Prescribing Information

For I.V. use in Infusion
For use only in Hospitalized patients (Intensive care unit / High dependency unit)

Ulinastatin for Injection

यु-ट्रिप
U-Tryp®
50,000 I.U. / 100,000 I.U. **(Liquid)**

DESCRIPTION:
Ulinastatin is a serine protease inhibitor that reduces the pro-inflammatory response as a result of sepsis, acute pancreatitis, trauma or surgery. Ulinastatin for Injection is available in clear colourless liquid.

COMPOSITION:
Each vial contains:
Ulinastatin J.P. ..... 50,000 I.U. / 100,000 I.U.
Water for Injection I.P. ..... q.s.

m-cresol B.P. (0.03% w/v), Sucrose I.P., Disodium hydrogen phosphate dihydrate B.P., Tween 80 I.P., Phosphoric acid I.P.

DOSAGE FORM:
Liquid Injection.

CLINICAL INDICATIONS:
1. Severe sepsis:
Sepsis is defined as a systemic inflammatory response syndrome (SIRS) in the presence of, or as a result of, suspected or proven infection[1-3]. Severe sepsis is defined as sepsis with one of the following features: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or dysfunction of two or more organs[4].

Indian incidence is estimated to be about 750,000 cases per year. The most common causes for sepsis are trauma, burns, abdominal sepsis and pneumonia. Septic shock is the most common cause of mortality in the intensive care unit. Despite aggressive treatment, mortality ranges from 15% in patients with sepsis to 40-60% in patients with septic shock. There is a continuum of clinical manifestations from SIRS to sepsis to severe sepsis to septic shock to Multiple Organ Dysfunction Syndrome (MODS).

Common predisposing factors for sepsis are diabetes mellitus, concurrent anticancer drugs and corticosteroids and immunocompromised status. The best two prognostic factors are APACHE II score and number of organ dysfunctions. In a large Indian hospital based study of 5,478 ICU admissions, SIRS with organ dysfunction was present in 25%, sepsis in 52.77%, severe sepsis in 16.45% with median APACHE II score =13 (IQR 13 to 14). The overall mortality in ICU patients was 12.08% but in patients with sepsis it was 59.26%.

2. Mild and severe acute pancreatitis:
The diagnosis of mild and severe acute pancreatitis requires 2 of the following 3 features: 1) upper abdominal pain of acute onset often radiating through to the back, 2) serum amylase or lipase activity greater than 3 times normal, and 3) findings on cross-sectional abdominal imaging consistent with acute pancreatitis. [11] In the early phase, which lasts only a week or so, the systemic manifestations are related to the host response to the cytokine cascade, which manifests as SIRS and/or the compensatory anti-inflammatory syndrome (CARS) that can predispose to infection. When SIRS or CARS persist, organ failure sets in. The late phase of acute pancreatitis, which can persist for weeks to months, is characterized by systemic signs of ongoing inflammation, local and systemic complications, and/or by transient or persistent organ failure.[11]
Acute pancreatitis is severe in around 20% patients, and is associated with high morbidity and mortality. Mortality is approximately 32% in the initial few days, mainly from organ failure, and later, if necrotic tissue becomes infected, 19% in the third week and 37% in the fourth.[12]

DOSAGE AND ADMINISTRATION:
For both severe sepsis and mild and severe acute pancreatitis:
Administer 1 to 2 vials of 100,000 I.U. of Ulinastatin (Reconstituted in 100ml of Dextrose 5% or 100ml of 0.9% Normal Saline) by intravenous infusion over 1 hour each time, 1-3 times per day for 3 to 5 days. The dosage may be adjusted according to the age of patients and the severity of symptoms.

USE IN SPECIAL POPULATION:
The safety for pregnant woman is NOT determined yet. Whether or not Ulinastatin should be administered to pregnant woman or potentially pregnant woman may be decided according to the patient's condition.
1. Ulinastatin is not used for nursing women in principle. If used, breast feeding should be stopped.
2. The safe dosage for children is NOT determined yet.

CONTRAINDICATIONS:
Hypersensitivity to the drug.

WARNINGS:
1. Not to be used for patients who are hypersensitive.
2. Not to used in lactating women.

PRECAUTIONS:
- Ulinastatin should be administered with caution if patient has history of allergy.
- Ulinastatin can NOT replace the traditional therapeutic methods (transfusion, oxygen therapy and antibiotics) for shocks.

