HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to prescribe Oncaspar® safely and effectively. See full prescribing information for Oncaspar®.

Oncaspar® (pegaspargase) Intravenous -or- Intramuscular Injection
Initial U.S. Approval: 1994

---RECENT MAJOR CHANGES--- 07/2006
Indications and Usage,
  First line acute lymphoblastic leukemia (ALL) (1.1)
Contraindications,
  History of serious thrombosis with prior L-asparaginase therapy (4)

---INDICATIONS AND USAGE---
Oncaspar® is indicated as a component of a multi-agent chemotherapeutic regimen for treatment of patients with:
- First line acute lymphoblastic leukemia (1.1)
- Acute lymphoblastic leukemia and hypersensitivity to asparaginase (1.2)

---DOSAGE AND ADMINISTRATION---
- 2,500 IU/m² intramuscularly (IM) or intravenously (IV) no more frequently than every 14 days. (2.1)
- For IM administration, limit the volume at a single injection site to 2 mL; if greater than 2 mL, use multiple injection sites. (2.2)
- For 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. (2.2)
- Do not administer Oncaspar® if drug has been frozen, stored at room temperature for more than 48 hours, or shaken or vigorously agitated. (2.3)

---DOSAGE FORMS AND STRENGTHS---
- 3,750 IU /5 mL single-use vial. (3)

---CONTRAINDICATIONS---
- History of serious thrombosis with Oncaspar® (4)
- History of serious thrombosis with prior L-asparaginase therapy (4)
- History of pancreatitis with prior L-asparaginase therapy (4)
- History of serious hemorrhagic events with prior L-asparaginase therapy (4)

---WARNINGS AND PRECAUTIONS---
- If the following occur - discontinue Oncaspar:
  Anaphylaxis or serious allergic reactions (5.1)
  Thrombosis (5.2)
  Pancreatitis (5.3)
- Glucose intolerance, in some cases irreversible, can occur (5.4)
- Coagulopathy can occur. Perform appropriate monitoring. (5.5)

---ADVERSE REACTIONS---
Most common adverse reactions (≥2%) are allergic reactions (including anaphylaxis), central nervous system (CNS) thrombosis, coagulopathy, elevated transaminases, hyperbilirubinemia, hyperglycemia, and pancreatitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ENZON PHARMACEUTICALS, INC at 1-800-836-4301 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2006
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 First Line Acute Lymphoblastic Leukemia (ALL)
Oncaspar® is indicated as a component of a multi-agent chemotherapeutic regimen for the first line treatment of patients with ALL.

1.2 Acute Lymphoblastic Leukemia and Hypersensitivity to Asparaginase
Oncaspar® is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL and hypersensitivity to native forms of L-asparaginase.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose
The recommended dose of Oncaspar® is 2,500 IU/m² intramuscularly (IM) or intravenously (IV). Oncaspar® should be administered no more frequently than every 14 days.

2.2 Instructions for Administration
When Oncaspar® is administered IM, the volume at a single injection site should be limited to 2 mL. If the volume to be administered is greater than 2 mL, multiple injection sites should be used.

When administered IV, Oncaspar® should be given 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.

2.3 Preparation and Handling Precautions
Do not administer Oncaspar® if drug has been:
- frozen
- stored at room temperature (+15°C to +25°C; 59°F to 77°F) for more than 48 hours
- shaken or vigorously agitated [see How Supplied/Storage and Handling (16)]

Parenteral drug products should be inspected visually for particulate matter, cloudiness, or discoloration prior to administration, whenever solution and container permit. If any of these are present, discard the vial.

3 DOSAGE FORMS AND STRENGTHS

3,750 IU / 5 mL single-use vial

4 CONTRAINDICATIONS

- History of serious allergic reactions to Oncaspar®
- History of serious thrombosis with prior L-asparaginase therapy
- History of pancreatitis with prior L-asparaginase therapy
- History of serious hemorrhagic events with prior L-asparaginase therapy

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Serious Allergic Reactions
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.

