The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. However, the incidence of antibody-activity in any assay may be influenced by several factors including sample handling, concomitant medications and underlying disease. Therefore, comparison of the incidence of antibodies to L-Asparginase with the incidence of antibodies to other products may be misleading.

DRUG INTERACTION
L-Asparaginase can diminish or abolish the effect of Methotrexate on malignant cells. Intravenous administration of L-Asparaginase concurrently with or immediately before a course of Vincristine and Prednisolone may elicit increased toxicity.

Drug/Laboratory Test Interaction
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 2-3 days after the first dose. Serum concentrations of thyroxine-binding globulin returned to pretreatment values within 4 weeks after the dose of L-Asparaginase.

USE IN SPECIFIC POPULATION
Pregnancy
Pregnancy Category C. In mice and rats, L-Asparaginase has been shown to retard the weight gain of nursing females and to decrease testes weights of testicular and ovarian asparagine levels in these organs. L-Asparaginase has been shown to result in a dose-dependent incidence of cataracts in rat offspring. L-Asparaginase has not been studied in pregnant women. 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 Use
See Clinical Studies.

Geriatric Use
Clinical studies of L-Asparaginase did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

CLINICAL PHARMACOLOGY
Mechanism of Action
The mechanism of action of L-Asparaginase 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 asparaginase synthetase and are dependent on an exogenous source of asparagine for survival. Depletion of asparaginase, which results from treatment with the enzyme L-Asparaginase, kills the leukemic cells. Normal cells, however, are less affected by the decrease in plasma asparagine levels.

Pharmacokinetics
The intracellular asparaginease activity and asparagine levels have been studied in clinical trials. In previously untreated, standard-risk ALL patients treated with native asparaginase, plasma asparagine levels decreased from a pretreatment average of 41 µM to less than 1 µM. In this study, intracellular asparagine levels in peripheral blood leukocytes decreased from 2.8 µM (pretreatment) to 0.3 µM at day 4 and 0.03 µM at day 7 of induction, respectively.

Pharmacodynamics
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 11 hours. Apparent volume of distribution was slightly greater than the plasma volume. Absolute bioavailability in patients treated with asparaginase decreased from 2.8 µM (pretreatment) to 0.3 µM (day 4) and 0.03 µM (day 7) of induction, respectively.

In a study in patients with leukemia and metastatic cancer treated intramuscularly or intravenously, plasma levels of asparaginase were reduced to 1 µM at 2 hours and 0.1 µM at 24 hours after dosing. In a study in patients with leukemia and metastatic cancer treated intramuscularly or intravenously, plasma levels of asparaginase were reduced to 1 µM at 2 hours and 0.1 µM at 24 hours after dosing.

NON-CLINICAL TOXICITY
Carcinogenesis, Mutagenesis, 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.

Animal Toxicology
Examinations and necropsies of pancreatic islets were observed in rabbits following a single, intravenous injection of 12,350 to 52,000 International Units of L-Asparaginase (approximately equivalent to 20 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 in 10,000 International Units (approximately equivalent to 2 times the recommended human dose, when adjusted for total body surface area).

STORAGE
Store vials refrigerated at 2-8°C (36-46°F). Protect from light. Do not freeze.

L-Asparaginase 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.

PRECAUTIONS
L-Asparaginase for Injection is supplied in flint glass vials containing 5,000 IU or 10,000 IU of L-Asparaginase as a sterile, lyophilized powder for injection for reconstitution.

Marketed by:
Getwell Oncology Pvt. Ltd.
(1 unit of Getwell)
494, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by:
Getwell Pharmaceuticals
4/4, Udyog Vihar, Phase-VI, Gurgaon - 122016, Haryana, India

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

L-Asparaginase for Injection
L-GINASE™
Antineoplastic Agent
FOR I.V., I.M., U. USE ONLY
Rx only

COMPOSITION
- L-Asparaginase for injection 5,000 IU.
- L-Asparaginase for injection 10,000 IU

DESCRIPTION
- L-Asparaginase for injection contains the enzyme L-Asparaginase Asparaginase, type E2-5. L-Asparaginase is not absorbed from the GI tract and hence must be administered IM or IV. The IM route maintains the efficacy and has not been shown to lose immunogenicity. When given by the IM route, not more than 2 ml, of the solution should be given at one injection site. L-Asparaginase activity is expressed in terms of International Units according 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 325 International Units per milligram of protein.

L-Asparaginase for Injection is for use as a sterile, white, lyophilized plug or powder. Each vial contains 10,000 International Units or 5,000 International Units of L-Asparaginase for Injection.

