PEGASPARGASE
ONCASPAR®

Enzon Pharmaceuticals, Inc.

(PEG-L-asparaginase)

DESCRIPTION

ONCASPAR, the ENZON PHARMACEUTICALS, INC. trademark for pegaspargase, is a modified version of the enzyme L-asparaginase. It is an oncolytic agent used in combination chemotherapy for the treatment of patients with acute lymphoblastic leukemia who are hypersensitive to native forms of L-asparaginase (as described in **CLINICAL PHARMACOLOGY**).

The generic name for **ONCASPAR®** is **pegaspargase**. The chemical name is monomethoxypolyethylene glycol succinimidyl L-asparaginase. L-asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5,000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of **ONCASPAR®** is derived from *Escherichia coli.* ENZON purchases the enzyme L-asparaginase in bulk from Merck & Co., Inc., West Point, PA 19486, U.S. License Number 2. Merck & Co., Inc. supplies bulk L-asparaginase as a licensed intermediate for further manufacture by ENZON into PEG-L-asparaginase. Merck & Co., Inc. can only assume responsibility for the bulk intermediate supplied to ENZON.

ONCASPAR® is supplied as an isotonic sterile solution in phosphate buffered saline, pH 7.3, for intramuscular or intravenous administration only. The solution is clear, colorless and contains no preservatives. It is supplied in 5 mL single-dose vials.

ONCASPAR® activity is expressed in International Units (IU) according to the recommendation of the International Union of Biochemistry. One IU of L-asparaginase is defined as that amount of enzyme required to generate 1 µmol of ammonia per minute at pH 7.3 and 37ºC.
Each milliliter of **ONCASPAR®** contains:

PEG-L-asparaginase	750 IU ± 20%
Monobasic sodium phosphate, USP	1.20 mg ± 5%
Dibasic sodium phosphate, USP	5.58 mg ± 5%
Sodium chloride, USP	8.50 mg ± 5%
Water for injection, USP	qs to 1.0 mL

The specific activity of **ONCASPAR®** is at least 85 IU per milligram protein.

CLINICAL PHARMACOLOGY

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. Rapid depletion of asparagine which results from treatment with the enzyme L-asparaginase, kills the leukemic cells. Normal cells, however, are less affected by the rapid depletion due to their ability to synthesize asparagine. This is an approach to therapy based on a specific metabolic defect in some leukemic cells which do not produce asparagine synthetase.[1]

In a study in predominately L-asparaginase naive adult patients with leukemia and lymphoma, initial plasma levels of L-asparaginase following intravenous administration were determined. Plasma half-life did not appear to be influenced by dose levels, and it could not be correlated with age, sex, surface area, renal or hepatic function, diagnosis or extent of disease. Apparent volume of distribution was equal to estimated plasma volume. L-asparaginase was measurable for at least 15 days following the initial treatment with **ONCASPAR®**. The enzyme could not be detected in the urine.[2]

In a study of newly diagnosed pediatric patients with acute lymphoblastic leukemia (ALL) who received either a single intramuscular injection of **ONCASPAR®** (2,500 IU/m^2), *E. coli* L-asparaginase (25,000 IU/m^2), or *Erwinia* L-asparaginase (25,000 IU/m^2), the plasma half-lives for the three forms of L-asparaginase were:[3]

PLASMA HALF-LIVES OF THREE FORMS OF L-ASPARAGINASE

TREATMENT GROUP	NO. OF PATIENTS	MEAN (DAYS)	STANDARD DEVIATION
ONCASPAR®	10	5.73	3.24
E. coli L-asparaginase	17	1.24	0.17
Erwinia L-asparaginase	10	0.65	0.13

In this same study of newly diagnosed pediatric ALL patients, the *in vivo* early leukemic cell kill after a single intramuscular injection of native *E. coli* L-asparaginase (25,000 IU/m^2), *Erwinia* L-asparaginase (25,000 IU/m^2), and **ONCASPAR®** (2,500 IU/m^2) during a five-day "investigational window" was studied.[4] Bone marrow aspirates were taken before and five days after a single dose of one of the three different forms of L-asparaginase. Rhodamine-123 (RH-123), a selectively incorporated fluorescent mitochondrial dye, was used in an *in vitro* assay on the bone marrow aspirates to ascertain cell viability. The percent reduction of viable lymphoblasts at day five for each group is presented in the following table:[4]

