ASPARAGINASE
ELSPAR®

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℞ only No. 411

WARNINGS
It is recommended that asparaginase be administered to patients only in a hospital setting under the supervision of a physician who is qualified by training and experience to administer cancer chemotherapeutic agents, because of the possibility of severe reactions, including anaphylaxis and sudden death. The physician must be prepared to treat anaphylaxis at each administration of the drug. In the treatment of each patient the physician must weigh carefully the possibility of achieving therapeutic benefit versus the risk of toxicity. (See WARNINGS and ADVERSE REACTIONS.)
Special handling procedures should be followed (see DOSAGE AND ADMINISTRATION, *Special Handling*).

DESCRIPTION
ELSPAR* (Asparaginase) contains the enzyme L-asparagine amidohydrolase, type EC-2, derived from *Escherichia coli*. It is a white crystalline powder that is freely soluble in water and practically insoluble in methanol, acetone and chloroform. Its activity is expressed in terms of International Units (I.U.) according to the recommendation of the International Union of Biochemistry. The specific activity of ELSPAR is at least 225 I.U. per milligram of protein and each vial contains 10,000 I.U. of asparaginase and 80 mg of mannitol, an inactive ingredient, as a sterile, white lyophilized plug or powder for intravenous or intramuscular injection after reconstitution.

CLINICAL PHARMACOLOGY
Action
In a significant number of patients with acute leukemia, particularly lymphocytic, the malignant cells are dependent on an exogenous source of asparagine for survival. Normal cells, however, are able to synthesize asparagine and thus are affected less by the rapid depletion produced by treatment with the enzyme asparaginase. This is a unique approach to therapy based on a metabolic defect in asparagine synthesis of some malignant cells. ELSPAR, derived from *Escherichia coli*, is effective in inducing remissions in some patients with acute lymphocytic leukemia.

Asparagine Dependence Test
An asparagine dependence test has been utilized during the investigational studies. In this test leukemic cells obtained from some marrow cultures could be shown to require asparagine *in vitro*, suggesting sensitivity to asparaginase therapy *in vivo*. However, present data indicate that the correlation between asparagine dependence in such tests and the final response to therapy is sufficiently poor that the test is not recommended as a basis for selection of patients for treatment.

Pharmacokinetics and Metabolism
In a study[1] in patients with metastatic cancer and leukemia, initial plasma levels of L-asparaginase following intravenous administration were correlated to dose. Daily administration resulted in a cumulative increase in plasma levels. Plasma half-life varied from 8 to 30 hours; it did not appear to be influenced by dosage, either single or repetitive, and could not be correlated with age, sex, surface area, renal or hepatic function, diagnosis or extent of disease. Apparent volume of distribution was approximately 70-80% of estimated plasma volume. There was some slow movement of asparaginase from vascular to extravascular, extracellular space. L-asparaginase was detected in the lymph. Cerebrospinal fluid levels were less than 1% of concurrent plasma levels. Only trace amounts appeared in the urine.
In a study[2] 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 39 to 49 hours. No asparaginase was detected in the urine.

INDICATIONS AND USAGE
ELSPAR is indicated in the therapy of patients with acute lymphocytic leukemia. This agent is useful primarily in combination with other chemotherapeutic agents in the induction of remissions of the disease in pediatric patients.[3,4] ELSPAR should not be used as the sole induction agent unless combination therapy is deemed inappropriate. ELSPAR is not recommended for maintenance therapy.

CONTRAINDICATIONS
ELSPAR is contraindicated in patients with pancreatitis or a history of pancreatitis. Acute hemorrhagic pancreatitis, in some instances fatal, has been reported following asparaginase administration.[4-7] Asparaginase is also contraindicated in patients who have had previous anaphylactic reactions to it.

WARNINGS
Allergic reactions to asparaginase are frequent and may occur during the primary course of therapy. They are not completely predictable on the basis of the intradermal skin test. Anaphylaxis and death have occurred even in a hospital setting with experienced observers. (See ADVERSE REACTIONS.)

