120 mm

270 mm

2471

For the use only of Registered Medical Practitioner or a Hospital or a Laboratory.

1101838 DS254/2

L-ASPARAGINASE FOR INJECTION

Lyophilised

WARNING

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. This drug has various toxic properties; therefore, both powder and solution must be handled and administered with care. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Special handling procedures should be reviewed prior to handling and followed diligently. The following data should be thoroughly reviewed before administering the compound.

COMPOSITION

Each vial contains:

L-Asparaginase	5000 I.U.
Glycine BP	q.s.

Each vial contains:

L-Asparaginase	10000 I.U.
Glycine BP	q.s.

DESCRIPTION

L-asparaginase is sterile, white lyophilised powder. It contains glycine, water for injection as excipients. It contains the enzyme L-asparagine amidohydro-lase, type EC-2, derived from Escherichia coli. L-asparaginase activity is expressed in terms of International Units (IU) to the recommendation of the International Union of Biochemistry. One International Unit of L-asparaginase is defined as that amount of enzyme required to generate 1 µmol of ammonia per minute at pH 7.3 and 37°C. The specific activity of L-asparaginase is at least 225 International Units per milligram of protein.

CLINICAL PHARMACOLOGY

Pharmacodynamics

L-asparaginase is a protein enzyme extracted from Escherichia coli which degrades asparagine by hydrolysis. L-asparaginase is an amino acid which is one of the basic constituents of cellular protein. As leukemic cells cannot synthesize asparagine endogenously, they are dependent on an exogenous source of asparagine for survival. L-asparaginase hydrolyses serum aspargine to nonfunctional aspartic acid and ammonia depriving tumour cells of required amino acid. Tumour cell proliferation is blocked due to interruption of aspargine dependent protein synthesis. Depletion of asparagine by treatment with L-asparaginase results in the death of cells unable to synthesize asparagine endogenously. Due to this special mechanism of action, cross-resistance with other cytostatic agents is not observed.

Pharmacokinetics

Tissue diffusion of L-asparaginase is low. It has a biphasic half-life ranging from 8 to 30 hours according to subject. Apparent volume of distribution is 70% to 80%. There is slow movement from vascular to extravascular, extracellular space. 24 hours after an IV dose of 1000 IU/kg, plasma concentrations were 8 to 20 IU/ml, while plasma concentrations after an IM injection were 50% lower.

INDICATIONS

- Acute lymphoblastic leukemia

CONTRAINDICATIONS

- Serious allergic reactions L-asparaginases
- Serious thrombosis with prior L-asparaginase therapy
- Pancreatitis with prior L-asparaginase therapy
- Serious hemorrhagic events with prior L-asparaginase therapy

DOSAGE AND ADMINISTRATION

Recommended Dose

The recommended dose of L-asparaginase is 6000 IU/m^2 intramuscularly (IM) or intravenously (IV) three times a week.

Intradermal skin test: This test should be performed prior to L-asparaginase treatment and when L-asparaginase is given after an interval of a week or more has elapsed between doses.

The skin test solution preparation: Reconstitute the vial to form 2000IU/ml concentration solution and withdraw 0.1 ml and inject it in another vial containing 9.9 ml of diluents, to yield 20IU/ml solution. Use 0.1ml for intradermal skin test. The skin test site should be observed for atleast one hour for the appearance of a wheal or erythema either of which indicates a positive reaction.

The 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 asparaginase 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 asparaginase provided adequate precautions are taken to treat an acute allergic reaction. This schedule begins with a total of 1IU 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. The number of doses necessary to reach the patients total doses for that day are calculated as given in table below,

L-asparaginase dosing based on total daily requirements

Injection number	Dose (IU)	Accumulated total dose (IU)
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 IU/Kg (total dose 4000IU) would receive injection 1 through 12 during desensitization.]

Instructions for Administration

When L-asparaginaseis 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.

When administered IV, give L-asparaginase 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.

Preparation and Handling Precautions

For IM administration, reconstitute L-asparaginase by adding 1 ml Sodium Chloride Injection to the 5000 IU vial.

L-Asparaginase DS (General Export)
Unfold Size: 120x 270 mm **(Front)**
Folds: (VF-VF) ZigZag-VF-VF
Folded Size: 120 X 22.5mm
Paper: 40 GSM Bible paper
Color: Black text on white paper
Artwork Code: DS254/2
Item Code: 1101838
Pharma Code: 2471

Naprod Packaging Development:

Artwork prepared by: Received from party		**PP No.:** INJ0610340, INJ0610341	
Artwork Approval Date:		**PP Date:** 01/01/2012	
Artwork Dept.	RA Dept.	Mktg. Dept.	P. D. Dept.
Production Dept.	QC Dept.	QA Dept.	Plant Head

Artwork History: Change Control No.:
1. DS size change from 170 X 190mm to 120 X 270mm as per Specification of semi autocartonator VP120. Artwork code change from DS254/1 to DS254/2.

