SERVIER ONCOLOGY:
Committed to therapeutic progress to serve patient needs

Servier Pharmaceuticals offers two distinct asparaginase therapies as components of a multi-agent chemotherapeutic regimen for your patients with acute lymphoblastic leukemia (ALL).

Frequently Asked Questions	ASPARLAS™ (calaspargase pegol-mknl)[1,2]	ONCASPAR® (pegaspargase)[3,4]
What is the approved age range?		
Indicated age groups	Pediatric and young adult patients aged 1 month to 21 years	Pediatric and adult patients
How do the half-life and drug substances differ between the two products?		
Half-life (days, mean) IV administration	~16 days	5.3 days
Mode of pegylation	Chemically stable carbamate bond of L-asparaginase (L-asparagine amidohydrolase) and monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate (SC) linker	Conjugate of L-asparaginase (L-asparagine amidohydrolase) and mPEG with a succinimidyl succinate (SS) linker
Can both products be administered in the same way?		
Recommended dose	2500 U/m^2	• Patients ≤21 years of age: 2500 U/m^2 • Patients >21 years of age: 2000 U/m^2
Dosage form and strength	• 3750 U/5 mL (750 U/mL) • Clear, colorless solution • Single-dose vial	
Route of administration	IV	IV or IM*
Administration schedule	No more frequently than every 21 days	No more frequently than every 14 days
Administration length of time (IV)	1 hour	1 to 2 hours
Can both products be stored similarly?		
Shelf life	36 months	8 months
Storage requirements	• Store refrigerated at 2°C to 8°C (36°F to 46°F) • Do not shake or freeze product • Protect from light • Do not store unopened vials at room temperature (15°C to 25°C [59°F to 77°F]) for more than 48 hours	

*IM dosing up to 2 mL per syringe. | Abbreviations: IM, intramuscular; IV, intravenous.

Please see Important Safety Information and Full Prescribing Information.

ASPARLAS
(calaspargase pegol-mknl)
750 units/mL injection

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of serious hypersensitivity reactions to pegylated L-asparaginase
- History of serious thrombosis during L-asparaginase therapy
- History of serious pancreatitis during previous L-asparaginase therapy
- History of serious hemorrhagic events during previous L-asparaginase therapy
- Severe hepatic impairment

WARNINGS and PRECAUTIONS

Hypersensitivity: Grade 3 and 4 hypersensitivity reactions including anaphylaxis have been reported in clinical trials with ASPARLAS with an incidence of 7% to 21%. Because of the risk of serious allergic reactions, administer ASPARLAS in a clinical setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Observe patients for 1 hour after administration. Discontinue ASPARLAS in patients with serious hypersensitivity reactions.

Pancreatitis: Cases of pancreatitis have been reported in clinical trials with ASPARLAS with an incidence of 12% to 16%. Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Assess serum amylase and/or lipase levels to identify early signs of pancreatic inflammation. Discontinue ASPARLAS in case of suspicion of pancreatitis. If pancreatitis is confirmed, do not resume ASPARLAS.

Thrombosis: Serious thrombotic events, including sagittal sinus thrombosis, have been reported in clinical trials with ASPARLAS with an incidence of 9% to 12%. Discontinue ASPARLAS in patients experiencing serious thrombotic events.

Hemorrhage: Hemorrhage associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia have been reported. Evaluate patients with signs and symptoms of hemorrhage with coagulation parameters including PT, PTT, and fibrinogen. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy.

Hepatotoxicity: Hepatotoxicity and abnormal liver function, including elevations of transaminase, bilirubin (direct and indirect), reduced serum albumin, and plasma fibrinogen can occur. Evaluate bilirubin and transaminases at least weekly during cycles of treatment that include ASPARLAS through 6 weeks after the last dose of ASPARLAS. In the event of serious liver toxicity, discontinue treatment with ASPARLAS and provide supportive care.

ADVERSE REACTIONS

The most common grade 3 and above adverse reactions (incidence ≥10%) for patients receiving ASPARLAS with multiagent chemotherapy observed in the DFCI clinical trial are elevated transaminases (52%), increased bilirubin (20%), pancreatitis (18%) and abnormal clotting studies (14%). There was 1 fatal adverse reaction (multi-organ failure in the setting of chronic pancreatitis associated with a pancreatic pseudocyst). Not all grade 1 and 2 adverse reactions were collected prospectively.

Please see Full Prescribing Information.

oncaspar
pegaspargase

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of serious hypersensitivity reactions, including anaphylaxis, to ONCASPAR or to any of the excipients.
- History of serious thrombosis with prior L-asparaginase therapy.
- History of pancreatitis, including pancreatitis related to prior L-asparaginase therapy.
- History of serious hemorrhagic events with prior L-asparaginase therapy.
- Severe hepatic impairment.

WARNINGS and PRECAUTIONS

Anaphylaxis and Serious Hypersensitivity Reactions: Anaphylaxis and serious hypersensitivity reactions can occur. The risk of serious hypersensitivity reactions is higher in patients with known hypersensitivity to *E. coli* derived L-asparaginase formulations. Observe patients for 1 hour after administration in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Discontinue ONCASPAR in patients with serious hypersensitivity reactions.

Thrombosis: Serious thrombotic events, including sagittal sinus thrombosis, can occur. Discontinue ONCASPAR in patients with serious thrombotic events.

Pancreatitis: Pancreatitis can occur. Fatal outcomes have been reported. Inform patients of the signs and symptoms of pancreatitis. Discontinue ONCASPAR in patients where pancreatitis is suspected. If pancreatitis is confirmed, do not resume ONCASPAR.

Glucose Intolerance: Glucose intolerance can occur. In some cases, glucose intolerance is irreversible. Monitor serum glucose.

Hemorrhage: Increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenemia can occur. Evaluate patients with signs and symptoms of hemorrhage with coagulation parameters including PT, PTT, and fibrinogen. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy.

Hepatotoxicity: Hepatotoxicity and abnormal liver function can occur. Evaluate bilirubin and transaminases at least weekly during cycles of treatment through at least 6 weeks after the last dose. In the event of serious liver toxicity, discontinue ONCASPAR.

ADVERSE REACTIONS

The most common grade 3 and 4 adverse reactions with ONCASPAR (>5%) included hypoalbuminemia, elevated transaminase, febrile neutropenia, hypertriglyceridemia, hyperglycemia, bilirubin increased, pancreatitis, abnormal clotting studies, embolic and thrombotic events, and hypersensitivity.

Please see Full Prescribing Information.

References: 1. ASPARLAS [package insert]. Boston, MA: Servier Pharmaceuticals Inc; 2019. **2.** US Food and Drug Administration. BLA 761102: ASPARLAS biologics license application approval [letter]. December 20, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/761102Orig1s000Ltr.pdf. Accessed September 26, 2019. **3.** ONCASPAR [package insert]. Boston, MA: Servier Pharmaceuticals Inc; 2019. **4.** Data on file. Boston, MA: Servier Pharmaceuticals Inc; 2019.