Once a patient has received ELSPAR as part of a treatment regimen, retreatment with this agent at a later time is associated with increased risk of hypersensitivity reactions. In patients found by skin testing to be hypersensitive to asparaginase, and in any patient who has received a previous course of therapy with asparaginase, therapy with this agent should be instituted or reinstituted only after successful desensitization, and then only if in the judgement of the physician the possible benefit is greater than the increased risk. Desensitization itself may be hazardous. (See DOSAGE AND ADMINISTRATION, *Intradermal Skin Test.*)

In view of the unpredictability of the adverse reactions to asparaginase, it is recommended that this product be used in a hospital setting. Asparaginase has an adverse effect on liver function in the majority of patients. Therapy with asparaginase may increase pre-existing liver impairment caused by prior therapy or the underlying disease. Because of this there is a possibility that asparaginase may increase the toxicity of other medications.[3,7]

The administration of ELSPAR *intravenously concurrently with or immediately before* a course of vincristine and prednisone may be associated with increased toxicity.[3] (See DOSAGE AND ADMINISTRATION, *Recommended Induction Regimens.*)

PRECAUTIONS

General

This drug may have toxic properties and must be handled and administered with care. ELSPAR may be irritating to eyes, skin, and the upper respiratory tract. Inhalation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided. (See DOSAGE AND ADMINISTRATION, *Special Handling.*)

Asparaginase has been reported to have immunosuppressive activity in animal experiments. Accordingly, the possibility that use of the drug in man may predispose to infection should be considered.

Asparaginase toxicity is reported to be greater in adults than in pediatric patients.[7]

Laboratory Tests

The fall in circulating lymphoblasts often is quite marked; normal or below normal leukocyte counts are noted frequently within the first several days after initiating therapy. This may be accompanied by a marked rise in serum uric acid. The possible development of uric acid nephropathy should be borne in mind. Appropriate preventive measures should be taken, e.g., allopurinol, increased fluid intake, alkalization of urine.[8,9] As a guide to the effects of therapy, the patient's peripheral blood count and bone marrow should be monitored frequently.

Frequent serum amylase determinations should be obtained to detect early evidence of pancreatitis. If pancreatitis occurs, therapy should be stopped and not reinstituted.

Blood sugar should be monitored during therapy with ELSPAR because hyperglycemia may occur.[4,6,7,10-13]

Drug Interactions

Tissue culture and animal studies indicate that ELSPAR can diminish or abolish the effect of methotrexate on malignant cells.[14] This effect on methotrexate activity persists as long as plasma asparagine levels are suppressed. These results would seem to dictate against the clinical use of methotrexate with ELSPAR, or during the period following ELSPAR therapy when plasma asparagine levels are below normal.

Drug/Laboratory Test Interactions

L-asparaginase has been reported to interfere with the interpretation of thyroid function tests by producing a rapid and marked reduction in serum concentrations of thyroxine-binding globulin within two days after the first dose. Serum concentrations of thyroxine-binding globulin returned to pretreatment values within four weeks of the last dose of L-asparaginase.[15]

Animal Toxicology

A one-month intravenous toxicity study of ELSPAR in dogs at doses of 250, 1000, and 2000 I.U./kg/day revealed reduced serum total protein and albumin with loss of body weight at the highest dose level and anorexia, emesis, and diarrhea at all dosage levels. A similar study in monkeys at doses of 100, 300, and 1000 I.U./kg/day also revealed reduction of serum total protein and albumin and body weight loss at all dosage levels. Bromsulfalein retention and fatty changes in the liver were noted in monkeys that were given 300 and 1000 I.U./kg/day. The rabbit was unusually sensitive to ELSPAR since a single intravenous dose of 1000 I.U./kg caused hypocalcemia associated with necrosis of the parathyroid cells, convulsions, and death in about one-third of the animals. Some rabbits that died showed small thymic and lymph node hemorrhages and necrosis of the germinal centers in the lymph nodes and spleen. The intravenous administration of calcium gluconate alleviated or prevented the adverse effects.

Changes in the pancreatic islets (not pancreatitis) ranging from edema to necrosis were observed in the rabbits in the acute intravenous toxicity studies (doses of 12,500 to 50,000 I.U./kg) but not in rabbits that received 1000 I.U./kg. The anatomical changes and the hypocalcemia found in the rabbits were not observed in the subacute intravenous studies in the dogs and monkeys.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The intraperitoneal injection of 2500 I.U./kg/day for 4 days in newborn Swiss mice resulted in a small increase in pulmonary adenomas; lymphatic leukemia was not increased.

L-asparaginase at concentrations of 152-909 I.U./plate was not mutagenic in the Ames microbial mutagen test with or without metabolic activation.

There are no adequate studies on the effects of asparaginase on fertility.