5.2 Thrombosis
Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving Oncaspar®. Discontinue Oncaspar® in patients with serious thrombotic events.

5.3 Pancreatitis

5.4 Glucose Intolerance
Glucose intolerance can occur in patients receiving Oncaspar®. In some cases, glucose intolerance is irreversible.

5.5 Coagulopathy
Increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenemia can occur in patients receiving Oncaspar®. Monitor coagulation parameters at baseline and periodically during and after treatment. Initiate treatment with fresh-frozen plasma to replace coagulation factors in patients with severe or symptomatic coagulopathy.

6 ADVERSE REACTIONS

The following serious adverse reactions occur with Oncaspar® treatment [see Warnings and Precautions (5)]:
- Anaphylaxis and serious allergic reactions
- Serious thrombosis
- Pancreatitis
- Glucose intolerance
- Coagulopathy

The most common adverse reactions with Oncaspar® are allergic reactions (including anaphylaxis), hyperglycemia, pancreatitis, central nervous system (CNS) thrombosis, coagulopathy, hyperbilirubinemia, and elevated transaminases.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice. First-Line ALL

The data presented below are derived from 2 studies in patients with standard-risk ALL who received Oncaspar® as a component of first-line multi-agent chemotherapy. Study 1 was a randomized (1:1), active-controlled study that enrolled 118 patients, with a median age of 4.7 years (1.1-9.9 years), of whom 54% were males and 65% White, 14% Hispanic, 8% Black, 8% Asian, and 6% other. Of the 59 patients in Study 1 who were randomized to Oncaspar®, 48 patients (81%) received all 3 planned doses of Oncaspar®, 6 (10%) received 2 doses, 4 (7%)
received 1 dose, and 1 patient (2%) did not receive the assigned treatment. Study 2 is an ongoing, multi-factorial design study in which all patients received Oncaspar® as a component of various multi-agent chemotherapy regimens; interim safety data are available for 2,770 patients. Study participants had a median age of 4 years (1-10 years), and were 55% male, 68% White, 18% Hispanic, 4% Black, 3% Asian, and 7% other. Per protocol, the schedule of Oncaspar® varied by treatment arm, with intermittent doses of Oncaspar® for up to 10 months.

In Study 1, detailed safety information was collected for pre-specified adverse reactions identified as asparaginase-induced adverse reactions and for grade 3 and 4 non-hematologic adverse reactions according to the Children’s Cancer Group (CCG) Toxicity and Complication Criteria. The per-patient incidence, by treatment arm, for these selected adverse reactions occurring at a severity of grade 3 or 4 are presented in Table 1 below:

### Table 1

<table>
<thead>
<tr>
<th>Study 1: Per-Patient Incidence of Selected Grade 3 and 4 Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncaspar® (n=58)</strong></td>
</tr>
<tr>
<td>Abnormal Liver Tests</td>
</tr>
<tr>
<td>Elevated Transaminases</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Central Nervous System</td>
</tr>
<tr>
<td>Thrombosis</td>
</tr>
<tr>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Clinical Allergic Reactions to Asparaginase</td>
</tr>
</tbody>
</table>

1 Aspartate aminotransferase, alanine aminotransferase.

2 Prolonged prothrombin time or partial thromboplastin time; or hypofibrinogenemia.

Safety data were collected in Study 2 only for National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0, grade 3 and 4 non-hematologic toxicities. In this study, the per-patient incidence for the following adverse reactions occurring during treatment courses in which patients received Oncaspar® 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.

### 6.2 Clinical Allergic Reactions

Clinical allergic reactions include the following: bronchospasm, hypotension, laryngeal edema, local erythema or swelling, systemic rash, and urticaria.

**First-Line ALL**

Among 58 Oncaspar®-treated patients enrolled in Study 1, clinical allergic reactions were reported in 2 patients (3%). One patient experienced a grade 1 allergic reaction and the other grade 3 hives; both occurred during the first delayed intensification phase of the study (see Table 2).