US-00776 11/20

SERVIER

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

ASPARLAS™ (calaspargase pegol - mknl) injection, for intravenous use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
ASPARLAS is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years. (1.1)

---------- DOSAGE AND ADMINISTRATION ----------
- Recommended Dosage: 2,500 units/m^2 intravenously no more frequently than every 21 days. (2.1)
- See Full Prescribing Information for important details regarding dosing modifications and preparation and administration. (2.2, 2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection: 3,750 units/5 mL (750 units/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
- History of serious hypersensitivity reactions to pegylated L-asparaginase. (4)
- History of serious thrombosis during L-asparaginase therapy. (4)
- History of serious pancreatitis related to previous L-asparaginase treatment. (4)
- History of serious hemorrhagic events during previous L-asparaginase therapy. (4)
- Severe hepatic impairment. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hypersensitivity: Observe patients for one hour after administration. Discontinue ASPARLAS in patients with serious hypersensitivity reactions. (5.1)
- Pancreatitis: Discontinue ASPARLAS in patients with pancreatitis. Monitor blood glucose (5.2)
- Thrombosis: Discontinue ASPARLAS for severe or life-threatening thrombosis. (5.3)
- Hemorrhage: Discontinue ASPARLAS for severe or life-threatening hemorrhage. Evaluate for etiology and treat. (5.4)
- Hepatotoxicity: Monitor for toxicity through recovery from cycle. Discontinue ASPARLAS for severe liver toxicity. (5.5)

---------- ADVERSE REACTIONS ----------
The most common (incidence ≥ 10%) grade ≥ 3 adverse reactions were elevated transaminase, bilirubin increased, pancreatitis and abnormal clotting studies. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Servier Pharmaceuticals LLC at 1-800-807-6124 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Lymphoblastic Leukemia

ASPARLAS is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ASPARLAS is 2,500 units/m^2 given intravenously no more frequently than every 21 days.

2.2 Dose Modifications

Monitor patients at least weekly, with bilirubin, transaminases, glucose and clinical examinations until recovery from the cycle of therapy. If an adverse reaction should occur, modify treatment according to Table 1.

Table 1. Dose Modifications

Adverse Reaction	Severity*	Action
Infusion Reaction or Hypersensitivity Reaction	Grade 1	• Reduce the infusion rate by 50%
	Grade 2	• Interrupt the infusion of ASPARLAS • Treat the symptoms • When symptoms resolve, resume the infusion and reduce the infusion rate by 50%
	Grade 3 to 4	• Discontinue ASPARLAS permanently
Hemorrhage	Grade 3 to 4	• Hold ASPARLAS. • Evaluate for coagulopathy and consider clotting factor replacement as needed. • Resume ASPARLAS with the next scheduled dose if bleeding is controlled.
Pancreatitis	Grades 3 to 4	• Hold ASPARLAS for elevations in lipase or amylase >3 times the ULN until enzyme levels stabilize or are declining • Discontinue ASPARLAS permanently if clinical pancreatitis is confirmed.
Thromboembolism	Uncomplicated deep vein thrombosis	• Hold ASPARLAS. • Treat with appropriate antithrombotic therapy • Upon resolution of symptoms consider resuming ASPARLAS, while continuing antithrombotic therapy.
	Severe or life-threatening thrombosis	• Discontinue ASPARLAS permanently. • Treat with appropriate antithrombotic therapy
Hepatotoxicity	Total bilirubin more than 3 times to no more than 10 times the upper limit of normal	• Hold ASPARLAS until Total bilirubin levels go down to ≤ 1.5 times the upper limit of normal
	Total bilirubin more than 10 times the upper limit of normal	• Discontinue ASPARLAS and do not make up for missed doses

*Grade 1 is mild, grade 2 is moderate, grade 3 is severe, and grade 4 is life-threatening

2.3 Preparation and Administration

ASPARLAS is a clear and colorless solution. Visually inspect parenteral drug products for particulate matter, cloudiness, or discoloration prior to administration. If any of these are present, discard the vial. Do not administer if ASPARLAS has been shaken or vigorously agitated, frozen, or stored at room temperature for more than 48 hours.

- Dilute ASPARLAS in 100 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP using sterile/aseptic technique. Discard any unused portion left in a vial.
- After dilution, administer immediately into a running infusion of either 0.9% sodium chloride or 5% dextrose, respectively.
- Administer the dose over a period of 1 hour.
- Do not infuse other drugs through the same intravenous line during administration of ASPARLAS.
- The diluted solution may be stored for up to 4 hours at room temperature (15°C to 25°C [59°F to 77°F]) or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours.
- Protect from light. Do not shake or freeze.

3 DOSAGE FORMS AND STRENGTHS

Injection: 3,750 units/5 mL (750 units/mL) clear, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

ASPARLAS is contraindicated in patients with:

- History of serious hypersensitivity reactions, including anaphylaxis, to pegylated L-asparaginase therapy *[see Warnings and Precautions (5.1)]*;
- History of serious thrombosis during previous L-asparaginase therapy *[see Warnings and Precautions (5.3)]*;
- History of serious pancreatitis during previous L-asparaginase therapy *[see Warnings and Precautions (5.2)]*;
- History of serious hemorrhagic events during previous L-asparaginase therapy *[see Warnings and Precautions (5.4)]*;
- Severe hepatic impairment *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Grade 3 and 4 hypersensitivity reactions including anaphylaxis have been reported in clinical trials with ASPARLAS with an incidence between 7 to 21% *[see Contraindications (4), Adverse Reactions (6.1)]*. Hypersensitivity reactions observed with other asparaginases include angioedema, lip swelling, eye swelling, erythema, blood pressure decreased, bronchospasm, dyspnea, pruritus and rash.

Because of the risk of serious allergic reactions (e.g., life-threatening anaphylaxis), administer ASPARLAS in a clinical setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, oxygen, intravenous steroids, antihistamines) *[see Dosage and Administration (2)]* and observe patients for 1 hour after administration. Discontinue ASPARLAS in patients with serious hypersensitivity reactions.

5.2 Pancreatitis

Cases of pancreatitis have been reported in clinical trials with ASPARLAS with an incidence between 12 to 16% *[see Adverse Reactions (6.1)]*. Hemorrhagic or necrotizing pancreatitis have been reported with other asparaginases.

Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Assess serum amylase and/or lipase levels to identify early signs of pancreatic inflammation. Discontinue ASPARLAS if pancreatitis is suspected; if pancreatitis is confirmed, do not resume ASPARLAS *[see Dosage and Administration (2.2)]*.

5.3 Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis, have been reported in clinical trials with ASPARLAS with an incidence of 9 to 12%. Discontinue ASPARLAS in patients experiencing serious thrombotic events *[see Dosage and Administration (2.2), Adverse Reactions (6.1)]*.

5.4 Hemorrhage

Hemorrhage associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia have been reported in patients receiving ASPARLAS *[see Adverse Reactions (6.1)]*. Evaluate patients with signs and symptoms of hemorrhage with coagulation parameters including PT, PTT, fibrinogen. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy *[see Dosage and Administration (2.2)]*.