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 I.U./kg (the recommended human dose). Resorptions, gross abnormalities and skeletal abnormalities were observed. The intravenous administration of 50 or 100 I.U./kg (one-twentieth or one-tenth of the human dose) 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 used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

Asparaginase toxicity is reported to be greater in adults than in pediatric patients.[7]

Geriatric Use

Clinical studies of ELSPAR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The adverse reactions included in this section were identified primarily in single-arm clinical trials, in which ELSPAR was administered as part of a multi-agent regimen or spontaneous post-marketing reports or published literature. Because these adverse reactions were identified in clinical trials that were not designed to isolate the adverse effects of ELSPAR or were reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors (1) seriousness of the reactions, (2) frequency of reporting, or (3) strength of causal connection to ELSPAR.

Allergic Reactions

Allergic reactions, including skin rashes, urticaria, arthralgia, respiratory distress, and acute anaphylaxis have been reported. (See WARNINGS.) Acute reactions have occurred in the absence of a positive skin test and during continued maintenance of therapeutic serum levels of ELSPAR.

Pancreatitis

Pancreatitis, sometimes fulminant and fatal, has occurred during or following therapy with ELSPAR.[4-7, 20] The complications of pancreatitis, including pancreatic pseudocyst and hemorrhagic pancreatitis, have also been reported.

Glucose Intolerance

Hyperglycemia with glucosuria and polyuria has been reported in low incidence. Serum and urine acetone usually have been absent or negligible in these patients; this syndrome thus resembles hyperosmolar, nonketotic, hyperglycemia induced by a variety of other agents. This complication usually responds to discontinuance of ELSPAR, judicious use of intravenous fluid, and insulin, but may be fatal on occasion.

Coagulopathy

In addition to hypofibrinogenemia, depression of various other clotting factors has been reported. Most marked has been a decrease in plasma levels of factors V and VIII with a variable decrease in factors VII and IX, and decreases in plasma levels of protein C, protein S, and antithrombin III. A decrease in circulating platelets has occurred in low incidence which, together with the increased levels of fibrin degradation products in the serum, may indicate development of a consumption coagulopathy. Bleeding has been a problem in only a minority of patients with demonstrable coagulopathy. However, intracranial hemorrhage and fatal bleeding associated with low fibrinogen levels have been reported.[6,7,21] Increased fibrinolytic activity, apparently compensatory in nature, also has occurred. Thrombotic cerebral vascular events, including sinus thromboses, have been reported.

Central Nervous System Toxicity

Some patients have shown central nervous system effects consisting of depression, somnolence, fatigue, coma, seizures, confusion, agitation, and hallucinations varying from mild to severe.[6,7,10,12,13] Rarely, a Parkinson-like syndrome has occurred, with tremor and a progressive increase in muscular tone. These side effects usually have reversed spontaneously after treatment was stopped. Therapy with ELSPAR is associated with an increase in blood ammonia during the conversion of asparagine to aspartic acid by the enzyme. No clear correlation exists between the degree of elevation of blood ammonia levels and the appearance of CNS changes.

Renal Toxicity

Azotemia, usually pre-renal, occurs frequently. Acute renal shut down and fatal renal insufficiency have been reported during treatment.[5] Proteinuria has occurred infrequently.

Hepatic Toxicity

A variety of liver function abnormalities have been reported, including elevations of AST(SGOT), ALT(SGPT), alkaline phosphatase, bilirubin (direct and indirect), and depression of serum albumin, cholesterol (total and esters), and plasma fibrinogen. Increases and decreases of total lipids have occurred.[22] Marked hypoalbuminemia associated with peripheral edema has been reported.[10] However, these abnormalities usually are reversible on discontinuance of therapy and some reversal may occur during the course of therapy. Fatty changes in the liver have been documented by biopsy. Fulminant drug-induced hepatitis resulting in irreversible hepatic failure has been reported. Malabsorption syndrome has been reported.[12]

Hematologic Toxicity

Rarely, transient bone marrow depression has been observed, as evidenced by a delay in return of hemoglobin or hematocrit levels to normal in patients undergoing hematologic remission of leukemia. Marked leukopenia has been reported.[23]

Other

Fatal hyperthermia has been reported.

Chills, fever, nausea, vomiting, anorexia, abdominal cramps, weight loss, headache, and irritability may occur and usually are mild.