**Previously Treated ALL**

Among 62 patients with relapsed ALL and prior hypersensitivity reactions to asparaginase, 35 patients (56%) had a history of clinical allergic reactions to native Escherichia (E.) coli L-asparaginase, and 27 patients (44%) had history of clinical allergic reactions to both native E. coli and native Erwinia L-asparaginase. Twenty (32%) of these 62 patients experienced clinical allergic reactions to Oncaspar® (see Table 2).

Among 112 patients with relapsed ALL with no prior hypersensitivity reactions to asparaginase, 11 patients (10%) experienced clinical allergic reactions to Oncaspar® (see Table 2).

### Table 2

**Incidence of Clinical Allergic Reactions, Overall and by Severity Grade**

<table>
<thead>
<tr>
<th>Patient Status</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously Hypersensitive Patients (n=62)</td>
<td>7 (11)</td>
<td>8 (13)</td>
<td>4 (6)</td>
<td>1 (2)</td>
<td>20 (32)</td>
</tr>
<tr>
<td>Non-Hypersensitive Patients (n=112)</td>
<td>5 (4)</td>
<td>4 (4%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>First Line (n=58)</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

### 6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity, defined as development of binding and/or neutralizing antibodies to the product.

In Study 1, Oncaspar®-treated patients were assessed for evidence of binding antibodies using an enzyme-linked immunosorbent assay (ELISA) method. The incidence of protocol-specified “high-titer” antibody formation was 2% in Induction (n=48), 10% in Delayed Intensification 1 (n=50), and 11% in Delayed Intensification 2 (n=44). There is insufficient information to determine whether the development of antibodies is associated with an increased risk of clinical allergic reactions, altered pharmacokinetics, or loss of anti-leukemic efficacy.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Oncaspar® with the incidence of antibodies to other products may be misleading.
No formal drug interaction studies, between Oncaspar® and other drugs, have been performed.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Oncaspar®. It is also not known whether Oncaspar® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Oncaspar® should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether Oncaspar® is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Oncaspar®, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

[see Clinical Studies(14.1)]

Geriatric Use

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.

Three patients received 10,000 IU/m² of Oncaspar® as an intravenous infusion. One patient experienced a slight increase in liver enzymes. A second 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. A third patient did not experience any adverse reactions.

Oncaspar® (pegaspargase) is a modified version of the enzyme L-asparaginase. To produce Oncaspar®, L-asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5,000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of Oncaspar® is derived from E. coli. Oncaspar® activity is expressed in International Units (IU) according to the recommendation of the International Union of Biochemistry. One IU of L-asparaginase is defined as that amount of enzyme required to generate 1 μmol of ammonia per minute at pH 7.3 and 37°C.

Oncaspar® is supplied as a clear, colorless, preservative-free, isotonic sterile solution in phosphate-buffered saline, pH 7.3. Each milliliter contains Oncaspar® 750 IU ± 20% (based on specific activity of at least 85 IU per milligram protein), 1.20 mg monobasic sodium phosphate, USP, 5.58 mg dibasic sodium phosphate, USP, and 8.50 mg sodium chloride, USP, in water for injection, USP.
were randomized 1:1 to Oncaspar® or native E. coli L-asparaginase as part of combination therapy. Oncaspar® was administered IM at a dose of 2,500 IU/m² on Day 3 of the 4-week induction phase and on Day 3 of each of two 8-week delayed intensification phases. Native E. coli L-asparaginase was administered IM at a dose of 6,000 IU/m² three times weekly for 9 doses during induction and for 6 doses during each delayed intensification phase.

The primary determination of effectiveness was based on demonstration of similar asparagine depletion (magnitude and duration) in the Oncaspar® and native E. coli L-asparaginase arms. The protocol-specified goal was achievement of asparagine depletion to a serum concentration of ≤1 μM. The proportion of patients with this level of depletion was similar between the 2 study arms during all 3 phases of treatment at the protocol-specified time points.

