

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Elspar safely and effectively. See full prescribing information for Elspar.

Elspar[®] (asparaginase)

For injection, intravenous or intramuscular

Initial U.S. Approval: 1978

RECENT MAJOR CHANGES

Warnings and Precautions

Glucose Intolerance (5.4) 01/2013

Neurotoxicity (5.7) 01/2013

Potential for Medication Errors (5.8) 01/2013

INDICATIONS AND USAGE

Elspar is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) (1)

DOSAGE AND ADMINISTRATION

- 6,000 International Units/m² intramuscularly (IM) or intravenously (IV) three times a week (2.1)
- Reconstitute in volume appropriate for the intended route of administration:
For IM administration, reconstitute in 2 mL (2.3)
For IV administration, reconstitute in 5 mL (2.3)
- For IM administration, limit the volume at a single injection site to 2 mL; if greater than 2 mL, use multiple injection sites. (2.2)
- For IV administration, give over ≥ 30 min through side arm of an infusion of Sodium Chloride Injection or Dextrose Injection 5% (D₅W). (2.2)
- Use reconstituted Elspar within eight hours. (2.3)

DOSAGE FORMS AND STRENGTHS

- 10,000 International Units as lyophilized powder in single-use vial (3)

CONTRAINDICATIONS

- Serious allergic reactions to Elspar or other *Escherichia coli*-derived L-asparaginases (4)

- Serious thrombosis with prior L-asparaginase therapy (4)
- Pancreatitis with prior L-asparaginase therapy (4)
- Serious hemorrhagic events with prior L-asparaginase therapy (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and other serious allergic reactions can occur. Observe patients for one hour after administration. Discontinue Elspar in patients with serious allergic reactions. (5.1)
- Serious thrombotic events, including sagittal sinus thrombosis, can occur. Discontinue Elspar in patients with serious thrombotic events. (5.2)
- Pancreatitis, in some cases fulminant or fatal, can occur. Evaluate patients with abdominal pain for pancreatitis. Discontinue Elspar in patients with pancreatitis. (5.3)
- Glucose intolerance, in some cases irreversible, can occur. Monitor serum glucose. (5.4)
- Coagulopathy can occur. Perform appropriate monitoring. (5.5)
- Hepatotoxicity including hepatic failure can occur. Perform appropriate monitoring. (5.6)
- Neurotoxicity, posterior reversible encephalopathy syndrome (PRES). (5.7)
- Potential for medication errors. (5.8)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck at 1-800-455-1141 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Elspar is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of Elspar is 6,000 International Units/m² intramuscularly (IM) or intravenously (IV) three times a week.

2.2 Instructions for Administration

When Elspar is administered IM, the volume at a single injection site should be limited to 2 mL. If a volume greater than 2 mL is to be administered, two injection sites should be used. Discard unused portion.

When administered IV, give Elspar over a period of not less than thirty minutes through the side arm of an infusion of Sodium Chloride Injection or Dextrose Injection 5% (D₅W). Discard unused portion.

2.3 Preparation and Handling Precautions

For IM administration, reconstitute Elspar by adding 2 mL Sodium Chloride Injection to the 10,000 unit vial. Withdraw volume of reconstituted Elspar containing calculated dose into sterile syringe. The reconstituted solution contains 5,000 international units (IU)/mL.

For IV administration, reconstitute Elspar by adding 5 mL Sterile Water for Injection or Sodium Chloride Injection to the 10,000 unit vial. Withdraw volume of reconstituted Elspar containing calculated dose into sterile syringe. The reconstituted solution contains 2,000 IU/mL.

Use reconstituted Elspar within eight hours.

Parenteral drug products should be inspected visually for particulate matter, cloudiness or discoloration prior to administration, whenever solution and container permit. If any of these are present, discard the solution. However, occasionally, a very small number of gelatinous fiber-like particles may develop on standing. Filtration through a 5.0 micron filter during administration will remove the particles with no resultant loss in potency.

3 DOSAGE FORMS AND STRENGTHS

10,000 International Units as lyophilized powder in single-use vial.

4 CONTRAINDICATIONS

- Serious allergic reactions to Elspar or other *Escherichia coli*-derived L-asparaginases
- Serious thrombosis with prior L-asparaginase therapy
- Pancreatitis with prior L-asparaginase therapy
- Serious hemorrhagic events with prior L-asparaginase therapy

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Serious Allergic Reactions

Serious allergic reactions can occur in patients receiving Elspar. The risk of serious allergic reactions is higher in patients with prior exposure to Elspar or other *Escherichia coli*-derived L-asparaginases. Observe patients for one hour after administration of Elspar in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (for example, epinephrine, oxygen, intravenous steroids, antihistamines). Discontinue Elspar in patients with serious allergic reactions.

5.2 Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving Elspar. Discontinue Elspar in patients with serious thrombotic events.

5.3 Pancreatitis

Pancreatitis, in some cases fulminant or fatal, can occur in patients receiving Elspar. Evaluate patients with abdominal pain for evidence of pancreatitis. Discontinue Elspar in patients with pancreatitis.