Immunogenicity

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).[16,17] Clinical hypersensitivity reactions to ELSPAR in studies were common ranging from 32.5%[18] to 75%.[16] In these studies, concomitant medications and dosing schedules varied. Patients with hypersensitivity reactions were more likely to have antibodies than those without hypersensitivity reactions.[16] Hypersensitivity reactions have been associated with increased clearance of ELSPAR.[19] Incidence of antibody formation was lower upon first administration of ELSPAR than second administration.[16,17] 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.[17]

The incidence of antibodies detected is highly dependent on the sensitivity and specificity of the assay, which have not been fully evaluated. Additionally, the observed incidence of anti-asparaginase antibody in an assay may be influenced by several factors, including serum sampling, timing, methodology, concomitant medications, underlying disease, and degree of immunosuppression. For these reasons, comparison of the incidence of antibodies to ELSPAR with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

The acute intravenous LD_{50} of ELSPAR for mice was about 500,000 I.U./kg and for rabbits about 22,000 I.U./kg.

DOSAGE AND ADMINISTRATION

This drug may have toxic properties and must be handled and administered with care. Special handling procedures should be reviewed prior to handling and followed diligently during reconstitution and administration. Inhalation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided. (See DOSAGE AND ADMINISTRATION, *Special Handling*.)

As a component of selected multiple agent induction regimens, ELSPAR may be administered by either the intravenous or the intramuscular route. When administered intravenously this enzyme should be given over a period of not less than thirty minutes through the side arm of an already running infusion of Sodium Chloride Injection or Dextrose Injection 5% (D_5W). ELSPAR has little tendency to cause phlebitis when given intravenously. Anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

When administering ELSPAR intramuscularly, 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.

Unfavorable interactions of ELSPAR with some antitumor agents have been demonstrated. It is recommended therefore, that ELSPAR be used in combination regimens only by physicians familiar with the benefits and risks of a given regimen. During the period of its inhibition of protein synthesis and cell replication, ELSPAR may interfere with the action of drugs such as methotrexate which require cell replication for their lethal effect. ELSPAR may interfere with the enzymatic detoxification of other drugs, particularly in the liver.

Recommended Induction Regimens:

When using chemotherapeutic agents in combination for the induction of remissions in patients with acute lymphocytic leukemia, regimens are sought which provide maximum chance of success while avoiding excessive cumulative toxicity or negative drug interactions.

One of the following combination regimens incorporating ELSPAR is recommended for acute lymphocytic leukemia in pediatric patients:

In the regimens below, Day 1 is considered to be the first day of therapy.

Regimen I [3]
Prednisone 40 mg/square meter of body surface area per day orally in three divided doses for 15 days, followed by tapering of the dosage as follows:

20 mg/square meter for 2 days, 10 mg/square meter for 2 days, 5 mg/square meter for 2 days, 2.5 mg/square meter for 2 days and then discontinue.

Vincristine sulfate 2 mg/square meter of body surface area intravenously once weekly on Days 1, 8, and 15 of the treatment period. The maximum single dose should not exceed 2.0 mg.

Asparaginase 1,000 I.U./kg/day intravenously for ten successive days beginning on Day 22 of the treatment period.

Regimen II [4]
Prednisone 40 mg/square meter of body surface area per day orally in three divided doses for 28 days (the total daily dose should be to the nearest 2.5 mg), following which the dosage of prednisone should be discontinued gradually over a 14 day period.

Vincristine sulfate: 1.5 mg/square meter of body surface area intravenously weekly for four doses, on Days 1, 8, 15, and 22 of the treatment period. The maximum single dose should not exceed 2.0 mg.

Asparaginase 6,000 I.U./square meter of body surface area intramuscularly on Days 4, 7, 10, 13, 16, 19, 22, 25, and 28 of the treatment period.

When a remission is obtained with either of the above regimens, appropriate maintenance therapy must be instituted. ELSPAR should not be used as part of a maintenance regimen. The above regimens do not preclude a need for special therapy directed toward the prevention of central nervous system leukemia.

It should be noted that ELSPAR has been used in combination regimens other than those recommended above. It is important to keep in mind that ELSPAR administered intravenously concurrently with or immediately before a course of vincristine and prednisone may be associated with increased toxicity. Physicians using a given regimen should be thoroughly familiar with its benefits and risks. Clinical data are insufficient for a recommendation concerning the use of combination regimens in adults. Asparaginase toxicity is reported to be greater in adults than in pediatric patients.