In all phases of treatment, serum asparagine concentrations decreased within 4 days the first dose of asparaginase in the treatment phase and remained low for approximately 3 weeks for both Oncaspar® and native E. coli L-asparaginase arms. Serum asparagine concentrations during the induction phase are shown in Figure 1. The patterns of serum asparagine depletion in the 2 delayed intensification phases are similar to the pattern of serum asparagine depletion in the induction phase.

**FIGURE 1**

**MEAN (± STANDARD ERROR) SERUM ASPARAGINE CONCENTRATIONS DURING STUDY 1 INDUCTION PHASE**

![Graph showing serum asparagine concentrations during Study 1 induction phase](image)

Note: Oncaspar® (2,500 IU/m² IM) was administered on Day 3 of the 4-week induction phase. Native E. coli L-asparaginase (6,000 IU/m² IM) was administered 3 times weekly for 9 doses during induction.

CSF asparagine concentrations were determined in 50 patients during the induction phase. CSF asparagine decreased by a mean pretreatment concentration of 3.1 μM to 1.7 μM on Day 4 ± 1 and 1.5 μM 25 ± 1 days after administration of Oncaspar®. These findings were similar to those observed in the native E. coli L-asparaginase treatment arm.

While the 3-year Event-Free Survival (EFS) for the Oncaspar® and native E. coli L-asparaginase study arms were similar and in the range of 80%, Study 1 was not designed to evaluate for differences in EFS rates.

### 14.2 ALL Patients Hypersensitive to Asparaginase

The safety and effectiveness of Oncaspar® was evaluated in 4 open-label studies enrolling a total of 42 patients with multiply relapsed, acute leukemia (39 (93%) with ALL) with a history of prior clinical allergic reaction to asparaginase. Hypersensitivity to asparaginase was defined by a history of systemic rash, urticaria, bronchospasm, laryngeal edema, hypotension, or local erythema, urticaria, or swelling, greater than 2 centimeters, for at least 10 minutes following administration of any form of native E. coli L-asparaginase. All patients received Oncaspar® at a dose of 2,000 or 2,500 IU/m² administered IM or IV every 14 days. Patients received Oncaspar® as a single agent or in combination with multi-agent chemotherapy. The re-induction response rate was 50% (95% confidence interval: 35%, 65%), based upon 36% complete remissions and 14% partial remissions. These results were similar to the overall response rates reported for patients with ALL receiving second-line, native E. coli L-asparaginase-containing re-induction chemotherapy. Anti-tumor activity was also observed with single-agent Oncaspar®. Three responses (1 complete remission and 2 partial remissions) were observed in 9 adult and pediatric patients with relapsed ALL and hypersensitivity to native E. coli L-asparaginase.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

**Dosage Form**

NDC 57665-002-02

3,750 IU/5 mL single-use vial individually packaged in a carton

**Storage and Handling**

Keep refrigerated at +2°C to +8°C (36°F to 46°F).

Use only one dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

- Do not administer Oncaspar® if the drug:
  - has been frozen
  - has been stored at room temperature (+15°C to +25°C; 59°F to 77°F) for more than 48 hours
  - has been shaken or vigorously agitated
  - is cloudy, discolored, and precipitate is present.

### 17 PATIENT COUNSELING INFORMATION

#### 17.1 Serious Allergic Reactions

Patients should be informed of the possibility of serious allergic reactions, including anaphylaxis, and to immediately report any swellings or difficulty breathing.

#### 17.2 Thrombosis

Patients should be advised to immediately report any severe headache. Arm or leg swelling, acute shortness of breath, and chest pain also should be reported immediately.

#### 17.3 Pancreatitis

Patients should be advised to immediately report any severe abdominal pain.
17.4 Glucose Intolerance
Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.

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