RHODAMINE-123 (*IN VIVO* CELL KILL)

TREATMENT GROUP	NO. OF PATIENTS	PERCENT REDUCTION OF VIABLE LYMPHOBLASTS AT DAY 5 MEAN ± S.D.
ONCASPAR®	21	55.7 ± 10.2
E. coli L-asparaginase	28	57.8 ± 10.1
Erwinia L-asparaginase	19	57.9 ± 13.8

In three pharmacokinetic studies, 37 relapsed ALL patients received **ONCASPAR®** at 2,500 IU/m^2 every two weeks. The plasma half-life of **ONCASPAR®** was 3.24 ± 1.83 days in nine patients who were previously hypersensitive to native L-asparaginase and 5.69 ± 3.25 days in 28 non-hypersensitive patients. The area under the curve was 9.50 ± 3.95 IU/mL/day in the previously hypersensitive patients, and 9.83 ± 5.94 IU/mL/day in the non-hypersensitive patients.

Hypersensitivity Reactions

Hypersensitivity reactions to *E. coli* L-asparaginase have been reported in the literature in 3% to 73% of patients.[1] Patients in **ONCASPAR®** clinical studies were considered to be previously hypersensitive if they experienced a systemic rash, urticaria, bronchospasm, laryngeal edema, or hypotension following administration of any form of native L-asparaginase. Patients were also considered to be previously hypersensitive if they experienced local erythema, urticaria, or swelling, greater than two centimeters, for at least ten minutes following administration of any form of native L-asparaginase. The National Cancer Institute *Common Toxicity Criteria (CTC)* were used to classify the severity of the hypersensitivity reactions. These are: grade 1 — transient rash (mild); grade 2 — mild bronchospasm (moderate); grade 3 — moderate bronchospasm and/or serum sickness (severe); grade 4 — hypotension and/or anaphylaxis (life-threatening). Additionally, most transient local urticaria were considered grade 2 hypersensitivity reactions, while most sustained urticaria distant from the injection site were considered grade 3 hypersensitivity reactions. In general, the moderate to life-threatening hypersensitivity reactions were considered dose-limiting; that is, they required L-asparaginase treatment to be discontinued.

In separate studies, **ONCASPAR®** was administered intravenously to 48 patients and intramuscularly to 126 patients. The incidence of hypersensitivity reactions when **ONCASPAR®** was administered intramuscularly was 30% in patients who were previously hypersensitive to native L-asparaginase and 11% in non-hypersensitive patients (p-value of 0.007). The incidence of hypersensitivity reactions when **ONCASPAR®** was administered intravenously was 60% in patients who were previously hypersensitive to native L-asparaginase and 12% in non-hypersensitive patients. Since only five previously hypersensitive patients received **ONCASPAR®** intravenously, no meaningful analysis of the incidence of hypersensitivity reactions was possible between either the previously hypersensitive and non-hypersensitive patients, or between the intravenous and intramuscular routes of administration.

The overall incidence of hypersensitivity reactions in 174 patients who received **ONCASPAR®** in five clinical studies is shown in the table below:

INCIDENCE OF ONCASPAR® HYPERSENSITIVITY REACTIONS

		CTC GRADE OF HYPERSENSITIVITY REACTION				
PATIENT STATUS	**N**	**1**	**2**	**3**	**4**	**TOTAL**
Previously Hypersensitive Patients	62	7	8	4	1	20 (32%)
Non-Hypersensitive Patients	112	5	4	1	1	11 (10%)
Total Patients	174	12	12	5	2	31 (18%)

The probability of previously hypersensitive or non-hypersensitive patients completing 8 doses of **ONCASPAR®** therapy without developing a dose-limiting hypersensitivity reaction was 77% and 95%, respectively.

All of the 62 hypersensitive patients treated with **ONCASPAR®** in five clinical studies had previous hypersensitivity reactions to one or more of the native forms of L-asparaginase. Of the 35 patients who had previous hypersensitivity reactions to *E. coli* L-asparaginase only, 5 (14%) had **ONCASPAR®** dose-limiting hypersensitivity reactions. Of the 27 patients who had hypersensitivity reactions to both *E. coli* and *Erwinia* L-asparaginase, 7 (26%) had **ONCASPAR®** dose-limiting hypersensitivity reactions. The overall incidence of dose-limiting hypersensitivity reactions in 174 patients treated with **ONCASPAR®** was 9% (19% in 62 hypersensitive and 3% in 112 non-hypersensitive patients). Of the total of 9% dose-limiting hypersensitivity reactions, 1% were anaphylactic (CTC grade 4) and the other 8% were ≤ CTC grade 3.