Use of ELSPAR as the sole induction agent should be undertaken only in an unusual situation when a combined regimen is inappropriate because of toxicity or other specific patient-related factors, or in cases refractory to other therapy. When ELSPAR is to be used as the sole induction agent for pediatric patients or adults, the recommended dosage regimen is 200 I.U./kg/day intravenously for 28 days.[5,7,24,25] When complete remissions were obtained with this regimen, they were of short duration, 1 to 3 months. ELSPAR has been used as the sole induction agent in other regimens.[6, 24, 27] Physicians using a given regimen should be thoroughly familiar with its benefits and risks.

Patients undergoing induction therapy must be carefully monitored and the therapeutic regimen adjusted according to response and toxicity.

Such adjustments should always involve decreasing dosages of one or more agents or discontinuation depending on the degree of toxicity.

Patients who have received a course of ELSPAR, if retreated, have an increased risk of hypersensitivity reactions. Therefore, retreatment should be undertaken only when the benefit of such therapy is weighed against the increased risk.

Intradermal Skin Test:
Because of the occurrence of allergic reactions, an intradermal skin test should be performed prior to the initial administration of ELSPAR and when ELSPAR is given after an interval of a week or more has elapsed between doses. The skin test solution may be prepared as follows: Reconstitute the contents of a 10,000 I.U. vial with 5.0 mL of diluent. From this solution (2,000 I.U./mL) withdraw 0.1 mL and inject it into another vial containing 9.9 mL of diluent, yielding a skin test solution of approximately 20.0 I.U./mL. Use 0.1 mL of this solution (about 2.0 I.U.) for the intradermal skin test. The skin test site should be observed for at least one hour for the appearance of a wheal or erythema either of which indicates a positive reaction. An allergic reaction even to the skin test dose in certain sensitized individuals may rarely occur. A negative skin test reaction does not preclude the possibility of the development of an allergic reaction.

Desensitization:
Desensitization should be performed before administering the first dose of ELSPAR on initiation of therapy in positive reactors, and on retreatment of any patient in whom such therapy is deemed necessary after carefully weighing the increased risk of hypersensitivity reactions. Rapid desensitization of the patient may be attempted with progressively increasing amounts of intravenously administered ELSPAR provided adequate precautions are taken to treat an acute allergic reaction should it occur. One reported schedule[24,25] begins with a total of 1 I.U. given intravenously and doubles the dose every 10 minutes, provided no reaction has occurred, until the accumulated total amount given equals the planned doses for that day.

For convenience the following table is included to calculate the number of doses necessary to reach the patient's total dose for that day:

Injection Number	ELSPAR Dose in I.U.	Accumulated Total Dose
1	1	1
2	2	3
3	4	7
4	8	15
5	16	31
6	32	63
7	64	127
8	128	255
9	256	511
10	512	1023
11	1024	2047
12	2048	4095
13	4096	8191
14	8192	16383
15	16384	32767
16	32768	65535
17	65536	131071
18	131072	262143

For example: A patient weighing 20 kg who is to receive 200 I.U./kg (total dose 4000 I.U.) would receive injections 1 through 12 during desensitization.

Directions for Reconstitution
This drug may have toxic properties and must be handled and administered with care. Inhalation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling ELSPAR. (See *Special Handling*.)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. When reconstituted, ELSPAR should be a clear, colorless solution. If the solution becomes cloudy, discard.

For Intravenous Use
Reconstitute with Sterile Water for Injection or with Sodium Chloride Injection. The volume recommended for reconstitution is 5 mL for the 10,000 unit vials. Ordinary shaking during reconstitution does not inactivate the enzyme. This solution may be used for direct intravenous administration within an eight hour period following restoration. For administration by infusion, solutions should be diluted with the isotonic solutions, Sodium Chloride Injection or Dextrose Injection 5%. These solutions should be infused within eight hours and only if clear.

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. Some loss of potency has been observed with the use of a 0.2 micron filter.

For Intramuscular Use
When ELSPAR is administered intramuscularly according to the schedule cited in the induction regimen, reconstitution is carried out by adding 2 mL Sodium Chloride Injection to the 10,000 unit vial. The resulting solution should be used within eight hours and only if clear.

Special Handling
L-asparaginase may be irritating to eyes, skin and the upper respiratory tract. It has also been shown to be embryotoxic and teratogenic by the intravenous route in animal studies. Due to the drug's potential toxic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of ELSPAR for administration. Inhalation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided. The National Institutes of Health presently recommends that the preparation of injectable antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet.[28] Personnel preparing drugs of this class should wear chemical resistant, impervious gloves, safety goggles, outer garments and shoe covers. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces and inhalation of vapors and dust. Appropriate techniques should be used to remove potentially contaminated clothing.