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

DOSEAGE AND ADMINISTRATION
This drug may have toxic properties and must be handled and administered with care. Special handling procedure should be reviewed prior to handling and followed diligently during reconstitution and administration. In handling of diluents and reconstituted product, contact with skin or mucous membranes, especially those of the eyes, must be avoided.

As a component of selected multiple agent induction regimens, L-Asparaginase may be administered either intravenously or intramuscularly. 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% (D5W). L-Asparaginase has little tendency to cause phlebitis when given intravenously. Analgesic reaction require the immediate use of oxyphene, oxygen and intravenous iatrogenic stress. When administering L-Asparaginase intramuscularly, the volume at a single injection site should be limited to 3 ml. If a volume greater than 3 ml is to be administered, two injection sites should be used. Unfavorable interaction of L-Asparaginase with some antimicrobial agents have been demonstrated. It is recommended therefore, that L-Asparaginase be used in combination regimens only by physicians familiar with the benefits and risks of each regimen. During the period of its inhibition of protein synthesis and cell replication, L-Asparaginase may interfere with the enzymatic desulfation 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 L-Asparaginase is recommended for acute lymphocytic leukemia in pediatric patients:

In the regimens below, Day 1 is considered to be the first day of therapy. L-Asparaginase is administered intramuscularly or intravenously. In the first regimen, L-Asparaginase is administered intramuscularly or intravenously.

Regimen I
Prednisone 40mg/m² of body surface area per day orally in three divided doses for 15 days, followed by tapering of the dosage as follows: 20mg/m² for 2 days, 10mg/m² for 2 days, 5mg/m² for 2 days.
2.5mg/m² for 2 days and another 2 days.
Vincristine Sulfate 2mg/m² of body surface area intravenously once weekly on Day 22 of the treatment period.

Regimen II
Prednisone 40mg/m² of body surface area per day orally in three divided doses for 28days (the total daily dose should be reduced to 25mg/m²), following which the dosage of prednisone should be discontinued gradually over a 14-day period.

Vincristine sulfate 1mg/m² of body surface area intravenously weekly for four days, on Days 1, 8, 15, and 22 of the treatment period, the maximum single dose should not exceed 0.4 mg. The IM route maintains the efficacy and has not been shown to lose immunogenicity. When given by the IM route, not more than 2 ml, of the solution should be given at one injection site. L-Asparaginase activity is expressed in terms of International Units according 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 325 International Units per milligram of protein. L-Asparaginase for Injection is for use as a sterile, white, lyophilized plug or powder. Each vial contains 10,000 International Units or 5,000 International Units of L-Asparaginase for Injection.
L-Asparaginase 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 L-Asparaginase is to be used as the sole induction agent for pediatric patients or adults, the recommended dosage regimen is 200 units/kg/day intravenously for 28 days. When complete remissions were obtained with this regimen, they were of short duration, 1 to 3 months. L-Asparaginase has been used as the sole induction agent in other regimens. Physicians using this 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 upon the degree of toxicity. Patients who have received a course of L-Asparaginase, 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 reaction, an intradermal skin test should be performed prior to the initial administration of L-Asparaginase and when L-Asparaginase is given again after an interval of one week or more has elapsed between doses. The skin test solution may be prepared as follows: Reconstitute the contents of a 10,000 unit vial with 5.0 ml of diluent. From this solution (2,000 units/ml) withdraw 0.1 ml and inject into another vial containing 9.9 ml of diluent, yielding a skin test solution of approximately 20.0 units/ml. Use 0.1 ml of this solution (about 2.0 units) for the intradermal skin test. The skin test should be observed for at least one hour for the appearance of a wheal or erythema either of which indicates a positive reaction. An allergy reaction even to the skin test dose in certain sensitized individuals may rarely occur. A negative skin test does not preclude the possibility of development of an allergic reaction.

Desensitization

Desensitization should be performed before administering the first dose of L-Asparaginase in initiation of therapy in positive responders and on rechallenge of any patient in whom such therapy is deemed necessary after carefully weighing the increased risk of hypersensitivity reactions. Rapid desensitization of the patients may be attempted with progressively increasing amounts if intravenously administered. L-Asparaginase provided adequate precautions are taken to treat an acute allergic reaction should it occur. One should start with a small dose and increase the dose every 10 minutes. Provided no reaction has occurred, until the accumulated total amount given equals the planned dose for that day.

For convenience the following table is included to calculate the number of doses necessary to reach the patient’s total dose fortified daily.