5.5 Hepatotoxicity

Hepatotoxicity and abnormal liver function, including elevations of transaminase, bilirubin (direct and indirect), reduced serum albumin, and plasma fibrinogen can occur. Evaluate bilirubin and transaminases at least weekly, during cycles of treatment that include ASPARLAS through 6 weeks after the last dose of ASPARLAS. In the event of serious liver toxicity, discontinue treatment with ASPARLAS and provide supportive care *[see Dosage and Administration (2.2), Contraindications (4), Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*.
- Pancreatitis *[see Warnings and Precautions (5.2)]*.
- Thrombosis *[see Warnings and Precautions (5.3)]*.
- Hemorrhage *[see Warnings and Precautions (5.4)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Study DFCI 11-001

The safety of ASPARLAS was investigated in Study DFCI 11-001, an open-label, randomized, active-controlled multicenter clinical trial that treated 237 children and adolescents with newly-diagnosed ALL or lymphoblastic lymphoma, with ASPARLAS 2,500 U/m^2 (n=118) or pegaspargase 2,500 U/m^2 (n=119) as part of a Dana Farber Cancer Institute (DFCI) ALL Consortium backbone therapy. The median age on enrollment was 5 years (range, 1-20) years. The majority of patients were male (62%) and white (70%). Most patients were considered standard risk (SR, 59%) and had B-cell lineage ALL (87%).

The median number of doses during the study was 11 doses for ASPARLAS (administered every three weeks) and 16 doses for pegaspargase (administered every two weeks). The median duration of exposure was 8 months for both ASPARLAS and pegaspargase.

There was 1 fatal adverse reaction (multi-organ failure in the setting of chronic pancreatitis associated with a pancreatic pseudocyst).

Table 2 summarizes the incidence of selected Grades ≥3 adverse reactions that occurred in 2 or more patients receiving ASPARLAS. Because not all grade 1 and 2 adverse reactions were collected prospectively, only grade 3 and 4 adverse events are presented in Table 2.

Table 2: Selected Grades ≥ 3 Adverse Reactions in Patients Receiving ASPARLAS With Multi-Agent Chemotherapy (Study DFCI 11-001)*

Adverse Reaction†	ASPARLAS 2,500 U/m^2 N=118	Pegaspargase 2,500 U/m^2 N=119
	Grades ≥3 n (%)§	Grades ≥3 n (%)§
Elevated transaminase	61 (52)	79 (66)
Bilirubin increased	24 (20)	30 (25)
Pancreatitis	21 (18)	29 (24)
Abnormal clotting studies	17 (14)	25 (21)
Diarrhea	10 (9)	6 (5)
Hypersensitivity	9 (8)	8 (7)
Embolic and thrombotic events	9 (8)	10 (8)
Sepsis	6 (5)	7 (6)
Dyspnea	5 (4)	1 (1)
Hemorrhages	5 (4)	5 (4)
Fungal infection	4 (3)	3 (3)
Pneumonia	4 (3)	8 (7)
Arrhythmia	2 (2)	1 (1)
Cardiac failure	2 (2)	1 (1)

***** ASPARLAS or pegaspargase were administered as a component of multi-agent chemotherapy regimens.

† Grouped terms: **Elevated transaminase**: Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased; **Bilirubin increased**: Bilirubin conjugated increased, Blood bilirubin increased; **Pancreatitis**: Amylase increased, Lipase increased, Pancreatic necrosis, Pancreatitis, Pancreatitis relapsing; **Abnormal clotting studies**: Activated partial thromboplastin time prolonged, Blood fibrinogen decreased; **Diarrhea**: Colitis, Diarrhea, Enterocolitis, Neutropenic colitis; **Hypersensitivity**: Anaphylactic reaction, Drug hypersensitivity, Hypersensitivity; **Embolic and thrombotic events SMQ**: Device related thrombosis, Disseminated intravascular coagulation, Embolism, Intracardiac thrombus, Intracranial venous sinus thrombosis, Pulmonary embolism, Superior sagittal sinus thrombosis, Thrombosis in device, Venous thrombosis, Venous thrombosis limb; **Sepsis**: Bacterial sepsis, Sepsis; **Dyspnea**: Hypoxia, Respiratory failure; **Hemorrhages SMQ** (excludes laboratory terms): Disseminated intravascular coagulation, Epistaxis, Hematoma, Hemorrhage intracranial, Melena, Esophageal ulcer hemorrhage, Small intestinal hemorrhage, Upper gastrointestinal hemorrhage; **Fungal infection**: Fungal infection, Hepatic infection fungal, Respiratory tract infection fungal, Splenic infection fungal, Systemic candida; **Pneumonia**: Lung infection, Pneumonia, Pneumonitis; **Arrhythmia**: Atrioventricular block complete, Sinus tachycardia, Ventricular arrhythmia; **Cardiac failure**: Ejection fraction decreased, Left ventricular dysfunction.

§ Grading is based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

In the subgroup of patients with B-cell lineage ALL, the complete remission rate in the ASPARLAS arm was 98% (95/97), compared to 99% in the pegaspargase arm; the Kaplan-Meier estimates of overall survival of the treatment arms were comparable.

Study AALL07P4

The safety of ASPARLAS was also evaluated in Study AALL07P4, an open-label, randomized, active-controlled, multicenter clinical trial that treated patients with newly-diagnosed high-risk B-precursor ALL using ASPARLAS 2,500 U/m^2 (n=43) or 2,100 U/m^2 (n=68), or pegaspargase 2,500 U/m^2 (n=52), as a

component of an augmented Berlin-Frankfurt-Münster (BFM) therapy regimen. The median age was 11 years (range 1 to 26 years); the median duration of exposure was 7 months for both ASPARLAS and pegaspargase. In this study, the induction mortality of patients treated with ASPARLAS was 2.8% (3 out of 111); there were no induction deaths among 52 patients treated with pegaspargase.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ASPARLAS in the studies described below with the incidence of antibodies in other studies or to other asparaginase products may be misleading.

Immunogenicity was assessed using enzyme linked immunosorbent assays (ELISA) in Study DFCI 11-001. Of 98 evaluable patients treated with ASPARLAS, 15 (15%) patients developed new or an increased titer of anti-drug antibodies (ADA) during treatment; 14 of these 15 patients were positive for anti-PEG antibodies. The presence of ADA correlated with the occurrence of hypersensitivity reactions. There is insufficient information to determine whether the development of antibodies is associated with altered pharmacokinetics (i.e., loss of asparaginase activity).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on published literature studies with L-asparaginase in pregnant animals, ASPARLAS can cause fetal harm when administered to a pregnant woman. There are no available data on ASPARLAS use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, intravenous administration of calaspargase pegol-mknl to pregnant rats during organogenesis at doses 0.2 to 1 times the maximum recommended human doses did not result in adverse developmental outcomes. Published literature studies in pregnant rabbits, however, suggest asparagine depletion may cause harm to the animal offspring *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In an embryofetal development study, calaspargase pegol-mknl was administered intravenously at doses of 75, 150, and 300 U/kg (0.2, 0.6 and 1 times the maximum recommended human dose, respectively, based on AUC) to pregnant rats during the period of organogenesis. Maternal toxicity of decreased body weight and food consumption was seen at all dose levels resulting in reductions in gravid uterine and placental weights, and slight reductions in fetal body weights. No evidence of structural abnormalities or embryo-fetal mortality were observed in this study at any of the doses tested. Published literature studies in which pregnant rabbits were administered L-asparaginase suggested harm to the animal offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of calaspargase pegol-mknl in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ASPARLAS and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

ASPARLAS can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended in females of reproductive potential prior to initiating ASPARLAS.

