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 L-Asparginase with the incidence of antibodies to other products may be misleading.

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

Drug/Laboratory Test Interaction
L-Asparginase 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-Asparginase.

USE IN SPECIFIC POPULATION
Pregnancy
Pregnancy Category C. In mice and rats L-Asparginase 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. L-Asparginase should be given to a pregnant woman only if clearly needed.
Nursing Mothers
It is not known whether L-Asparginase 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-Asparginase, 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-Asparginase 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-Asparginase 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.
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.
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.

NON-CLINICAL TOXICITY
Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term carcinogenicity studies in animals have been performed with L-Asparginase.
No relevant studies addressing mutagenic potential have been conducted. L-Asparginase 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
Edema and necrosis of pancreatic islets were observed in rabbits following a single, intravenous injection of 12,500 to 50,000 International Units L-Asparginase/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).

STORAGE
Keep vials refrigerated at 2-8°C (36-46°F). Protect from light. Do not freeze.
L-Asparginase for Injection 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.

PRESENTATION
L-Asparginase for Injection is supplied in flint glass vials containing 5,000 I.U or 10,000 I.U of L-Asparginase as a sterile , Lyophilized powder for Injection for reconstitution.

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

Manufactured by:
Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

0700LGDM1212

GETWELL

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

L-Asparginase for Injection

L-GINASE™

Antineoplastic Agent
FOR I.M./I.V. USE ONLY
Rx only

COMPOSITION
L-Asparginase for injection 5,000 I.U.
Each sterile lyophilized vial contains
L-Asparginase 5,000 I.U
L-Asparginase for Injection 10,000 I.U
Each Sterile lyophilized vial contains
L-Asparginase 10,000 I.U

DESCRIPTION
L-Asparginase for Injection contains the enzyme L-Asparagine Amidohydrolase, type EC-2. Asparginase 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 be less immunogenic. When given by the IM route, not more than 2mL of the solution should be given at one injection site. L-Asparginase activity is expressed in terms of International Units according to the recommendation of the International Union of Biochemistry. One International Unit of Asparginase 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 Asparginase is at least 225 International Units per milligram of protein.
L-Asparginase for Injection is provided as a sterile, white lyophilized plug or powder. Each vial contains 10,000 International Units or 5,000 International Units of Lyophilized L-Asparginase for Injection.

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

OOSAGEANO AOMINISTRATION
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 halation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided.
As a component of selected multiple agent induction regimens, L-Asparginase 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 thorugh the side arm of an already running infusion of sodium chloride injection or dextrose injection 5%(D_5W). L-Asparginase has little tendency to cause phlebitis when given intravenously. Anaphylactic reaction require the immediate use of epinephrine, oxygen and intravenous steroids.
When administering L-Asparaginase intramuscularly, the volume at a single injection site should be limited to 2mL. If a volume greater than 2mL is to be administered, two injection sites should be used. Unfavorable interaction of L-Asparginase with some antitumor agents have been demonstrated. It is recommended therefore, that L-Asparginase 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, L-Asparaginase 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, regimnes 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 lymphocytuc leukemia in pediatric patients:
In the regimens below, Day 1 is considered to be first day of theraphy.
Regimen I
Prednisone 40mg/m^2 of body surface area per day orally in three divided doses for 15 days, followed by tapering of the dosage as follows:
20mg/m^2 for 2 days, 10mg/m^2 for 2 days, 5mg/m^2 for 2 days.
2.5mg/m^2 for 2 days and then discontinue.
Vincristine Sulfate 2mg/m^2 of bosy surgace area intravenously once weekly on Day 22 of the treatment period.
Regimen II
Prednisone 40mg/m^2 of the body surface area per day orally in three divided doses for 28days (the total daily dose should be to the nearest 2.5mg), following which the dosage of predinisone should be discontinued gradually over a 14 day period.
Vincristine sulfate 1.5mg/m^2 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 2.0mg.
Inject L-Asparginase 6,000 I.U/m^2 of the 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. L-Asparginase should not be used as part of a maintenance regimen. The above regimens do not preclude a need for special theraphy directed toward the prevention of central nervous system leukemia.
It should be noted that L-Asparginase has been used in combination regimens other than those recommended above. It is important to keep in mind that L-Asparginase 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. Asparginase toxicity is reported to be greater in adults than in pediatric patients.