Clinical Activity

ONCASPAR® was evaluated as part of combination therapy in four open label studies comprising 42 multiply-relapsed, previously hypersensitive acute leukemia patients [39 (93%) with ALL] at a dose of 2,000 or 2,500 IU/m^2 administered intramuscularly or intravenously every 14 days during induction combination chemotherapy. The reinduction response rate was 50% (36% complete remissions and 14% partial remissions), with a 95% confidence interval of 35% to 65%. This response rate is comparable to that reported in the literature for relapsed patients treated with native L-asparaginase as part of combination chemotherapy.[1]

ONCASPAR® was also shown to have some activity as a single agent in multiply-relapsed hypersensitive ALL patients, the majority of whom were pediatric. Treatment with **ONCASPAR®** resulted in three responses (one complete remission and two partial remissions) in nine previously hypersensitive patients who would not have been able to receive any further L-asparaginase treatment.

ONCASPAR® was also studied in non-hypersensitive, relapsed ALL patients who were randomized to receive two doses of **ONCASPAR®** at 2,500 IU/m^2 every 14 days or twelve doses of *E. coli* L-asparaginase at 10,000 IU/m^2 three times a week during a 28-day induction combination chemotherapy regimen (which included vincristine and prednisone). Although the enrollment in this study was too small to be conclusive, the data showed that for 20 patients there was no significant difference between the overall response rates of 60% and 50%, respectively, or the complete remission rates of 50% and 50%, respectively.

ONCASPAR® was administered during maintenance therapy regimens to 33 previously hypersensitive patients. The average number of doses received during maintenance therapy was 5.8 (range of 1 to 24) and the average duration of maintenance therapy was 126 (range of 1 to 513) days for this patient population.

INDICATIONS AND USAGE

ONCASPAR® is indicated for patients with acute lymphoblastic leukemia who require L-asparaginase in their treatment regimen, but have developed hypersensitivity to the native forms of L-asparaginase **(SEE CLINICAL PHARMACOLOGY)**. **ONCASPAR®**, like native L-asparaginase, is generally used in combination with other chemotherapeutic agents, such as vincristine, methotrexate, cytarabine, daunorubicin, and doxorubicin.[1,5] Use of **ONCASPAR®** as a single agent should only be undertaken when multi-agent chemotherapy is judged to be inappropriate for the patient.

CONTRAINDICATIONS

ONCASPAR® is contraindicated in patients with pancreatitis or a history of pancreatitis. **ONCASPAR®** is contraindicated in patients who have had significant hemorrhagic events associated with prior L-asparaginase therapy. **ONCASPAR®** is also contraindicated in patients who have had previous serious allergic reactions, such as generalized urticaria, bronchospasm, laryngeal edema, hypotension, or other unacceptable adverse reactions to **ONCASPAR®**.

WARNINGS

It is recommended that **ONCASPAR®** be given under the supervision of an individual who is qualified by training and experience to administer cancer chemotherapeutic agents.

Especially in patients with known hypersensitivity to the other forms of L-asparaginase, hypersensitivity reactions to **ONCASPAR®** , including life-threatening anaphylaxis, may occur during therapy. As a routine precaution, patients should be kept under observation for one hour with resuscitation equipment and other agents necessary to treat anaphylaxis (epinephrine, oxygen, intravenous steroids, etc.) available.

PRECAUTIONS

General

This drug may be a contact irritant, and the solution must be handled and administered with care. Gloves are recommended. Inhalation of vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. In case of contact, wash with copious amounts of water for at least 15 minutes. Anaphylactic reactions require the immediate use of epinephrine, oxygen, intravenous steroids, and antihistamines. Patients taking **ONCASPAR®** are at higher than usual risk for bleeding problems, especially with simultaneous use of other drugs that have anticoagulant properties, such as aspirin, and non-steroidal anti-inflammatories **(SEE DRUG INTERACTIONS)**. **ONCASPAR®** may have immunosuppressive activity. Therefore, it is possible that use of the drug in patients may predispose the patient to infection. Severe hepatic and central nervous system toxicity following multi-agent chemotherapy that includes **ONCASPAR®** may occur. Caution appears warranted when treating patients with **ONCASPAR®** given in combination with hepatotoxic agents, particularly when liver dysfunction is present.