Contraception

Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with ASPARLAS and for at least 3 months after the last dose. Counsel patients to use non-hormonal method(s) of contraception since ASPARLAS can render hormonal contraceptives ineffective.

8.4 Pediatric Use

The safety and effectiveness of ASPARLAS in the treatment of ALL have been established in pediatric patients 1 month to < 17 years (no data for the age group < 1 month old). Use of ASPARLAS in these age groups is supported by evidence from an adequate and well-controlled trial with additional safety from a second trial. The trials included 208 children with ALL or lymphoblastic lymphoma treated with ASPARLAS; there were 19 infants (1 month to < 2 years old), 128 children (2 years to < 12 years old), and 61 adolescents (12 years to < 17 years old). There were no clinically meaningful differences in safety or nadir serum asparaginase activity across age groups *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

11 DESCRIPTION

Calaspargase pegol-mknl contains an asparagine specific enzyme derived from *Escherichia coli*, as a conjugate of L-asparaginase (L-asparagine amidohydrolase) and monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate (SC) linker. The SC linker is a chemically stable carbamate bond between the mPEG moiety and the lysine groups of L-asparaginase.

L-asparaginase is a tetrameric enzyme that is produced endogenously by *E. coli* and consists of identical 34.5 kDa subunits. Approximately 31 to 39 molecules of SC-PEG are linked to L-asparaginase; the molecular weight of each SC-PEG molecule is about 5 kDa. The activity of ASPARLAS is expressed in units (U).

ASPARLAS injection is supplied as a clear, colorless, preservative-free, isotonic sterile solution in phosphate-buffered saline, pH 7.3 that requires dilution prior to intravenous infusion. Each vial of ASPARLAS contains 3,750 units in 5 mL of solution. Each milliliter contains 750 units of calaspargase pegol-mknl; dibasic sodium phosphate, USP (5.58 mg); monobasic sodium phosphate, USP (1.20 mg); and sodium chloride, USP (8.50 mg) in water for injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

L-asparaginase is an enzyme that catalyzes the conversion of the amino acid L-asparagine into aspartic acid and ammonia. The pharmacological effect of ASPARLAS is thought to be based on selective killing of leukemic cells due to depletion of plasma L-asparagine. Leukemic cells with low expression of asparagine synthetase have a reduced ability to synthesize L-asparagine, and therefore depend on an exogenous source of L-asparagine for survival.

12.2 Pharmacodynamics

Calaspargase pegol-mknl pharmacodynamic (PD) response was assessed through measurement of plasma and cerebrospinal fluid (CSF) asparagine concentrations *via* an LC-MS/MS assay.

Asparagine concentrations in plasma (N=41) were maintained below the assay limit of quantification for more than 18 days following a single dose of ASPARLAS 2,500 U/m^2 during the induction phase. Mean CSF asparagine concentrations decreased from a pretreatment concentration of 0.8 µg/mL (N=10) to 0.2 µg/mL on Day 4 (N=37) and remained decreased at 0.2 µg/mL (N=35) 25 days after the administration of a single dose of ASPARLAS 2,500 U/m^2 in the induction phase.

12.3 Pharmacokinetics

Calaspargase pegol-mknl pharmacokinetics (PK) were assessed through measurement of plasma asparaginase activity *via* a coupled enzymatic assay.

The plasma asparaginase activity pharmacokinetics were characterized in 43 patients (1 to 26 years) with newly diagnosed high risk B-precursor ALL treated with a multidrug backbone therapy. **Table 3** summarizes the plasma asparaginase activity pharmacokinetic parameters after a single dose of ASPARLAS 2,500 U/m^2 in the induction phase.

Table 3: Plasma Asparaginase Activity Pharmacokinetic Parameters After a Single Dose of ASPARLAS 2,500 U/m^2 in Patients with ALL in Study AALL07P4

Parameter	Arithmetic Mean (%CV) N=43
General	
C_{max} (U/mL)	1.62 (23.0)
$AUC_{0\text{-}25day}$ (day·U/mL)	16.9 (23.2)*
$AUC_{0-\infty}$ (day·U/mL)†	25.5 (30.4)*
Absorption	
T_{max} (h)†	1.17 (1.05, 5.47)‡
Distribution	
Vss (L)	2.96 (84.3)*
Elimination	
$t_{1/2}$ (day)§	16.1 (51.9)*
Clearance (L/day)	0.147 (76.1)*

* N= 42 evaluable subjects.
† T_{max} generally near end of a 1 hour calaspargase pegol-mknl intravenous (IV) infusion.
‡ Median (10^{th}, 90^{th} percentiles).
§ Plasma asparaginase activity pharmacokinetics are nonlinear following ASPARLAS administration.

Specific Populations

The impact of renal and hepatic impairment on the PK of calaspargase pegol-mknl is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and impairment of fertility studies have not been conducted with calaspargase pegol-mknl.

14 CLINICAL STUDIES

14.1 Acute Lymphoblastic Leukemia

The determination of efficacy was based on a demonstration of the achievement and maintenance of nadir serum asparaginase activity (NSAA) above the level of 0.1 U/mL using ASPARLAS 2500 U/m^2 intravenously every 3 weeks. The pharmacokinetics of ASPARLAS were studied when used in combination with multiagent chemotherapy in 124 patients with B cell lineage acute lymphoblastic leukemia (ALL). Among these patients, the median age was 11.5 years (range 1 – 26); 62 (50%) were male, 102 (82%) white, 6 (5%) Asian, 5 (4%) Black or African American, 2 (2%) Native Hawaiian or Pacific Islander and 9 (7%) other or unknown. The results showed that 123 (99%, 95% CI: 96% - 100%) of the 124 patients maintained NSAA > 0.1 U/mL at weeks 6, 12, 18, 24 and 30.

16 HOW SUPPLIED/STORAGE AND HANDLING

ASPARLAS (calaspargase pegol - mknl) injection is supplied as a clear, colorless, preservative-free sterile solution in a single-dose vial containing 3,750 units of calaspargase pegol-mknl per 5 mL solution (NDC 72694-515-01).

Store ASPARLAS refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake or freeze product. Unopened vials may be stored at room temperature (15°C to 25°C [59°F to 77°F]) for no more than 48 hours.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity

Inform patients on the possibility of serious allergic reactions, including anaphylaxis. Instruct the patient on the symptoms of allergic reactions and to seek medical advice immediately if they experience such symptoms *[see Warnings and Precautions (5.1)]*.

