaspar is an E.coli-derived pegylated form of asparaginase approved in 1994 to treat individuals with ALL and hypersensitivity to native asparaginase. It now carries an indication to be used as a component of multi-agent chemotherapeutic regimen for first-line treatment of ALL. Erwinaze is an E.chrysanthemi-derived form of asparaginase approved in 2011 to treat individuals with ALL and hypersensitivity to E.coli-derived asparaginase. It is administered more frequently than pegylated forms of the enzyme. Rylaze, another E.chrysanthemi-derived asparaginase product, was approved in 2021 for individuals with hypersensitivity to E.coli-derived asparaginase. It is administered via IM injection every 48 hours. Asparlas (calaspargase pegol) was recently FDA approved as another first line option in ALL for patients aged 1 month to 21 years. Similar to Oncaspar, Asparlas is an E.coli-derived pegylated form of asparaginase with a slightly different mPEG moiety which allows it to be dosed no more frequently than every 3 weeks compared with the biweekly dosing of Oncaspar.

The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of asparagine specific enzymes. NCCN notes that asparaginase-based chemotherapy regimens are recommended for extranodal NK/T-cell lymphomas, nasal type (a rare subtype of non-hodgkins lymphoma), with pegaspargase-based regimens preferred.. NCCN also notes that Asparlas may be substituted for pegaspargase in patients ≤21 years of age for more sustained asparaginase activity. NCCN removed the 2A recommendation for Asparlas in Extranodal NK/T-cell lymphomas, and nasal type for Asparlas and Oncaspar.

### Silent inactivation

In cases of hypersensitivity, anti-asparaginase antibodies may be present that neutralize circulating asparaginase and in some cases may present without clinical signs, a phenomenon known as silent inactivation.

Silent Inactivation is caused by neutralizing anti-drug antibodies (to asparaginase or PEG) resulting in asparaginase inactivity without the development of overt allergy symptoms. It can be identified with (trough) asparaginase activity levels below the lower limit of quantification (LLQ) occurring in patients without clinical allergy, preferably measured in 2 independent samples to minimize the number of patients tested false positive. Specifically, with the use of pegaspargase (given every two weeks), a day 7 asparaginase activity level below 0.1 IU/mL and/or a day 14 level below the LLQ would be consistent with silent inactivation (van der Sluis 2016).

Eight hundred eighteen patients (age 1-18 years) with ALL were enrolled in the Dutch Childhood Oncology Group-ALL11 protocol and received PEGasp. Three hundred twelve patients stratified in the medium-risk arm were randomly assigned to receive 14 individualized PEGasp doses once every two weeks in either a noncontinuous or continuous schedule after the first three doses in induction (EudraCT: 2012-000067-25). Hypersensitivity reactions were defined as allergies, allergic-like reactions, and silent inactivation. Secondary end points were other asparaginase-related toxicities, asparaginase activity and antibody levels, and outcome.

During induction, 27 of 818 patients (3.3%) experienced hypersensitivity reactions. After random assignment, 4 of 155 (2.6%) in the continuous treatment arm versus 17 of 157 (10.8%) patients in the noncontinuous treatment arm had hypersensitivity reactions (P < .01), of which two (1.3%) versus 13 (8.3%) were inactivating reactions (P < .01). The occurrence of inactivating hypersensitivity reactions was seven times lower in the continuous arm (odds ratio, 0.15 [0.032-0.653]). In addition, antibody levels were significantly lower in the continuous arm (P < .01). With exception of a lower incidence of increased amylase in the continuous arm, there were no significant differences in total number of asparaginase-associated toxicities between arms. However, the timing of the toxicities

was associated with the timing of the asparaginase administrations. No difference in 5-year cumulative incidence of relapse, death, or disease-free survival was found between both treatment arms (van der Sluis 2024).