5.4 Glucose Intolerance

Glucose intolerance can occur in patients receiving Elspar. In some cases, glucose intolerance is irreversible. Cases of diabetic ketoacidosis have been reported. Monitor serum glucose.

5.5 Coagulopathy

Increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenemia can occur in patients receiving Elspar. CNS hemorrhages have been observed. Monitor coagulation parameters at baseline and periodically during and after treatment. Initiate treatment with fresh-frozen plasma to replace coagulation factors in patients with severe or symptomatic coagulopathy.

5.6 Hepatotoxicity and Abnormal Liver Function

Fulminant hepatic failure occurs. Hepatotoxicity and abnormal liver function, including elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin (direct and indirect), and depression of serum albumin, and plasma fibrinogen can occur. Fatty changes in the liver have been documented on biopsy. Evaluate hepatic enzymes and bilirubin pretreatment and periodically during treatment.

5.7 Neurotoxicity

Patients treated with Elspar in a combination with other chemotherapeutic agents have been reported to develop posterior reversible encephalopathy syndrome (PRES). PRES is a neurological disorder with clinical symptoms of headache, seizures, visual disturbances, altered mental status, and hypertension. Symptoms can be nonspecific, and diagnosis requires confirmation by radiological procedures. Interrupt use of Elspar if PRES is suspected or diagnosed. Prompt blood pressure and seizure control is advised.

5.8 Potential for Medication Errors

Medication errors involving Elspar have occurred. In particular, different formulations and routes of administration (I.M. and I.V.) of asparaginase have been interchanged inappropriately, which may result in subtherapeutic blood levels of asparaginase or additional toxicity related to an overdose. Prior to administering Elspar, the formulation of asparaginase should be confirmed. Do not confuse or substitute *E. coli* asparaginase, Erwinia asparaginase, and pegylated *E. coli* asparaginase [polyethylene glycol (PEG) asparaginase].

6 ADVERSE REACTIONS

The following serious adverse reactions occur with Elspar treatment [*see Warnings and Precautions (5)*]:

- Anaphylaxis and serious allergic reactions
- Serious thrombosis
- Pancreatitis
- Glucose intolerance
- Coagulopathy
- Hepatotoxicity and abnormal liver function
- Posterior reversible encephalopathy syndrome

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

6.1 Clinical Trials and Post-Marketing Experience

The adverse reactions included in this section were identified in single-arm clinical trials in which Elspar was administered as part of a multi-agent regimen or from spontaneous post-marketing reports or published literature.

Because these adverse events were identified in clinical trials that were not designed to isolate the adverse effects of Elspar or were 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.

Serious Adverse Reactions

Anaphylaxis and serious allergic reactions. Allergic reactions have occurred with the first dose and with subsequent doses of Elspar. The risk of serious allergic reactions appears to be higher in patients with prior exposure to Elspar or other *Escherichia coli*-derived L-asparaginases.

Serious thrombosis, including sagittal sinus thrombosis

Pancreatitis, in some cases fulminant or fatal

Glucose intolerance, in some cases irreversible

Coagulopathy, including increased prothrombin time, increased partial thromboplastin time, and decreased fibrinogen, protein C, protein S and antithrombin III. CNS hemorrhages have been reported.

Hepatotoxicity, in some cases fatal, can occur.

Central Nervous System effects including coma, seizures, and hallucinations.

Common Adverse Reactions

Azotemia, liver function abnormalities, including hyperbilirubinemia, and elevated transaminases.

Other

Hyperammonemia, diabetic ketoacidosis, and hyperlipidemia including hypertriglyceridemia and hypercholesterolemia

6.2 Immunogenicity

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

Elspar is a bacterial protein and can elicit antibodies in patients treated with the drug. In 2 prospectively designed clinical trials (N=59 and 24), approximately one quarter of the patients developed antibodies that bound to Elspar as measured by enzyme-linked immunosorbent assays (ELISA). Clinical hypersensitivity reactions to Elspar in studies were common ranging from 32.5% to 75%. In these studies, concomitant medications and dosing schedules varied. Patients with hypersensitivity reactions were more likely to have antibodies than those without hypersensitivity reactions. Hypersensitivity reactions have been associated with increased clearance of Elspar. Incidence of antibody formation was lower upon first administration of Elspar than second administration. The frequency of antibody formation in adults relative to children is unknown. There is insufficient information to comment on neutralizing antibodies; however, higher levels of antibody correlated with a decrease in asparaginase activity.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications and underlying disease. Therefore, comparison of the incidence of antibodies to Elspar with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug interaction studies between Elspar and other drugs have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. In mice and rats Elspar has been shown to retard the weight gain of mothers and fetuses when given in doses of more than 1000 International Units/kg (approximately equivalent to the recommended human dose, when adjusted for total body surface area). Resorptions, gross abnormalities and skeletal abnormalities were observed. The intravenous administration of 50 or 100 International Units/kg (approximately equivalent to 10 to 20% of the recommended human dose, when adjusted for total body surface area) to pregnant rabbits on Day 8 and 9 of gestation resulted in dose dependent embryotoxicity and gross abnormalities. There are no adequate and well-controlled studies in pregnant women. Elspar should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