Pancreatitis

Instruct patients on the signs and symptoms of pancreatitis and to seek immediate medical attention if they experience severe abdominal pain *[see Warnings and Precautions (5.2)]*.

Instruct patients on the risk of hyperglycemia and glucose intolerance. Advise patients to seek medical advice if they experience excessive thirst or any increase in the volume or frequency of urination *[see Dosage and Administration (2.2)]*.

Thombosis

Instruct patients on the risk of thrombosis and to seek medical advice immediately if they experience severe headache, arm or leg swelling, shortness of breath, or chest pain *[see Warnings and Precautions (5.3)]*.

Hemorrhage

Advise patients to report any unusual bleeding or bruising to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Hepatotoxicity

Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.5)]*.

Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*

Advise females of reproductive potential to use effective non-hormonal contraceptionduring treatment with ASPARLAS and for at least 3 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with ASPARLAS and for at least 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:

Servier Pharmaceuticals LLC
Boston, MA 02210
U.S. License No. 2125

I-008-21-US-D

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

ONCASPAR (pegaspargase) injection, for intramuscular or intravenous use
Initial U.S. Approval: 1994

----------INDICATIONS AND USAGE----------
ONCASPAR is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for treatment of pediatric and adult patients with:
- First-line acute lymphoblastic leukemia (1.1)
- Acute lymphoblastic leukemia and hypersensitivity to asparaginase (1.2)

---------- DOSAGE AND ADMINISTRATION ----------
- Administered intramuscularly or intravenously no more frequently than every 14 days. (2.1)
- Patients ages 21 years and younger: 2,500 International Units/m^2. (2.1)
- Patients ages over 21 years: 2,000 International Units/m^2. (2.1)
- For intramuscular administration, limit the volume at a single injection site to 2 mL; if greater than 2 mL, use multiple injection sites. (2.3)
- For intravenous administration, give over a period of 1 to 2 hours in 100 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP through an infusion that is already running. (2.3)
- Do not administer ONCASPAR if drug has been frozen, stored at room temperature for more than 48 hours, or shaken or vigorously agitated. (16)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Injection: 3,750 International Units/5 mL (750 International Units/mL) solution in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
- History of serious hypersensitivity reactions to 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)
- Severe hepatic impairment. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Anaphylaxis or serious hypersensitivity reactions: Observe patients for 1 hour after administration. Discontinue ONCASPAR in patients with serious hypersensitivity reactions. (5.1)
- Thrombosis: Discontinue ONCASPAR in patients with serious thrombotic events. (5.2)
- Pancreatitis: Evaluate patients with abdominal pain for pancreatitis. Discontinue ONCASPAR in patients with pancreatitis. (5.3)
- Glucose intolerance: Monitor serum glucose. (5.4)
- Hemorrhage: Discontinue ONCASPAR for severe or life-threatening hemorrhage. Evaluate for etiology and treat. (5.5)
- Hepatotoxicity: Monitor for toxicity through recovery from cycle. Discontinue ONCASPAR for severe liver toxicity. (5.6)

---------- ADVERSE REACTIONS ----------
The most common (>5%) grade ≥3 adverse reactions with ONCASPAR included hypoalbuminemia, elevated transaminase, febrile neutropenia, hypertriglyceridemia, hyperglycemia, bilirubin increased, pancreatitis, abnormal clotting studies, embolic and thrombotic events, and hypersensitivity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Servier Pharmaceuticals, at 1-800-807-6124 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 pediatric and adult 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 pediatric and adult patients with ALL and hypersensitivity to native forms of L-asparaginase.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Patients 21 years of age or Younger

The recommended dose of ONCASPAR for patients up to and including 21 years of age is 2,500 International Units/m^2 intramuscularly or intravenously no more frequently than every 14 days.

Patients More Than 21 years of age

The recommended dose of ONCASPAR for adult patients more than 21 years of age is 2,000 International Units/m^2 intramuscularly or intravenously no more frequently than every 14 days.

2.2 Dose Modifications

Monitor patients at least weekly, with bilirubin, transaminases, glucose and clinical examinations until recovery from the cycle of therapy. If an adverse reaction should occur, modify treatment according to Table 1.

Table 1. Dose Modifications

Adverse Reaction	Severity*	Action
Infusion Reaction/ Hypersensitivity Reaction	Grade 1	• Reduce the infusion rate by 50%
	Grade 2	• Interrupt the infusion of ONCASPAR • Treat the symptoms • When symptoms resolve, resume the infusion and reduce the infusion rate by 50%
	Grade 3 to 4	• Discontinue ONCASPAR permanently
Hemorrhage	Grade 3 to 4	• Hold ONCASPAR. • Evaluate for coagulopathy and consider clotting factor replacement as needed. • Resume ONCASPAR with the next scheduled dose if bleeding is controlled.
Pancreatitis	Grades 3 to 4	• Hold ONCASPAR for elevations in lipase or amylase >3 x ULN until enzyme levels stabilize or are declining • Discontinue ONCASPAR permanently if clinical pancreatitis is confirmed.
Thromboembolism	Uncomplicated deep vein thrombosis	• Hold ONCASPAR. • Treat with appropriate antithrombotic therapy • Upon resolution of symptoms consider resuming ONCASPAR, while continuing antithrombotic therapy.

	Severe or life-threatening thrombosis	• Discontinue ONCASPAR permanently. • Treat with appropriate antithrombotic therapy.
Hepatotoxicity	Total bilirubin more than 3 times to no more than 10 times the upper limit of normal	• Hold ONCASPAR until total bilirubin is ≤ 1.5 times the upper limit of normal
	Total bilirubin more than 10 times the upper limit of normal	• Discontinue ONCASPAR and do not make up for missed doses
*Grade 1 is mild, grade 2 is moderate, grade 3 is severe, and grade 4 is life-threatening		

2.3 Preparation and Administration

Administer ONCASPAR in a healthcare setting with appropriate medical support and resuscitation equipment to manage hypersensitivity reactions, should they occur *[see Warnings and Precautions (5.1)]*.

ONCASPAR is a clear and colorless solution. Visually inspect parenteral drug products for particulate matter, cloudiness, or discoloration prior to administration. If any of these are present, discard the vial.

When ONCASPAR is administered intramuscularly:

- Limit the volume at a single injection site to 2 mL.
- If the volume to be administered is greater than 2 mL, use multiple injection sites.

When ONCASPAR is administered intravenously:

- Dilute ONCASPAR with 100 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, using aseptic technique.
- After dilution, administer immediately into a running infusion of either 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP, respectively.
- Administer over a period of 1-2 hours.
- Do not infuse other drugs through the same intravenous line during administration of ONCASPAR.
- The diluted solution should be used immediately. If immediate use is not possible, the diluted solution should be stored refrigerated at 2°C to 8°C (36°F to 46°F) for up to 48 hours. Protect infusion bags from direct sunlight.

ONCASPAR does not contain a preservative. Use only one dose per vial; discard unused product.