Several other guidelines for proper handling and disposal of antineoplastic drugs have been published and should be considered.[29-34]

Accidental Contact Measures

Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part should be washed immediately with soap and water. Medical attention should be sought. If inhaled, remove from exposure and seek medical attention. (See PRECAUTIONS, *General* and DOSAGE AND ADMINISTRATION.)

HOW SUPPLIED

ELSPAR is a white lyophilized plug or powder supplied as follows:
NDC 67386-411-51 in sterile 10 mL vial containing 10,000 I.U. of asparaginase and 80 mg mannitol, an inactive ingredient.

Storage

Store at 2 to 8°C (36 to 46°F). ELSPAR does not contain a preservative. Unused, reconstituted solution should be stored at 2 to 8°C (36 to 46°F) and discarded after eight hours, or sooner if it becomes cloudy.

REFERENCES

1. Ho, D.H.W.; Thetford, B.S.; Carter, C.J.K.; Frei, E., III: Clinical pharmacologic studies of L-asparaginase, Clin. Pharmacol. Ther. *11*:408-417, May-June 1970.

2. Ho, D.H.W.; Yap, H.Y.; Brown, N.; Benjamin, R.S.; Friereich, E.J.; Blumenschein, G.R.; Bodey, G.P.: Clinical pharmacology of intramuscularly administered L-asparaginase, J. Clin. Pharmacol. *21*:72-78, Feb.-Mar. 1981.

3. Jones, B., et al: Blood *42*: 1015, Dec. 1973 (Abstract: Optimal Use of Asparaginase in Acute Lymphocytic Leukemia of Childhood).

4. Ortega, J.A.; Nesbit, M.E.; Donaldson, M.H.; Hittle, R.E.; Weiner, J.; Karon, M.; Hammond, D.: L-asparaginase, vincristine and prednisone for induction of first remission in acute lymphocytic leukemia, Cancer Research *37*: 535-540, Feb. 1977.

5. Haskell, C.M.; Canellos, G.P.; Leventhal, B.G.; Carbone, P.P.; Block, J.B.; Serpick, A.A.; Selawry, O.S.: L-asparaginase: Therapeutic and toxic effects in patients with neoplastic disease, New Engl. J. Med. *281*: 1028-1034, 1969.

6. Ohnuma, T., et al: Treatment of adult leukemia with L-asparaginase (NCS-109229), Cancer Chemo. Reports Part 1 *55*(3): 269- 275, June 1971.

7. Zubrod, C.G.: The clinical toxicities of L-asparaginase in the treatment of leukemia and lymphoma, Pediat. *45*: 555-559, Apr. 1970.

8. Holland, J.F.; Glidewell, O.J.: Oncologists' Reply: Survival Expectancy in Acute Lymphocytic Leukemia, New Engl. J. Med., Vol. *287*: 769-777, 1972.

9. Wintrobe, M.M.: "Clinical Hematology," ed. 6, Philadelphia, Lea & Febiger, 1969, 1044.

10. Oettgen, H.F.; Stephenson, P.A.; Schwartz, M.K.; Leeper, R.D.; Tallal, L.; Tan, C.C.; Clarkson, B.D.; Golbey, R.B.; Krakoff, I.H.; Karnofsky, D.A.; Murphy, M.L.; Burchenal, J.H.: The toxicity of E. coli L-asparaginase in man, Cancer. *25*:253-278, Feb. 1970.

11. Khan, A.; Adachi, M.; Hill, J.M.: Diabetogenic effect of L-asparaginase, J. Clin. Endocrinol. & Metab. *29*: 1373-1376, Oct. 1969.

12. Ohnuma, T.; Holland, J.F.; Freeman, A.; Sinks, L.F.: Biochemical and Pharmacological Studies with Asparaginase in Man, Cancer Research Vol. *30*: 2297-2305, 1970.

13. Whitecar, J.P., Jr.; Bodey, G.P.; Harris, J.E.; Friereich, E.J.: L-asparaginase, New Engl. J. Med. *282*: 732-734, Mar. 26, 1970 (in Current Concepts).

