The Children's Oncology Group AALL1732 Protocol for High-Risk B-Cell ALL

Patients are classified as high risk (HR) if they are aged ≥10 years and/or have a white blood cell count ≥50,000/μL.[1]

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

Amendment: Option for ASPARLAS substitution

In conjunction with the April 5, 2021, amendment to AALL1732, ASPARLAS (calaspargase pegol-mknl) may now be used as an option instead of pegaspargase in the 1732 protocol for patients aged <22 years starting in Delayed Intensification. Patients ≥22 years of age must receive pegaspargase.[2]

ASPARLAS is approved as a part of a multi-agent chemotherapy regimen in patients with ALL aged 1 month to 21 years.[3]

Please see Important Safety Information on reverse and ASPARLAS Full Prescribing Information.

	Induction (35 days)[4]	Consolidation (8 weeks)[4]	Interim Maintenance I (9 weeks)[4]	Delayed Intensification 1st Part (4 weeks)[4]	Delayed Intensification 2nd Part (5 weeks)[4]	Interim Maintenance II (8 weeks)[4]	Maintenance (12-week cycles over 2 years after the start of IM I)[4]
Vincristine (1.5 mg/m²)[a]	Days 1, 8, 15, 22	Days 15, 22, 43, 50	Days 1, 15, 29, 43	Days 1, 8, 15	Days 43, 50	Days 1, 11, 21, 31, 41	Day 1 of each cycle
Prednisolone (30 mg/m² BID) (patients aged ≥10 years)	Days 1-28						Days 1-5 of each cycle
Dexamethasone (5 mg/m² BID) (patients aged <10 years)	Days 1-14			Days 1-7, 15-21			
Daunorubicin (25 mg/m²)	Days 1, 8, 15, 22						
IT cytarabine (30-70 mg)[b]	Day 1						
Pegaspargase (2500 IU/m²)[c]	Day 4	Days 15, 43					
Calaspargase pegol (2500 IU/m²)				Day 4	Day 43	Days 2, 23[2]	
IT methotrexate (8-15 mg)[d,e]	Days 8, 29	Days 1, 8, 15, 22	Days 1, 29	Day 1	Days 29, 36	Days 1, 31	Day 1 of each cycle; Day 29 of cycles 1, 2
Mercaptopurine (25-75 mg/m²)[f,g]		Days 1-14, 29-42	Days 1-14, 15-28, 29-42, 43-56				Daily
Cytarabine (75 mg/m²)[g]		Days 1-4, 8-11, 29-32, 36-39			Days 29-32, 36-39		
Cyclophosphamide (1000 mg/m²)[g]		Days 1, 29			Day 29		
HD methotrexate (5000 mg/m²)[h]			Days 1, 15, 29, 43				
Doxorubicin (25 mg/m²)				Days 1, 8, 15			
Thioguanine (60 mg/m²)					Days 29-42		
Capizzi methotrexate (Start: 100 mg/m²)						Days 1, 11, 21, 31, 41	
Oral methotrexate (20 mg/m²)[e,i]							Weekly
Additional Treatment for Patients Randomized to the Inotuzumab Arm							
Inotuzumab (0.5 mg/m²)[j,k]			Block 1: Days 1, 8, 15		Block 2: Days 1, 8, 15		

[a] Maximum dose: 2 mg.[4] [b] Patients aged 1-1.99 years: 30 mg, aged 2-2.99 years: 50 mg, and aged ≥3 years: 70 mg; IT cytarabine dose given at the time of diagnostic lumbar puncture OR on day 1; patients with CNS2 status receive additional twice-weekly doses during induction (refer to protocol for more details).[4] [c] Patients aged <22 years: 2500 IU/m², aged ≥22 years: 2000 IU/m².[5] [d] Patients aged 1-1.99 years: 8 mg, aged 2-2.99 years: 10 mg; aged 3-8.99 years: 12 mg, and aged ≥9 years: 15 mg; patients with CNS3 receive an additional dose on days 15 and 22 of induction, but omit doses on day 15 and 22 of consolidation.[4] [e] Maintenance given as 12-week cycles repeated over 2 years; IT methotrexate on day 29 is only given during the first 2 cycles and is mutually exclusive with oral methotrexate on day 29.[4] [f] Consolidation: 60 mg/m²; Interim Maintenance: 25 mg/m²; Maintenance: 75 mg/m².[4] [g] Patients should have an absolute neutrophil count of ≥750/μL and platelets ≥75,000/μL to begin day 36 therapy in consolidation.[4] [h] Followed by 15 mg/m² leucovorin 42, 48, and 54 hours after start of each HD methotrexate infusion.[4] [i] Given on days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 of each 12-week cycle during maintenance; omitted on days when IT methotrexate is administered.[4] [j] Patients in the experimental inotuzumab treatment arm receive IT methotrexate on day 1 of consolidation only.[4] [k] Block 1 Inotuzumab is started after Consolidation. Block 2 Inotuzumab is started on day 64 of Interim Maintenance I.[4]

Abbreviations: ALL, acute lymphoblastic leukemia; BID, twice daily; CNS, central nervous system; HD, high dose; IM, interim maintenance; IT, intrathecal.

Important Safety Information

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.

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 treatment
- 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 ASPARLAS Full Prescribing Information.

References: **1.** Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol*. 1996;14(1):18-24. **2.** Personal communication from the Children's Oncology Group leadership. **3.** ASPARLAS [package insert]. Boston, MA: Servier Pharmaceuticals LLC; 2020. **4.** Children's Oncology Group. AALL1732. Phase 3 randomized trial of inotuzumab ozogamicin (IND#:133494, NSC#: 772518) for newly diagnosed high-risk B-ALL; risk-adapted post-induction therapy for high-risk B-ALL, mixed phenotype acute leukemia, and disseminated B-LLy. February 26, 2021. **5.** ONCASPAR [package insert]. Boston, MA: Servier Pharmaceuticals LLC; 2020.

US-01860 07/21

SERVIER

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

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:

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