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

8.4 Pediatric Use

[See *Clinical Studies (14)*]

8.5 Geriatric Use

Clinical studies of Elspar did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Elspar (asparaginase) contains the enzyme L-asparagine amidohydrolase, type EC-2, derived from *Escherichia coli*. Elspar activity is expressed in terms of International Units according to the recommendation of the International Union of Biochemistry. One International Unit of asparaginase is defined as that amount of enzyme required to generate 1 μ mol of ammonia per minute at pH 7.3 and 37°C. The specific activity of Elspar is at least 225 International Units per milligram of protein.

Elspar is provided as a sterile, white lyophilized plug or powder. Each vial contains 10,000 International Units of asparaginase and 80 mg of mannitol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of Elspar is thought to be based on selective killing of leukemic cells due to depletion of plasma asparagine. Some leukemic cells are unable to synthesize asparagine due to a lack of asparagine synthetase and are dependent on an exogenous source of asparagine for survival. Depletion of asparagine, which results from treatment with the enzyme L-asparaginase, kills the leukemic cells. Normal cells, however, are less affected by the depletion due to their ability to synthesize asparagine.

12.2 Pharmacodynamics

The relationship between asparaginase activity and asparagine levels has been studied in clinical trials. In previously untreated, standard-risk ALL patients treated with native asparaginase in whom plasma enzyme activity was greater than 0.1 International Units/

mL, plasma asparagine levels decreased from a pretreatment average level of 41 μM to less than 3 μM . In this study, cerebrospinal fluid asparagine levels in patients treated with asparaginase decreased from 2.8 μM (pretreatment) to 1.0 μM and 0.3 μM at day 7 and day 28 of induction, respectively.

12.3 Pharmacokinetics

In a study in patients with metastatic cancer and leukemia, daily intravenous administration of L-asparaginase resulted in a cumulative increase in plasma levels. Plasma half-life varied from 8 to 30 hours. Apparent volume of distribution was slightly greater than the plasma volume. Asparaginase levels in cerebrospinal fluid were less than 1% of concurrent plasma levels.

In a study in which patients with leukemia and metastatic cancer received intramuscular L-asparaginase, peak plasma levels of asparaginase were reached 14 to 24 hours after dosing. Plasma half-life was 34 to 49 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term carcinogenicity studies in animals have been performed with Elspar.

No relevant studies addressing mutagenic potential have been conducted. Elspar did not exhibit a mutagenic effect when tested against *Salmonella typhimurium* strains in the Ames assay.

No studies have been performed on impairment of fertility.

13.2 Animal Toxicology

Edema and necrosis of pancreatic islets were observed in rabbits following a single, intravenous injection of 12,500 to 50,000 International Units Elspar/kg (approximately equivalent to 25 to 100-fold the recommended human dose, when adjusted for total body surface area). These changes were not reflective of pancreatitis, and were not observed in rabbits following a single intravenous injection of 1000 International Units/kg (approximately equivalent to two times the recommended human dose, when adjusted for total body surface area).

14 CLINICAL STUDIES

Elspar was evaluated in an open-label, multi-center, single-arm study in which 823 patients less than 16 years of age with previously untreated acute lymphoblastic or acute undifferentiated leukemia received Elspar as a component of multi-agent chemotherapy for induction of first remission. Elspar was administered at a dose of 6,000 International Units/m² intramuscularly 3 times a week for a total of 9 doses. Of 815 evaluable patients, 758 (93%) achieved a complete remission. In a previous study, in a similar patient population, which utilized an initial induction chemotherapy regimen containing the same agents without Elspar, 429 of 499 (86%) patients achieved a complete remission.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dosage Form

NDC 67386-411-51

10,000 International Units as lyophilized powder in single dose vial individually packaged in a carton.

Storage and Handling

Keep vials refrigerated at 2-8°C (36-46°F).

Elspar does not contain a preservative. Store unused, reconstituted solution at 2-8°C (36-46°F) and discard after eight hours, or sooner if it becomes cloudy.

17 PATIENT COUNSELING INFORMATION

Advise patients to contact health care professional immediately to report any of the following:

- swelling of the face, arms or legs, with or without pain in the arm or leg
- acute difficulty in breathing/shortness of breath
- severe headache, seizures, change in mental status
- new onset chest pain
- severe abdominal pain

Advise patients to inform their healthcare professional of:

- excessive thirst or an increase in the volume or frequency of urination
- pregnancy

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PRINCIPAL DISPLAY PANEL

NDC 67386-411-51

12 Single Use Vials

Discard Unused Portion

Asparaginase

Elspar®

Contains the enzyme L-asparagine amidohydrolase, type EC-2, derived from *Escherichia coli*.

10,000 International Units/Vial

For intramuscular or intravenous use only

No U.S. standard of potency. No preservative.

R_x only