Use of L-Asparginase 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-Asparginase is to be used as the sole indication agent for pediatric patients or adults, the recommended dosage regimen is 200I.U/kg/day intravenously for 28days. When complete remissions were obtained with this regimen, they were of short duration, 1 to 3 months. L-Asparginase has been used as the sole induction agent in other regimens. 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.

Suck 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 L-Asparginase, if retreated, have an increased risk of hypersensitivity reactions. Therefore. Retreatment should be undertaken only when the benefit of suck therapy is weighed against the increased risk.

Intradermal Skin Test

Because of the occurrence of allergic reaction, an interdermal skin test should be performed prior to the initial administration of L-Asparginase and when L-Asparginase is given agter 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 5.0mL of diluents. From this solution (2,000 I.U/mL) withdraw 0.1mL and inject it into another vial containing 9.9mL of diluents, yielding a skin test solution of approximately 20.0 I.U/mL. Use 0.1mL of this solution (about 2.0I.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 etythema either of which indicates a positive reaction. An allerfiv 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

Desentization should be performed before administering the first dose of L-Asparaginase on intiation of therapy in positive reactors and on retreatment of any patient in whom suck 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-Asparginase provided adequate precautions are taken to treat an acute allergic reaction should it occur. One reported sechdule 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	L-Asparginase 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	512
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

Direction of 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 L-Asparginase.

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

For Intravenous use

Reconstitute with sodium chloride injection. The volume recommended for reconstitution is 5mL for the 5000 unit and 10mL for 10,000 unit vials. 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%.

For Intramuscular Use

When L-Asparginase is administrated intramuscularly according to the sechdule cited in the induction regimen, reconstitution is carried out by adding 2ml Sodium Chloride Injection to the 10,000 unit Vial. The reconstituted solution contains 5,000 international units (IU)/mL.

Special Handling

L-Asparginase may be irritating to eyes, skin and the upper respiratory tract. It has also been shown to be embryotoxic and teratogonic by the intravenous route in animal studies. Due to the drug's potential toxic properties, appropriate precautions including the use of appropriate safety equiptmentare recommended for the preparation of L-Asparginase for administration. Inhalation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided.

Accidental Contact Measures

If accidental eyes contact occur, copious irrifation for at least 15 mintutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic sondultation. If 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.

Parentral 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.

DOSAGE FORM AND STRENGTH

5,000 International Units or10,000 International Units as lyophilized powder in single-use vial.

OVERDOSE

The acute intravenous LD_{50} of L-Asparginase for mice was about 50,000 I.U/kg and for rabbits about22,000 I.U/kg

CONTRAINDICATIONS

Serious allergic reactions to L-Asparginase or other Escherichia coli-derived L-asparaginase.
Serious thrombosis with prior L-asparaginase therapy
Pancreatitis with prior L-Asparaginasetherapy
Serious hemorrhagic events with prior L-Asparginasetherapy

WARNING AND PRECAUTION

Anaphylaxis and Serious Allergic Reactions

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

Thrombosis

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

Pancreatitis

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

Glucose Intolerence

Glucose intolerance can occur in patients receiving L-Asparginase. 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-Asparginase. 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.

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.

ADVERSE REACTION

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

•Anaphylaxis and serious allergic reactions
•Serious thrombosis
•Pancreatitis
•Glucose intolerance
•Coagulopathy
•Hepatotoxicityand abnormal liverfunction

The most common adverse reactions with L-Asparginase 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-Asparginase 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 L-Asparginase 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-Asparginase. The risk of serious allergic reactions appears to be higher in patients with prior exposure to L-Asparginase 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, liverfunction abnormalities, including hyperbilirubinemia, and elevated transaminases.

Other

Hyperlipidemia including hypertriglyceridemia and hypercholesterolemia

Immunogenicity

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

L-Asparginase 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 L-Asparginase as measured by enzyme-linked immunosorbent assays (ELISA). Clinical hypersensitivity reactions to L-Asparginase 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 L-Asparginase. Incidence of antibody formation was lower upon first administration of L-Asparginase 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 Asparginase activity.