DRUG INTERACTION:
No drug interactions have been reported or noted.

UNDESIRABLE EFFECTS OR ADVERSE REACTION:
1. Rare cases of rash, itching and pain at the site of injection.
2. Rare cases of allergy.
3. Rare cases of elevation of SGOT and SGPT.
4. Rare cases of nausea, vomiting and diarrhea.

OVERDOSE:
No specific antidote is recommended in case of accidental overdose.

PHARMACOLOGICAL EFFECTS:
Ulinastatin is a protease inhibitor extracted from human urine. Ulinastatin inhibits inflammatory markers: trypsin, pancreatic elastase, polymorphonuclear leukocyte elastase and the endotoxin-stimulated production of TNF alpha and interleukin 1, 8 and 6. It inhibits coagulation and fibrinolysis and promotes microperfusion. Thus, Ulinastatin is an effective agent for immune modulation to prevent organ dysfunction and promote homeostasis.

CLINICAL STUDIES :
1. A prospective, multicentric, double-blind, randomised, phase III clinical study was conducted to compare the efficacy and safety of intravenous Ulinastatin versus placebo along with standard supportive care in subjects of severe sepsis. Of the 122 randomized subjects, 114 completed the study (55 subjects in the Ulinastatin group and 59 subjects in the control group). The 28 day all-cause mortality was 4 subjects in the Ulinastatin group vs 12 in the placebo group (p=0.0448). This difference was statistically significant. 10 subjects in the Ulinastatin group and 20 subjects in the Placebo group had new organ dysfunction (p=0.0569). Though there was a trend towards less incidence of new organ failure in the Ulinastatin group, this was just short of statistical significance. Mean hospital stay in the Ulinastatin group was 13.59±6.83 days vs. 26.21±5.36 days in the Placebo group. This difference was statistically significant (p=0.001). Number of ventilator free days up to day 28 end-of-study were 19.44±10.61 days in the Ulinastatin group and 10.18±12.54 days in the Placebo group. This difference was found to be statistically significant (p=0.019). There were no infusion related toxicities in the study. Thus, treatment with Ulinastatin effectively reduced mortality in patients with severe sepsis when used as an adjunctive therapy in addition to standard therapy and ICU care. The reduction in mortality was accompanied by a shorter stay in the hospital and a shorter duration of ventilator and vasopressor usage with no side-effects seen in the study population.
2. A prospective, multicenter, double-blind, randomized, phase III clinical study was conducted to compare the efficacy and safety of intravenous ulinastatin versus placebo along with standard supportive care in subjects with mild and severe acute pancreatitis. Of the 135 randomized subjects, 129 completed the study (62 subjects in the mild group and 67 subjects in the severe group). Efficacy was evaluated in the MITT population of 65 subjects in the Ulinastatin group and 64 subjects in the Placebo group. The 22-day all-cause mortality was reduced significantly from 18.8% in the placebo group to 2.8% in the Ulinastatin group in the severe pancreatitis subjects. New-onset organ failure decreased from 90% in the placebo group to 34% in the Ulinastatin group; this was statistically significant. Hospital stay was shorter in the Ulinastatin group. The reduction of Serum CRP was comparable in the two treatment groups. There was only one incidence of infusion-related toxicity (transient rash). The number of adverse events, all of a non-serious nature, were less in the study group vs control group (in mild patients 24 vs 34 and in severe patients 23 vs 45). Thus, treatment with Ulinastatin effectively reduced mortality and morbidity in patients with severe pancreatitis when used as an adjunctive therapy in addition to standard therapy. The reduction in mortality was accompanied by a shorter stay in the hospital and less complications.

PHARMACOKINETICS:
- After intravenous injection of 300,000 I.U./10ml into healthy man, its concentration in blood decreases linearly.
- The half life of Ulinastatin is about 40 minutes.
- 6 hours after the administration, 24% of Ulinastatin is discharged in urine.

INCOMPATIBILITIES:
None Reported.

SHELF LIFE:
Two years from date of manufacturing.

PACKING INFORMATION:
- Pack containing 1 vial of 50,000 I.U. of Ulinastatin.
- Pack containing 1 vial of 100,000 I.U. of Ulinastatin.

STORAGE AND HANDLING INSTRUCTIONS:
Storage temperature 2°C to 8°C. Protect from light. Any unused portion should be discarded.

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Manufactured in India by :
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