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<th>Injection Number</th>
<th>L-Asparaginase dose in IU</th>
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Direction of Reconstitution

This drug may have toxic properties and must be handled and administered with care. Inhalation of dust or aerosol, with contact of skin or mucous membranes, especially when the eyes, must be avoided. Appropriate protective equipment should be worn when handling L-Asparaginase. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. When reconstituted, L-Asparaginase should be a clear, colorless solution. If the solution becomes cloudy, discard.

In Intravenous Use

Reconstitute with sodium chloride injection. The volume recommended for reconstitution is 5 ml for the 500 unit and 10 ml for the 10,000 unit vial. Dissolve without shaking. This solution may be used for direct intravenous administration. For administration by infusion, solutions should be diluted with the isotonic solutions, Sodium Chloride injection or Dextrose Injection 5%.

In Intramuscular Use

When L-Asparaginase 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 5,000 international units (IU)/ml.

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 potential toxic properties, appropriate precautions including the use of appropriate safety equipment and the use of protective clothing, gloves, etc. and the use of detergent solutions or chloroform to remove the drug from skin or mucous membranes should be observed.

Accidental Contact Measures

If a patient comes in contact with L-Asparaginase activity, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ephrastic: irrigating solution should be instituted immediately, followed by procaine penicillin or an aminoglycoside. If accidental skin contact occurs, 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. 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, the solution should be discarded. However, occasionally, a very small number of gelatinous, fish-like particles may develop on standing. Filtration through a 0.2 micron filter during filtration will remove these particles with no resultant loss in potency.

DOSAGE FORM AND STRENGTH

5,000 International Units or 10,000 International Units as a lyophilized powder in single-use vial.

ODSRE

The acute intravenous LD₅₀ of L-Asparaginase for mice was about 50,000 IU/kg and for rats about 23,200 IU/kg.

CONTRAINDICATIONS

Serious allergic reactions to L-Asparaginase or other Escherichia coli-derived L-Asparaginase. Serious thrombosis with prior L-Asparaginase therapy. Pancreatitis with prior L-Asparaginase therapy. Serous hemorhagic events with prior L-Asparaginase therapy.

WARNING AND PRECAUTION

Anaphylaxis and Serious Allergic Reactions

Serious allergic reactions can occur in patients receiving L-Asparaginase for injection. The risk of serious allergic reactions is higher in patients with prior exposure to L-Asparaginase or other Escherichia coli-derived 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. CNS hemorrhages have been observed. Monitor coagulation parameters at baseline and periodically during and after therapy. Initiate treatment with new-frozen plasma to replace coagulopathy factors in patients with severe or symptomatic coagulopathy.

Hepatotoxicity and Abnormal Liver Function

Full hepatic failure occurs. Hepatotoxicity and abnormal liver function, including elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin and other hepatic impairment and hepatic depression of serum albumin, and plasma fibrinogen levels occurs. Failure changes in the liver have been documented on biopsy. Evaluate hepatic enzymes and bilirubin pretreatment and periodically during treatment.

ADVERSE REACTION

The following serious adverse reactions occur with L-Asparaginase treatment [see Warnings and Precautions (5)].

- Anaphylaxis and serious allergic reactions
- Severe thrombosis
- Hepatotoxicity
- Gastrointestinal
- Glucose intolerance
- Coagulopathy
- Nephrotoxicity and renal dysfunction

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

Clinical Trials and Post-Marketing Experience

The adverse reactions included in this section were identified in single-arm clinical trials in which L-Asparaginase was administered as part of a multi-agent regimen in patients with acute lymphoblastic leukemia. Because these adverse events were identified in clinical trials that were not designed to isolate the adverse effects of L-Asparaginase 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 L-Asparaginase. The risk of serious allergic reactions appears to be higher in patients with prior exposure to L-Asparaginase or other Escherichia coli-derived L-Asparaginase.

Serious thrombosis, including sagittal sinus thrombosis

Pancreatitis, in some cases fulminant total

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

Acne, liver function abnormalities, including hyperbilirubinemia, and elevated transaminases. Other

Hypoglycemia including hyperglycemia and hyperchloremia

Immunogenicity

As with any therapeutic proteins, there is a potential for immunogenicity, defined as development of binding and neutralizing antibodies to the product. L-Asparaginase is a bacterial protein and can elicit antibodies in patients treated with the drug. In 2 prospectively designed clinical trials (N=50 and 24), approximately one quarter of the patients developed antibodies that bound to L-Asparaginase as measured by enzyme-linked immunosorbent assays (ELISA). Clinical hypersensitivity reactions to L-Asparaginase in studies were common ranging from 12.5.10% 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 L-Asparaginase. Incidence of antibody formation was lower upon first administration of L-Asparaginase than second administration. The frequency of antibody formation is 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 L-asparaginase activity.