Patients undergoing **ONCASPAR®** therapy must be carefully monitored and the therapeutic regimen adjusted according to response and toxicity. Physicians using a given treatment regimen incorporating **ONCASPAR®** should be thoroughly familiar with its benefits and risks.

Information For Patients

Patients should be informed of the possibility of hypersensitivity reactions, including immediate anaphylaxis, to **ONCASPAR®** . Patients taking **ONCASPAR®** are at higher than usual risk for bleeding problems. Patients should be instructed that the simultaneous use of **ONCASPAR®** with other drugs that may increase the risk of bleeding should be avoided **(SEE DRUG INTERACTIONS)**. **ONCASPAR®** may affect the ability of the liver to function normally in some patients. Therapy with **ONCASPAR®** may increase the toxicity of other medications **(SEE DRUG INTERACTIONS)**. **ONCASPAR®** may have immunosuppressive activity. Therefore, it is possible that use of the drug in patients may predispose the patient to infection. Patients should notify their physicians of any adverse reactions that occur.

Laboratory Tests

A fall in circulating lymphoblasts is often noted after initiating therapy. This may be accompanied by a marked rise in serum uric acid. As a guide to the effects of therapy, the patient's peripheral blood count and bone marrow should be monitored.

Frequent serum amylase determinations should be obtained to detect early evidence of pancreatitis **(SEE CONTRAINDICATIONS)**. Blood sugar should be monitored during therapy with **ONCASPAR®** because hyperglycemia may occur. When using **ONCASPAR®** in conjunction with hepatotoxic chemotherapy, patients should be monitored for liver dysfunction.

ONCASPAR® may affect a number of plasma proteins; therefore, monitoring of fibrinogen, PT and PTT may be indicated.

Drug Interactions

Unfavorable interactions of L-asparaginase with some antitumor agents have been demonstrated.[1] It is recommended, therefore, that **ONCASPAR®** be used in combination regimens only by physicians familiar with the benefits and risks of a given regimen. Depletion of serum proteins by **ONCASPAR®** may increase the toxicity of other drugs which are protein bound. Additionally, during the period of its inhibition of protein synthesis and cell replication, **ONCASPAR®** may interfere with the action of drugs such as methotrexate, which require cell replication for their lethal effects. **ONCASPAR®** may interfere with the enzymatic detoxification of other drugs, particularly in the liver. Physicians using a given treatment regimen should be thoroughly familiar with its benefits and risks.

Imbalances in coagulation factors have been noted with the use of **ONCASPAR®** predisposing to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy, such as coumadin, heparin, dipyridamole, aspirin, or non-steroidal anti-inflammatories.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenic studies in animals have not been performed with **ONCASPAR®** nor have studies been performed on impairment of fertility. **ONCASPAR®** did not exhibit a mutagenic effect when tested against *Salmonella typhimurium* strains in the Ames assay.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with **ONCASPAR®** . It is also not known whether **ONCASPAR®** can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. **ONCASPAR®** should be given to a pregnant woman only if clearly needed.

Nursing Mothers

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

ONCASPAR® ADVERSE REACTIONS

Adverse reactions have been reported in adults and pediatric patients. Overall, the adult patients treated with **ONCASPAR®** had a somewhat higher incidence of known L-asparaginase toxicities, except for hypersensitivity reactions, than the pediatric patients treated with **ONCASPAR®** .

Excluding hypersensitivity reactions, the most frequently occurring known L-asparaginase related toxicities and adverse experiences reported for the 174 patients in clinical studies were chemical hepatotoxicities and coagulopathies, the majority of which did not result in any significant clinical events. The incidence of significant clinical events included clinical pancreatitis (1%), hyperglycemia requiring insulin therapy (3%), and thrombosis (4%).

The following adverse reactions related to **ONCASPAR®** were reported for 174 patients in five clinical studies.

The adverse reactions reported most frequently (greater than 5%) were allergic reactions (which may have included rash, erythema, edema, pain, fever, chills, urticaria, dyspnea, or bronchospasm), SGPT increase, nausea and/or vomiting, fever, and malaise.