3 DOSAGE FORMS AND STRENGTHS

Injection: 3,750 International Units/5 mL (750 International Units/mL) clear, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

ONCASPAR is contraindicated in patients with a:

- History of serious hypersensitivity reactions, including anaphylaxis, to ONCASPAR or to any of the excipients *[see Warnings and Precautions (5.1)]*.
- History of serious thrombosis with prior L-asparaginase therapy *[see Warnings and Precautions (5.2)]*.
- History of pancreatitis, including pancreatitis related to prior L-asparaginase therapy *[see Warnings and Precautions (5.3)]*.

- History of serious hemorrhagic events with prior L-asparaginase therapy *[see Warnings and Precautions (5.5)]*.
- Severe hepatic impairment *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Serious Hypersensitivity Reactions

Anaphylaxis and serious hypersensitivity reactions can occur in patients receiving ONCASPAR. The risk of serious hypersensitivity reactions is higher in patients with known hypersensitivity to (*E.) coli* derived L-asparaginase formulations. Other hypersensitivity reactions can include angioedema, lip swelling, eye swelling, erythema, blood pressure decreased, bronchospasm, dyspnea, pruritus, and rash.

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 hypersensitivity reactions *[see Dosage and Administration (2.2)]*.

5.2 Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving ONCASPAR. Discontinue ONCASPAR in patients with serious thrombotic events *[see Dosage and Administration (2.2)]*.

5.3 Pancreatitis

Pancreatitis can occur in patients receiving ONCASPAR. Hemorrhagic or necrotizing pancreatitis with fatal outcomes have been reported.

Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Assess serum amylase and/or lipase levels to confirm early signs of pancreatic inflammation. Discontinue ONCASPAR in patients where pancreatitis is suspected. If pancreatitis is confirmed, do not resume ONCASPAR *[see Dosage and Administration (2.2)]*.

5.4 Glucose Intolerance

Glucose intolerance can occur in patients receiving ONCASPAR. In some cases, glucose intolerance is irreversible. Monitor serum glucose.

5.5 Hemorrhage

Increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenemia can occur in patients receiving ONCASPAR. Evaluate patients with signs and symptoms of hemorrhage with coagulation parameters including PT, PTT, fibrinogen. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy. Discontinue ONCASPAR for severe or life-threatening hemorrhage. *[see Dosage and Administration (2.2)]*.

5.6 Hepatotoxicity

Hepatotoxicity and abnormal liver function, including elevations of transaminase, bilirubin (direct and indirect), reduced serum albumin, and plasma fibrinogen can occur. Evaluate bilirubin and transaminases at least weekly during cycles of treatment that include ONCASPAR through at least 6 weeks after the last dose of ONCASPAR. In the event of serious liver toxicity, discontinue treatment with ONCASPAR and provide supportive care *[see Dosage and Administration (2.2)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Anaphylaxis and serious hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Thrombosis *[see Warnings and Precautions (5.2)]*
- Pancreatitis *[see Warnings and Precautions (5.3)]*
- Glucose intolerance *[see Warnings and Precautions (5.4)]*
- Hemorrhage *[see Warnings and Precautions (5.5)]*
- Hepatotoxicity *[see Warnings and Precautions (5.6)]*

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.

The most common grade 3 and 4 adverse reactions (>5%) included: hypoalbuminemia, elevated transaminase, febrile neutropenia, hypertriglyceridemia, hyperglycemia, bilirubin increased, pancreatitis, abnormal clotting studies, embolic and thrombotic events, and hypersensitivity.

First-Line Treatment of Acute Lymphoblastic Leukemia (ALL)

Study CCG-1962 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 race. 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.

In Study CCG-1962, detailed safety information was collected for pre-specified adverse reactions identified as asparaginase-induced adverse reactions and for grade 3 and 4 nonhematologic 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 2 below:

Table 2. Incidence of Selected Grades 3 and 4 Adverse Reactions in Study CCG-1962

	ONCASPAR (n=58)	**Native *E. coli* L-Asparaginase (n=59)**
Abnormal Liver Tests	3 (5%)	5 (8%)
Elevated Transaminases*	2 (3%)	4 (7%)
Hyperbilirubinemia	1 (2%)	1 (2%)
Hyperglycemia	3 (5%)	2 (3%)
Central Nervous System Thrombosis	2 (3%)	2 (3%)
Coagulopathy†	1 (2%)	3 (5%)
Pancreatitis	1 (2%)	1 (2%)
Allergic Reactions to Asparaginase	1 (2%)	0

* Aspartate aminotransferase, alanine aminotransferase.

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

The safety of ONCASPAR was investigated in Study DFCI 11-001, an open-label, randomized, active-controlled multicenter clinical trial that included 119 children and adolescents with newly-diagnosed ALL or lymphoblastic lymphoma treated with ONCASPAR in combination with the Dana Farber Cancer Institute (DFCI) ALL Consortium backbone therapy. The median age on enrollment was 4 years (range, 1-18 years). The majority of patients were male (60%) and white (75%). Most patients were considered standard risk ALL (59%) and had B-cell lineage ALL (87%).

The median number of doses of ONCASPAR during the study was 16 doses (one dose during induction therapy then administered every two weeks during post induction therapy). The median duration of exposure to ONCASPAR was 8 months. Table 3 summarizes the incidence of selected Grades ≥ 3 adverse reactions that occurred in 8 or more patients receiving ONCASPAR. Because not all grade 1 and 2 adverse reactions were collected prospectively, only grade 3 and 4 adverse reactions are presented in Table 3.

Table 3: Incidence of Selected Grades ≥ 3 Adverse Reactions in Patients Receiving ONCASPAR With Multi-Agent Chemotherapy in Study DFCI 11-001

Adverse Reaction†	**ONCASPAR 2500 IU/m² N=119 Grade ≥ 3‡ n (%)**
Elevated transaminase†	79 (66)
Febrile neutropenia	48 (40)
Hypertriglyceridemia	36 (30)
Hypoalbuminemia	33 (28)
Bilirubin increased†	30 (25)
Hyperglycemia	29 (24)
Pancreatitis†	29 (24)
Abnormal clotting studies†	25 (21)
Embolic and thrombotic events†	10 (8)
Hypersensitivity†	8 (7)

† Grouped terms: **Elevated transaminase**: Alanine aminotransferase increased, Aspartate aminotransferase increased; **Pancreatitis**: Amylase increased, Lipase increased, Pancreatitis, Pancreatitis relapsing; **Bilirubin increased**: Bilirubin conjugated increased, Blood bilirubin increased; **Abnormal clotting studies**: Activated partial thromboplastin time prolonged, Blood fibrinogen decreased; **Febrile neutropenia**: Febrile neutropenia; **Embolic and thrombotic events**: Embolism, Pulmonary embolism, Thrombosis in device, Venous thrombosis, Venous thrombosis limb; **Hypersensitivity**: Hypersensitivity, Anaphylactic reaction, Drug hypersensitivity.
‡ Grading is based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Previously Treated ALL

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 or in combination with multi-agent chemotherapy *[see Clinical Studies (14.2)]*. The toxicity 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 3). The most common adverse reactions of ONCASPAR were clinical allergic reactions, elevated transaminases, hyperbilirubinemia, and coagulopathies. The most common serious adverse events due to ONCASPAR treatment were thrombosis (4%), hyperglycemia requiring insulin therapy (3%), and pancreatitis (1%).