A continuous dosing schedule of PEGasp is an effective approach to prevent antibody formation and inactivating hypersensitivity reactions. The continuous PEGasp schedule did not increase toxicity and did not affect the efficacy of the therapy. (van der Sluis, 2024)

Definitions and Measures

Acute leukemia: A type of leukemia where the number of leukemic cells develops rapidly and these abnormal cells do not perform the normal functions of the white blood cells.

Hypersensitivity: An exaggerated response by the immune system to a drug or other substance.

Leukemia: A type of cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

Lymphoid leukemia: Leukemia that starts in lymphoid cells is called lymphoid, lymphoblastic, or lymphocytic leukemia.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Erwinaze (asparaginase [erwinia chrysanthemi]); Rylaze (asparaginase erwinia chrysanthemi (recombinant)-rywn)

Requests for Erwinaze (asparaginase [erwinia chrysanthemi]) or Rylaze (asparaginase erwinia chrysanthemi (recombinant)-rywn) may be approved if the following criteria are met:

- I. Individual has a diagnosis of one of the following:
  - A. Acute lymphoblastic lymphoma or acute lymphocytic (lymphoblastic) leukemia (ALL) (Label); **OR**
  - B. Extranodal Natural Killer T-cell lymphoma (ENKL) (NCCN 2A);
- AND
- II. Individual has developed a documented systemic allergic reaction or anaphylaxis to prior treatment with *E. Coli* – derived asparaginase OR have silent inactivation [defined as a day 7 asparaginase activity level below 0.1 IU/mL and/or a day 14 level below the lower limit of quantification (LLQ)];
- AND
- III. Individual does not have any of the following contraindications:
  - A. History of serious thrombosis with prior L-asparaginase therapy; **OR**
  - B. History of serious pancreatitis with prior L-asparaginase therapy; **OR**
  - C. History of serious hemorrhagic events with prior L-asparaginase therapy.

Formatted: Font: Italic

Requests for Erwinaze (asparaginase [erwinia chrysanthemi]) or Rylaze (asparaginase erwinia chrysanthemi (recombinant)-rywn) may not be approved if above criteria are not met and for all other indications.

Oncaspar (pegaspargase)

Requests for Oncaspar (pegaspargase) may be approved if the following criteria are met:

- I. Individual has a diagnosis of one of the following:
  - A. Acute lymphoblastic lymphoma or acute lymphocytic (lymphoblastic) leukemia (ALL); **OR**
  - B. Extranodal natural killer T-cell lymphoma (ENKL) (NCCN 2A);
- AND
- II. Individual does not have any of the following contraindications:
  - A. History of serious thrombosis with prior L-asparaginase therapy; **OR**
  - B. History of serious pancreatitis with prior L-asparaginase therapy; **OR**
  - C. History of serious hemorrhagic events with prior L-asparaginase therapy; **OR**
  - D. Severe hepatic impairment.

Requests for Oncaspar (pegaspargase) may not be approved if above criteria are not met and for all other indications.

### Asparlas (calaspargase pegol-mknl)

Requests for Asparlas (calaspargase pegol-mknl) may be approved if the following criteria are met:

- I. Individual is age 1 month to 21 years (Label, NCCN 2A); **AND**
  - II. Individual has a diagnosis of acute lymphoblastic lymphoma or acute lymphocytic (lymphoblastic) leukemia (ALL);
- AND**
- III. Individual does not have any of the following contraindications:
    - A. History of serious hypersensitivity reactions, including anaphylaxis, to pegylated L-asparaginase therapy; **OR**
    - B. History of serious thrombosis with prior L-asparaginase therapy; **OR**
    - C. History of serious pancreatitis with prior L-asparaginase therapy; **OR**
    - D. History of serious hemorrhagic events with prior L-asparaginase therapy; **OR**
    - E. Severe hepatic impairment.

Requests for Asparlas (calaspargase pegol-mknl) may not be approved if above criteria are not met and for all other indications.

### Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

#### Erwinaze (asparaginase), asparaginase, Rylaze (asparaginase recombinant), Oncaspar (pegaspargase)

##### HCPCS

|              |                                                                       |
|--------------|-----------------------------------------------------------------------|
| <u>J9019</u> | <u>Injection, asparaginase (Erwinaze), 1,000 iu</u>                   |
| <u>J9020</u> | <u>Injection, asparaginase, not otherwise specified, 10,000 units</u> |
| <u>J9021</u> | <u>Injection, asparaginase, recombinant, (Rylaze), 0.1 mg</u>         |
| <u>J9266</u> | <u>Injection, pegaspargase, per single dose vial [Oncaspar]</u>       |

##### ICD-10 Diagnosis

|                      |                                                                                |
|----------------------|--------------------------------------------------------------------------------|
| <u>C83.50-C83.59</u> | <u>Lymphoblastic (diffuse) lymphoma</u>                                        |
| <u>C84.20-C84.29</u> | <u>Other mature T/NK-cell lymphomas</u>                                        |
| <u>C84.90-C84.99</u> | <u>Mature T/NK-cell lymphomas, unspecified</u>                                 |
| <u>C86.00</u>        | <u>Extranodal NK/T-cell lymphoma, nasal type not having achieved remission</u> |
| <u>C91.00-C91.02</u> | <u>Acute lymphoblastic leukemia (ALL)</u>                                      |

#### Asparlas (calaspargase pegol-mknl)

##### HCPCS

|              |                                                                |
|--------------|----------------------------------------------------------------|
| <u>J9118</u> | <u>Injection, calaspargase pegol-mknl, 10 units [Asparlas]</u> |
|--------------|----------------------------------------------------------------|

##### ICD-10 Diagnosis

|                      |                                           |
|----------------------|-------------------------------------------|
| <u>C83.50-C83.59</u> | <u>Lymphoblastic (diffuse) lymphoma</u>   |
| <u>C91.00-C91.02</u> | <u>Acute lymphoblastic leukemia (ALL)</u> |

##### HCPGS

|              |                                                                       |
|--------------|-----------------------------------------------------------------------|
| <u>J9019</u> | <u>Injection, asparaginase (Erwinaze), 1,000 iu</u>                   |
| <u>J9020</u> | <u>Injection, asparaginase, not otherwise specified, 10,000 units</u> |
| <u>J9021</u> | <u>Injection, asparaginase, recombinant, (Rylaze), 0.1 mg</u>         |
| <u>J9266</u> | <u>Injection, pegaspargase, per single dose vial (Oncaspar)</u>       |
| <u>J9118</u> | <u>Injection, calaspargase pegol-mknl, 10 units [Asparlas]</u>        |

ICD-10-Diagnosis

|               |                                                                                                                                                                                                    |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| C83.50-C83.59 | Lymphoblastic (diffuse) lymphoma [Erwinaze (asparaginase), asparaginase not otherwise specified, Rylaze (asparaginase recombinant), Oncaspar (pegaspargase), Asparlas (calaspargase pegol-mknl)]   |
| C84.Z0-C84.Z9 | Other mature T/NK-cell lymphomas [Erwinaze (asparaginase), asparaginase not otherwise specified, Rylaze (asparaginase recombinant), Oncaspar (pegaspargase)]                                       |
| C84.90-C84.99 | Mature T/NK-cell lymphomas, unspecified [Erwinaze (asparaginase), asparaginase not otherwise specified, Rylaze (asparaginase recombinant), Oncaspar (pegaspargase)]                                |
| C91.00-C91.02 | Acute Lymphoblastic Leukemia (ALL) [Erwinaze (asparaginase), asparaginase not otherwise specified, Rylaze (asparaginase recombinant), Oncaspar (pegaspargase), Asparlas (calaspargase pegol-mknl)] |