120 mm

270 mm

For IV administration, reconstitute L-asparaginase by adding 2.5 ml Sterile Water for Injection or Sodium Chloride Injection to the 5000 IU vial.
For IM administration, reconstitute L-asparaginase by adding 2 ml Sodium Chloride Injection to the 10,000 IU vial. For IV administration, reconstitute L-asparaginase by adding 5 ml Sterile Water for Injection or Sodium Chloride Injection to the 10,000 IU vial. Withdraw volume of reconstituted L-asparaginase containing calculated dose into sterile syringe.
Ordinary shaking during reconstitution does not inactivate the enzyme.
This solution may be used for direct intravenous administration within 8 hours following restoration.
For administration by infusion solution should be diluted with isotonic solution, sodium chloride injection or dextrose injection 5%. These solutions should be infused within 8 hours and only if clear.

After reconstitution: The reconstituted solution should be stored at a temperature between 2°C and 8°C. Use reconstituted L-asparaginase within 8 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.

Accidental contact: This drug may be a contact irritant, so must be handled with care. In case of contact wash with copious amount of water.

OVERDOSAGE
Not available in human. The acute intravenous LD50 of L-asparaginase for mice was about 500,000 IU/kg and for rabbits about 22,000 IU/kg.

ADVERSE REACTIONS
Most common: Adverse reactions with L-asparaginases are allergic reactions (including anaphylaxis), hyperglycemia, pancreatitis, central nervous system (CNS) thrombosis, coagulopathy, hyperbilirubinemia, and elevated transaminases.

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

Less common: Coagulopathy, including increased prothrombin time, increased partial thromboplastin time, and decreased fibrinogen, protein C, protein S and antithrombin III. CNS hemorrhages, Central Nervous System effects including fatigue, agitation, somnolence, coma, seizures, and hallucinations, elevation of AST, ALT, alkaline phosphatase, bilirubin.

Rare: Serious thrombosis, including sagittal sinus thrombosis Pancreatitis, fulminant or fatal Glucose intolerance, bone marrow suppression, hyperglycemia with glucosuria, azotemia, renal insufficiency.

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

WARNINGS AND PRECAUTIONS
Anaphylaxis and Serious Allergic Reactions: Serious allergic reactions can occur in patients receiving L-asparaginase. The risk of serious allergic reactions is higher in patients with prior exposure to L-asparaginase. Observe patients for one hour after administration of L-asparaginase in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (for example, epinephrine, oxygen, intravenous steroids, antihistamines).Discontinue L-asparaginase in patients with serious allergic reactions.

Thrombosis: Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving L-asparaginase . Discontinue L-asparaginase in patients with serious thrombotic events.

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

Intolerence: Glucose intolerance can occur in patients receiving L-asparaginase. In some cases, glucose intolerance is irreversible. Monitor serum glucose.

Coagulopathy: Increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenemia can occur in patients receiving L-asparaginase. 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term carcinogenicity studies in animals have been performed with L-asparaginase. No relevant studies addressing mutagenic potential have been conducted. L-asparaginase 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.

Use In Specific Populations
Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. L-asparaginase should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether L-asparaginase 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 L-asparaginase , a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Geriatric Use: Asparaginase toxicity is reported to be greater in adults than in pediatric patients.

DRUG INTERACTIONS
- L- asparaginase may diminish or abolish methotrexate's effect on malignant cells. This effect persists as long as plasma L-asparaginase level are suppressed. Don't use methotrexate with or following L- asparaginase.
- Intravenous administration of L- asparaginase concurrently with or immedietly before a course of vincristine and prednisone may increase toxicity.
- Drug/Lab test interaction: L- asparaginase interfere with interpretation of thyroid function tests.

STORAGE
Store between 2°C and 8°C. Protect from light. Do not freeze.

PRESENTATION
L-Asparaginase for Injection are available in packs containing L-Asparaginase 5,000 I.U. per vial and 10,000 I.U. per vial.

Manufactured in India by :
Naprod Life Sciences Pvt. Ltd.
304, Town Centre, Andheri - Kurla Road,
Andheri (E), Mumbai - 400 059.
Works : G-17/1, M.I.D.C.,
Boisar, Dist - Thane (INDIA).

120 x 270mm

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