Allergic Reactions

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

Among 58 ONCASPAR-treated patients enrolled in Study CCG-1962, 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 4).

Among 62 patients with relapsed ALL and prior hypersensitivity reactions to asparaginase, 35 patients (56%) had a history of clinical allergic reactions to native *E. coli* L-asparaginase, and 27 patients (44%) had a history of clinical allergic reactions to both native Escherichia (*E.) coli* and native *Erwinia* L-asparaginase. Twenty (32%) of these 62 patients experienced clinical allergic reactions to ONCASPAR (see Table 4).

Among 112 patients with relapsed ALL with no prior hypersensitivity reactions to asparaginase, 11 patients (10%) experienced clinical allergic reactions to ONCASPAR (see Table 4).

Table 4. Incidence of Clinical Allergic Reactions, Overall and by Severity Grade

	Toxicity Grade, n (%)				
Patient Status	**1**	**2**	**3**	**4**	**Total**
Previously Hypersensitive Patients (n=62)	7 (11)	8 (13)	4 (6)	1 (2)	20 (32)
Non-Hypersensitive Patients (n=112)	5 (4)	4 (4)	1 (1)	1 (1)	11 (10)
First-Line (n=58)	1 (2)	0	1 (2)	0	2 (3)

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other asparaginase products may be misleading.

In Study CCG-1962, 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). In study CCG 1962, there is insufficient information to determine whether the development of antibodies is associated with an increased risk of clinical allergic reactions or altered pharmacokinetics (i.e., loss of asparaginase activity).

In Study DFCI 11-001, of the 100 evaluable patients treated with ONCASPAR, 19 (19%) patients developed anti-drug antibodies (ADA) during treatment; 18 of these 19 patients were positive for anti-PEG antibodies. The presence of ADA correlated with the occurrence of hypersensitivity reactions. There is insufficient information to determine whether the development of antibodies is associated with altered pharmacokinetics (i.e., loss of asparaginase activity).

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ONCASPAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Coagulopathy.
Gastrointestinal disorders: Hepatic impairment, pancreatic cyst, pancreatitis.
Immune system disorders: Anaphylactic shock, hypersensitivity reaction.
Investigations: Blood cholesterol increased.
Metabolism and nutrition disorders: Hyperglycemia, hyperammonemia.
Vascular disorders: Hemorrhage including central nervous system hemorrhage, thrombosis including superior sagittal sinus thrombosis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary

Based on published literature studies with L-asparaginase in pregnant animals, ONCASPAR can cause fetal harm when administered to a pregnant woman. There are no available data on ONCASPAR use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Published literature studies in pregnant animals suggest asparagine depletion may cause harm to the animal offspring *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriages for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with ONCASPAR to evaluate its effect on reproduction and fetal development. Published literature studies in which pregnant rabbits were administered L-asparaginase or pregnant rats were deprived of dietary asparagine suggested harm to the animal offspring.

8.2 Lactation

Risk summary

There are no data on the presence of pegaspargase in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONCASPAR and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

ONCASPAR can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy

Pregnancy testing is recommended for females of reproductive potential prior to initiating ONCASPAR.

Contraception

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ONCASPAR and for at least 3 months after the last dose. Counsel patients to use non-hormonal method(s) of contraception, since ONCASPAR can render hormonal contraceptives ineffective.

8.4 Pediatric Use

The safety and effectiveness of ONCASPAR in the treatment of ALL have been established in pediatric patients. Use of ONCASPAR in these age groups is supported by evidence of efficacy as first-line treatment from one adequate and well-controlled trial, and evidence of efficacy for treatment of patients with hypersensitivity to asparaginase from four adequate and well-controlled trials *[see Clinical Studies (14.1)]*, and safety data from 7 total trials. The pediatric patients treated with ONCASPAR 2,500 International Units/m^2 on these trials included 26 infants (1 month to <2 years old), 165 children (2 years to <12 years old), and 39 adolescents (12 to 17 years old).

8.5 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.

10 OVERDOSAGE

Three patients received 10,000 International Units/m^2 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.

There is no specific antidote for ONCASPAR overdosage. In case of overdose, monitor patients closely for signs and symptoms of adverse reactions, and appropriately manage with symptomatic and supportive treatment.

11 DESCRIPTION

Pegaspargase is a conjugate of monomethoxypolyethylene glycol (mPEG) and L-asparaginase (L-asparagine amidohydrolase), an asparagine specific enzyme. L-asparaginase is a tetrameric enzyme that is produced endogenously by *E. coli* and consists of identical 34.5 kDa subunits. Approximately

69 to 82 molecules of mPEG are linked to L-asparaginase; the molecular weight of each mPEG molecule is about 5 kDa. ONCASPAR activity is expressed in International Units.

ONCASPAR (pegaspargase) injection is supplied as a clear, colorless, preservative-free, isotonic sterile solution in phosphate-buffered saline, pH 7.3, for intramuscular use or for dilution prior to intravenous infusion. Each vial of ONCASPAR contains 3,750 International Units of pegaspargase in 5 mL of solution. Each milliliter contains 750 International Units of pegaspargase, dibasic sodium phosphate, USP (5.58 mg), monobasic sodium phosphate, USP (1.20 mg), and Sodium Chloride, USP (8.50 mg) in Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

L-asparaginase is an enzyme that catalyzes the conversion of the amino acid L-asparagine into aspartic acid and ammonia. The pharmacological effect of ONCASPAR is thought to be based on selective killing of leukemic cells due to depletion of plasma L-asparagine. Leukemic cells with low expression of asparagine synthetase have a reduced ability to synthesize L-asparagine and therefore depend on an exogenous source of L-asparagine for survival.

12.2 Pharmacodynamics

Pharmacodynamic activity was assessed through serial measurements of asparagine in sera and cerebrospinal fluid (CSF).

In Study CCG-1962, pharmacodynamics were assessed in 57 newly diagnosed pediatric patients with standard-risk ALL who received three intramuscular doses of ONCASPAR (2,500 International Units/m^2), one each during induction and two delayed intensification treatment phases *[see Clinical Studies (14.1)]*.

In Study AALL07P4, the pharmacodynamic response of pegaspargase was assessed in 47 evaluable patients with newly diagnosed high risk B-precursor ALL. Asparagine concentrations in plasma (N=42) were maintained below the assay limit of quantification for at least 11 days following a single dose of ONCASPAR 2,500 International Units/m^2 during the induction phase. CSF asparagine concentration was decreased from a mean pretreatment concentration of 0.6 µg/mL (N=20) to 0.2 µg/mL on Day 4 (N=41) and remained decreased at 0.2 µg/mL (N=39) 25 days after the administration of a single dose of ONCASPAR in the induction phase.

12.3 Pharmacokinetics

Pharmacokinetic assessments were based on an enzymatic assay measuring asparaginase activity after intramuscular (IM, CCG-1962) and intravenous (IV, AALL07P4) administration of 2,500 International Units/m^2 in patients with ALL.