14. Capizzi, R.L.: Schedule-dependent synergism and antagonism between methotrexate and asparaginase, Biochem. Pharmacol. *23*: 151-161, 1974.

15. Garnick, M.B.; Larsen, P.R.: Acute deficiency of thyroxine-binding globulin during L-asparaginase therapy, New Engl. J. Med. *301*:252-253, Aug. 2, 1979.

16. Wang, B.; Relling, M.V.; Storm, M.C.;Woo, M.H.; Ribeiro, R.; Pui, C.H.; Hak, L.J.: Evaluation of immunologic crossreaction of antiasparaginase antibodies in acute lymphoblastic leukemia (ALL) and lymphoma patients, Leukemia *17*: 1583-1588, 2003.

17. Avramis, V.I.; Sencer, S.; Periclou, A.P.; Sather, H.; Bostrom, B.C.; Cohen, L.J.; Ettinger, A.G.; Ettinger, L.J.; Franklin, J.; Gaynon, P.S.; Hilden, J.M.; Lange, B.; Majlessipour, F.; Mathew, P.; Needle, M.; Neglia, J.; Reaman, G.; Holcenberg, J.S.: A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study, Blood *99*: 1986-1994, 2002.

18. Woo, M.H.; Hak, L.J.; Storm, M.C.; Sandlund, J.T.; Ribeiro, R.C.; Rivera, G.K.; Rubnitz, J.E.; Harrison, P.L.; Wang, B.; Evans, W.E.; Pui, C.H.; Relling, M.V.: Hypersensitivity or development of antibodies to asparaginase does not impact treatment outcome of childhood acute lymphoblastic leukemia, J. Clin. Oncol. *18*(7): 1525-1532, Apr. 2000.

19. Asselin, B.L.: The three asparaginases: Comparative pharmacology and optimal use in childhood leukemia, Adv. Exp. Med. Biol. *457*: 621-629, 1999.

20. McLean, R.; Martin, S.; Lam-Po-Tang, P.R.L. Fatal case of L-asparaginase induced pancreatitis, Lancet 2: 1401-1402, Dec. 18, 1982.

21. Lederman, G.S.: Stroke due to treatment with L-asparaginase in an adult, N. Engl. J. Med. *307*(26): 1643, Dec. 23, 1982.

22. Storti, E.; Quaglino, D.: Dysmetabolic and neurologic complications in leukemic patients treated with L-asparaginase, in Experimental and Clinical Effects of L-asparaginase," E. Grundman & H.F. Oettgen (ed.), New York, Springer-Verlag, 1970, pp. 344-349.

23. Oehlers, M.J.; Fetawadjieff, W.; Woodliff, H.J.: Profound leukopenia following asparaginase treatment in a patient with acute lymphoblastic leukemia, Med. J. Aust. 2: 907-909, Nov.1, 1969.

24. Clarkson, B.; Krakoff, I.; Burchenal, J.; Karnofsky, D.; Golbey, R.; Dowling, M.; Oettgen, H.; Lipton, A.: Chemical results of treatment with E. coli L-asparaginase in adults with leukemia, lymphoma, and solid tumors, Cancer. *25*: 279-305, Feb. 1970.

25. Tallal, L.; Tan, C.; Oettgen, H.; Wollner, N.; McCarthy, M.; Helson, L.; Burchenal, J.; Karnofsky, D.; Murphy, M.L.: E. coli L- asparaginase in the treatment of leukemia and solid tumors in 131 children, Cancer. *25*: 306-320, Feb. 1970.

26. Pratt, C.B.; Johnson, W.W.: Duration and severity of fatty metamorphosis of the liver following L-asparaginase therapy, Cancer. *28*: 361-364, Aug. 1971.

27. Pratt, C.B.; Simone, J.V.; Zee, P.; Aur, R.J.; Johnson, W.W.: Comparison of daily versus weekly L-asparaginase for the treatment of childhood acute leukemia, J. Pediat. *77*: 474-483, Sept. 1970.

28. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

29. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics, JAMA *253*: 1590-1592, 1985.

30. National Study Commission on Cytotoxic Exposure – Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

31. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents, Med. J. Australia *1*: 426-428, 1983.

32. Jones, R.B., et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center, Ca-A Cancer Journal for Clinicians Sept/Oct, 258-263, 1983.

33. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, Am. J. Hosp. Pharm. *47*: 1033-1049, 1990.

34. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines), Am. J. Health-Syst. Pharm. *53*: 1669-1685, 1996.

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