The adverse reactions reported occasionally (greater than 1% but less than 5%) were anaphylactic reactions, dyspnea, injection site hypersensitivity, lip edema, rash, urticaria, abdominal pain, chills, pain in the extremities, hypotension, tachycardia, thrombosis, anorexia, diarrhea, jaundice, abnormal liver function test, decreased anticoagulant effect, disseminated intravascular coagulation, decreased fibrinogen, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, increased thromboplastin, injection site pain, injection site reaction, bilirubinemia, hyperglycemia, hyperuricemia, hypoglycemia, hypoproteinemia, peripheral edema, increased SGOT, arthralgia, myalgia, convulsion, headache, night sweats, and paresthesia.

The adverse reactions reported rarely (less than 1%) were bronchospasm, petechial rash, face edema, lesional edema, sepsis, septic shock, chest pain, endocarditis, hypertension, constipation, flatulence, gastrointestinal pain, hepatomegaly, increased appetite, liver fatty deposits, coagulation disorder, increased coagulation time, decreased platelet count, purpura, increased amylase, edema, excessive thirst, hyperammonemia, hyponatremia, weight loss, bone pain, joint disorder, confusion, dizziness, emotional lability, somnolence, increased cough, epistaxis, upper respiratory infection, erythema simplex, pruritus, hematuria, increased urinary frequency, and abnormal kidney function.

The following **ONCASPAR®** related adverse reactions have been observed in patients with hematologic malignancies, primarily acute lymphoblastic leukemia (approximately 75%), non-Hodgkins lymphoma (approximately 13%), acute myelogenous leukemia (approximately 3%), and a variety of solid tumors (approximately 9%):

HYPERSENSITIVITY REACTIONS: A variety of hypersensitivity reactions have occurred. These reactions may be acute or delayed, and include acute anaphylaxis, bronchospasm, dyspnea, urticaria, arthralgia, erythema, induration, edema, pain, tenderness, hives, swelling, lip edema, chills, fever, and skin rashes **(SEE WARNINGS AND CONTRAINDICATIONS)**.

PANCREATIC FUNCTION: Pancreatitis, sometimes fulminant and fatal, has occurred. Increased serum amylase and lipase have also occurred.

LIVER FUNCTION: A variety of liver function abnormalities have been observed, including elevations of SGOT, SGPT, and bilirubin (direct and indirect). Jaundice, ascites, and hypoalbuminemia, which may be associated with peripheral edema, have been observed. These abnormalities usually are reversible on discontinuance of therapy, and some reversal may occur during the course of therapy. Fatty changes in the liver and liver failure have occurred.

HEMATOLOGIC: Hypofibrinogenemia, prolonged prothrombin times, prolonged partial thromboplastin times, and decreased antithrombin III have been observed. Superficial and deep venous thrombosis, sagittal sinus thrombosis, venous catheter thrombosis, and atrial thrombosis have occurred. Leukopenia, agranulocytosis, pancytopenia, thrombocytopenia, disseminated intravascular coagulation, severe hemolytic anemia, and anemia have been observed. Clinical hemorrhage (which may be fatal), easy bruisability, and ecchymosis have also been observed.

METABOLIC: Mild to severe hyperglycemia has been observed in low incidence, and usually responds to discontinuation of **ONCASPAR®** and the judicious use of intravenous fluid and insulin. Hypoglycemia, increased thirst and hyponatremia, uric acid nephropathy, hyperuricemia, hypoproteinemia, and peripheral edema have also been observed. Hypoalbuminemia, proteinuria, weight loss, and metabolic acidosis have occurred. Therapy with **ONCASPAR®** is associated with an increase in blood ammonia during the conversion of L-asparagine to aspartic acid by the enzyme.

NEUROLOGIC: Status epilepticus and temporal lobe seizures, somnolence, coma, malaise, mental status changes, dizziness, emotional lability, headache, lip numbness, finger paresthesia, mood changes, night sweats, and a Parkinson-like syndrome have occurred. Mild to severe confusion, disorientation, and paresthesia have also occurred. These side effects usually have reversed spontaneously after treatment was stopped.

RENAL: Increased BUN, increased creatinine, urinary frequency, hematuria due to thrombocytopenia, severe hemorrhagic cystitis, renal dysfunction, and renal failure have been observed.

CARDIOVASCULAR: Chest pain, subacute bacterial endocarditis, hypertension, severe hypotension, and tachycardia have occurred.