Document History

- Revised: 08/15/2025
- Document History:
- 08/15/2025 – Select Review: Add use in silent inactivation for asparaginase enzyme (Erwinaze and Rylaze) criteria. Coding Reviewed: Separated Asparlas from other agents. Added ICD-10-CM C86.00 to Erwinaze, asparaginase not otherwise classified, Rylaze, and Oncaspar.
  - 02/21/2025 – Annual Review: No Changes. Coding Reviewed: Added applicable agents to diagnosis descriptions. Added Erwinaze, asparaginase, Rylaze, Oncaspar, and Asparlas to C83.50-C83.59 and C91.00-C91.02. Added Erwinaze, asparaginase, Rylaze, and Oncaspar to C84.Z0-C84.Z9 and C84.90-C84.99.
  - 08/16/2024 – Annual Review: Add Erwinaze back to the criteria document. New manufacturer to come in 2024. Coding Reviewed: Added ICD-10-CM C84.90-C84.99 and C84.Z0-C84.Z9 (Effective 02/23/2024), removed C86.1 (effective 02/23/2024).
  - 02/23/2024 – Annual Review: Remove Erwinaze, no longer available. Add NCCN 2A use in ENKT cell lymphoma for Rylaze. Update Oncaspar criteria to remove NCCN recommendation for use in Hepatosplenic T-cell lymphoma. Add references. Wording and formatting updates. Coding Reviewed: No changes.
  - 02/24/2023 – Annual Review: Update criteria for Erwinaze, Oncaspar and Asparlas. Coding Reviewed: Added ICD-10-CM C86.1. Removed ICD-10-CM C86.0.
  - 02/25/2022 – Annual Review: No changes. Coding Reviewed: No changes.
  - 08/20/2021 – Select Review: Add new agent Rylaze to clinical criteria; update criteria to align with label. Coding reviewed: Added HCPCS J3590, J9999, C9399 for Rylaze. Coding Reviewed: Added J9021. Removed J3590, J9999, C9399.
  - 02/19/2021 – Annual Review: No changes. No changes. Coding Reviewed: No changes.
  - 02/21/2020– Annual Review: Roll in criteria from ING-CC-0138 Asparlas (calaspargase pegol-mknl). No changes to criteria. Coding Reviewed: Added HCPCS code J9118 for Asparlas.
  - 05/17/2019– Annual Review: First review of asparaginase specific enzymes. Add new contraindication to Oncaspar criteria. Add references for off label indications.

References

- DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>.
- DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
- Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2024; Updated periodically.
- NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on December 28, 2024.
  - Acute Lymphoblastic Leukemia. V3.2024. Revised December 20, 2024.
  - Pediatric Acute Lymphoblastic leukemia. V2.2025. Revised December 16, 2024.
  - T-Cell Lymphomas. V1.2025. Revised November 11, 2024.
- van der Sluis IM, Brigitha LJ, Fiocco M, de Groot-Kruseman HA, Bierings M, van den Bos C, de Haas V, Hoogerbrugge PM, Tissing WJE, Veening MA, Pieters R. Continuous PEGasparaginase Dosing Reduces Hypersensitivity Reactions in Pediatric ALL: A Dutch Childhood Oncology Group ALL11 Randomized Trial. J Clin Oncol. 2024 May 10;42(14):1676-1686. doi: 10.1200/JCO.23.01797. Epub 2024 Feb 2. PMID: 38306592; PMCID: PMC11095866.
- van der Sluis IM, Vrooman LM, Pieters R, Baruchel A, Escherich G, Goulden N, Mondelaers V, Sanchez de Toledo J, Rizzari C, Silverman LB, Whitlock JA. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. Haematologica. 2016 Mar;101(3):279-85. doi: 10.3324/haematol.2015.137380. PMID: 26928249; PMCID: PMC4815719.

Federal and state laws or requirements, contract language, and Plan utilization management programs or policies may take precedence over the application of this clinical criteria.

Formatted: Space After: 0 pt

Formatted: Indent: Left: 0.25"

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association