Absorption

The mean maximum asparaginase activity (C_{max}) was reached at approximately 1 IU/mL (n=45-52) on Day 5 after a single IM injection. The mean half-life of absorption from the IM site was 1.7 days. The relative bioavailability was 82% following the first IM dose and 98% following repeat dosing.

The mean C_{max} and the area under the curve ($AUC_{0\text{-}inf}$) was 1.6 IU/mL and 16.6 IU/mL*day, respectively, after a single IV infusion (n=47) during the induction phase.

Distribution

The mean volume of distribution at steady state was estimated to be 1.86 L/m^2 after a single IM injection and approximately 2 L after a single IV infusion based on non-compartmental analysis.

Elimination

The mean elimination half-life was approximately 5.8 days following a single IM injection and 5.3 days following a single IV infusion. The clearance was 0.17 L/m^2/day and 0.2 L/day, respectively, for a single IM and IV dose.

Specific Populations

The impact of renal and hepatic impairment on the pharmacokinetics of ONCASPAR is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility studies have not been conducted with pegaspargase.

14 CLINICAL STUDIES

14.1 First-Line Treatment of ALL

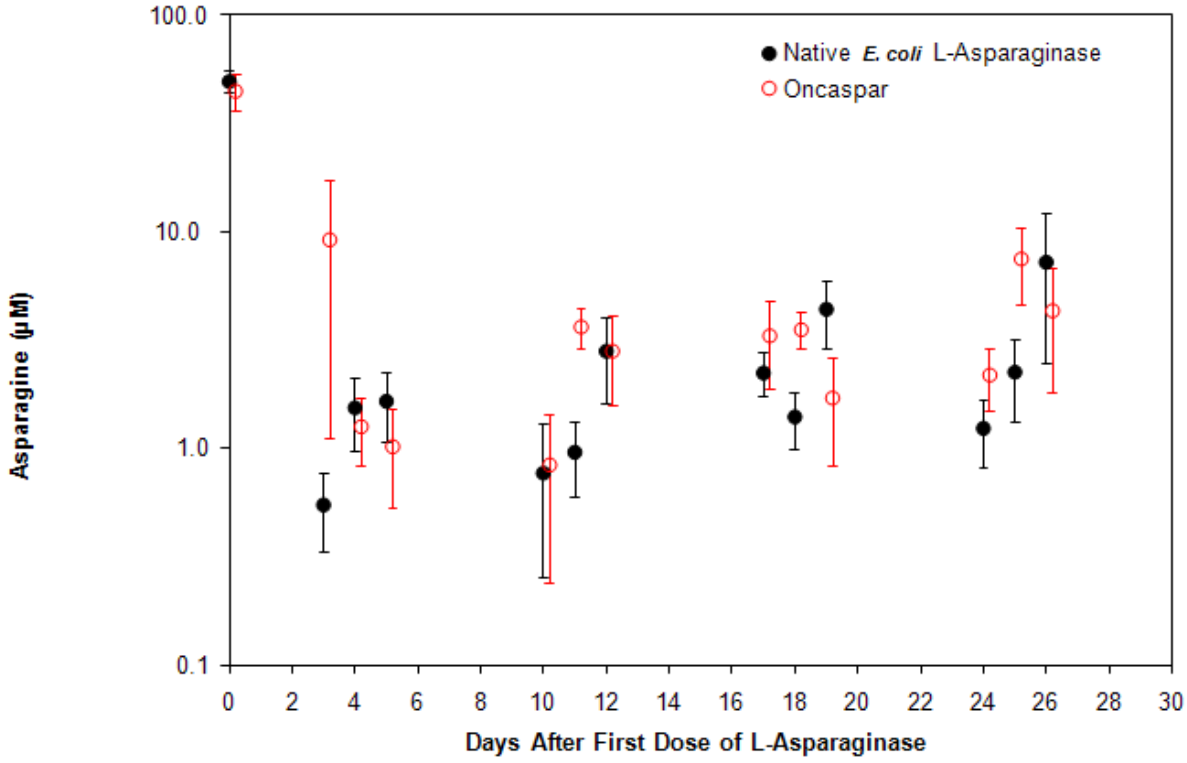
Study CCG-1962

The safety and effectiveness of ONCASPAR was evaluated in an open-label, multicenter, randomized, active-controlled study (Study CCG-1962). In this study, 118 pediatric patients aged 1 to 9 years with previously untreated standard-risk ALL were randomized 1:1 to ONCASPAR or native *E. coli* L-asparaginase as part of combination therapy. ONCASPAR was administered intramuscularly at a dose of 2,500 International Units/m^2 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 intramuscularly at a dose of 6,000 International Units/m^2 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 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 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 CCG-1962 Induction Phase



Note: ONCASPAR (2,500 International Units/m^2 intramuscular) was administered on Day 3 of the 4-week induction phase. Native *E. coli* L-asparaginase (6,000 International Units/m^2 intramuscular) 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 from a mean pre-treatment concentration of 3.1 µM to 1.7 µM on Day 4±1 and 1.5 µM at 25±1 days after administration of ONCASPAR. These findings were similar to those observed in the native *E. coli* L-asparaginase treatment arm.

Concentrations of asparaginase activities greater than 0.1 International Units/mL were observed in over 90% of the samples from patients treated with ONCASPAR during Induction, Delayed Intensification 1, and Delayed Intensification 2 for approximately 20 days.

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 CCG-1962 was not designed to evaluate for differences in EFS rates.

14.2 Patients with ALL 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 International Units/m^2 administered intramuscularly or intravenously 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

ONCASPAR (pegaspargase) injection is supplied as a sterile, clear, colorless, preservative-free solution in Type I single-dose vial containing 3,750 International Units of pegaspargase per 5 mL (750 International Units per mL) solution (NDC 72694-954-01).

Store ONCASPAR refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. *Do not shake or freeze product*. Unopened vials may be stored at room temperature (15°C to 25°C [59°F to 77°F]) for no more than 48 hours.

17 PATIENT COUNSELING INFORMATION

Anaphylaxis and Serious Hypersensitivity Reactions

Inform patients of the possibility of serious allergic reactions, including anaphylaxis, and to seek immediate medical care for any swellings or difficulty breathing *[see Warnings and Precautions (5.1)]*.

Thrombosis

Instruct patients on the risk of thrombosis and hemorrhage and to seek immediate medical attention if they experience severe headache, arm or leg swelling, shortness of breath, or chest pain *[see Warnings and Precautions (5.2)]*.

Pancreatitis

Instruct patients on the signs and symptoms of pancreatitis and to seek immediate medical attention if they experience severe abdominal pain *[see Warnings and Precautions (5.3)]*.

Glucose Intolerance

Instruct patients on the risk of hyperglycemia and glucose intolerance. Advise patients to immediately report excessive thirst or increase in the volume or frequency of urination *[see Warnings and Precautions (5.4)]*.

Hemorrhage

Advise patients to report any unusual bleeding or bruising to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Hepatotoxicity

Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ONCASPAR and for at least 3 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with ONCASPAR and for at least 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

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