DIGESTIVE: Anorexia, constipation, decreased appetite, diarrhea, indigestion, flatulence, gas, gastrointestinal pain, mucositis, hepatomegaly, elevated gamma-glutamyltranspeptidase, increased appetite, mouth tenderness, severe colitis, and nausea and/or vomiting have been observed.

MUSCULOSKELETAL: Diffuse and local musculoskeletal pain, arthralgia, joint stiffness, and cramps have occurred.

RESPIRATORY: Cough, epistaxis, severe bronchospasm, and upper respiratory infection have been observed.

SKIN/APPENDAGES: Itching, alopecia, fever blister, purpura, hand whiteness and fungal changes, nail whiteness and ridging, erythema simplex, jaundice, and petechial rash have occurred.

GENERAL: Localized edema, injection site reactions (including pain, swelling, or redness), malaise, infection, sepsis, fatigue, and septic shock may occur.

OVERDOSAGE

Three patients received 10,000 IU/m^2 of **ONCASPAR®** as an intravenous infusion. One patient experienced a slight increase in liver enzymes. A second patient developed a rash ten minutes after the start of the infusion, which was controlled with the administration of an antihistamine and by slowing down the infusion rate. A third patient did not experience any adverse reactions.

DOSAGE AND ADMINISTRATION

As a component of selected multiple agent regimens, the recommended dose of **ONCASPAR®** is 2,500 IU/m^2 every 14 days by the intramuscular route or intravenous route of administration.

The preferred route of administration, however, is the intramuscular route because of the lower incidence of hepatotoxicity, coagulopathy, and gastrointestinal and renal disorders compared to the intravenous route of administration.

The safety and effectiveness of **ONCASPAR®** have been established in patients with known previous hypersensitivity to L-asparaginase whose ages ranged from 1 to 21 years old. The recommended dose of **ONCASPAR®** for children with a body surface area ≥ 0.6 m^2 is 2,500 IU/m^2 administered every 14 days. The recommended dose of **ONCASPAR®** for children with a body surface area < 0.6 m^2 is 82.5 IU/kg administered every 14 days.

Do not administer ONCASPAR® if there is any indication that the drug has been frozen. Although there may not be an apparent change in the appearance of the drug, the activity of ONCASPAR® is destroyed after freezing.

When administering **ONCASPAR®** intramuscularly, the volume at a single injection site should be limited to 2 mL. If the volume to be administered is greater than 2 mL, multiple injection sites should be used.

When administered intravenously, **ONCASPAR®** should be given over a period of 1 to 2 hours in 100 mL of sodium chloride or dextrose injection 5%, through an infusion that is already running.

Anaphylactic reactions require the immediate use of antihistamines, epinephrine, oxygen, and intravenous steroids.

Use of **ONCASPAR®** as the sole induction agent should be undertaken only in an unusual situation when a combined regimen, which uses other chemotherapeutic agents such as vincristine, methotrexate, cytarabine, daunorubicin, or doxorubicin, is inappropriate because of toxicity or other specific patient-related factors, or in patients refractory to other therapy. When **ONCASPAR®** is to be used as the sole induction agent, the recommended dosage regimen is also 2,500 IU/m^2 every 14 days.

When a remission is obtained, appropriate maintenance therapy may be instituted. **ONCASPAR®** may be used as part of a maintenance regimen.

Parenteral drug products should be inspected visually for particulate matter, cloudiness or discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Dosage Form

ONCASPAR®: Use only one dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

Sterile solution for injection in ready to use single-use vials. Preservative free.

Quantity per Individual Container
5 mL per vial containing 750 IU/mL **ONCASPAR®** in a clear, colorless, phosphate buffered saline solution, pH 7.3. Each vial contains 3,750 IU of **ONCASPAR®** .

Handling and Storage
Avoid excessive agitation. DO NOT SHAKE.
Keep refrigerated at +2˚C to +8˚C (36˚F to 46˚F).
Do not use if cloudy or if precipitate is present.
Do not use if stored at room temperature (+15˚C to +30˚C; 59˚F to 77˚F) for more than 48 hours.
DO NOT FREEZE. Do not use product if it is known to have been frozen. Freezing destroys activity, which cannot be detected visually.

NDC 57665-002-02

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Revised 4/05

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PN 200-030-C