FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Oncaspar® (pegaspargase) injection, for intramuscular or intravenous use

• First line acute lymphoblastic leukemia (1.1)
• Acute lymphoblastic leukemia and hypersensitivity to asparaginase (1.2)

CONTRAINDICATIONS

Full prescribing information for Oncaspar

WARNINGS AND PRECAUTIONS

• History of serious thrombosis with prior L-asparaginase therapy. (4)
• History of pancreatitis with prior L-asparaginase therapy. (4)
• History of serious hepatic events with prior L-asparaginase therapy. (4)

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)

STUDY 1: PER-PATIENT INCIDENCE OF SELECTED GRADE 3 AND 4 ADVERSE REACTIONS

Adverse reactions were collected in Study 1 only for National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0, grade 3 and 4 hematologic and non-hematologic toxicities. In this study, the per-patient incidence and clinical severity profile of Oncaspar® are similar to that reported above with the exception of clinical allergic reactions (see Table 2). The most common adverse reactions of Oncaspar® were similar to those reported with asparaginase-induced adverse reactions and for grade 3 and 4 non-hematologic adverse reactions according to the Children’s Oncology Group (COG) 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.

STUDY 1: PER-PATIENT INCIDENCE OF SELECTED GRADE 3 AND 4 ADVERSE REACTIONS

Oncaspar® (n=69) Native

E. coli L-Asparaginase (n=69)

Abnormal Liver Tests

Elevated Transaminases

Hypertension

Hyperglycemia

CNS Thrombosis

Coagulopathy

Pancreatitis

Adverse reaction information was obtained from 5 clinical trials that enrolled a total of 174 patients with relapsed ALL who received Oncaspar® as a single agent in combination with multi-agent chemotherapy. The toxicology profile of Oncaspar® in patients with previously treated relapsed ALL is similar to that reported above with the exception of clinical allergic reactions (see Table 2). The most common adverse reactions of Oncaspar® were clinical allergic reactions, elevated transaminases, hyperbilirubinemia, and coagulopathy. The most common serious adverse events due to Oncaspar® treatment were thrombosis (4%), hyperglycemia requiring insulin therapy (3%), and pancreatitis (1%).

Clinical Allergic Reactions

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

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### 6.3 Immunochemistry

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. A titer was considered test-positive if antibody titer was ≥1:500. On follow-up administration of Oncaspar® at the same dose used in Study 1, 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 loss of therapeutic activity. Patients who continued to receive the product were monitored for the development of antibodies and for 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, the antibody formation rates observed in any assay cannot be directly compared to those observed in the native Oncaspar®.

#### 8.4 Pediatric Use

Oncaspar® has been studied in several pediatric trials. The safety and effectiveness of Oncaspar® in pediatric patients was established in two pediatric studies, Study 1 and Study 2. In Study 1, 37 patients with relapsed ALL were treated with 2,500 International Units/m² intramuscularly for 2 weeks. The plasma half-life of Oncaspar® was 3.2 ± 1.8 days in 9 patients who were previously hypersensitive to native E. coli L-asparaginase and 9.7 ± 3.2 days in 28 non-hypersensitive patients. The area under the plasma concentration-time curve (AUC) was 9.5 ± 4.0 International Units/mL/day in the previously hypersensitive patients and 9.8 ± 6.0 International Units/mL/day in the non-hypersensitive patients.

#### 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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**TABLE 2**

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

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In all phases of treatment, serum asparaginase concentrations decreased within 4 weeks of 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. Serum asparaginase concentrations during the induction phase are shown in Figure 1. The paterns of serum asparaginase depletion in the 2 delayed intensification phases are similar to that of serum asparaginase depletion in the induction phase.

#### FIGURE 1

| MEAN ± STANDARD ERROR CONCENTRATIONS OF SERUM ASPARAGINE DURING STUDY 1 INDUCTION PHASE |

<table>
<thead>
<tr>
<th>Days After First Dose of L-Asparaginase</th>
</tr>
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<tbody>
<tr>
<td>8</td>
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</tbody>
</table>

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

CSF asparaginase concentrations were determined in 50 patients during the induction phase. CSF asparaginase decreased from a mean pretreatment concentration of 3.1 ± 1.7 μM on Day 4 ± 1 and 1.5 ± 2 μM at 25 ± 15 days after the last dose 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 groups were similar, there was no statistical difference between the groups.

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