1. NAME OF THE MEDICINAL PRODUCT

U – TRYP 100,000 IU [Ulinastatin for Injection 100,000 IU (Liquid)]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vial Contains :

Ulinastatin J.P.....100,000 IU

Name of the component	Quantity/ ml	Overages	Specification	Justification for use of Ingredient
Ulinastatin	27,500 IU*	10%	J.P.	Active Pharmaceutical Ingredient
m-Cresol	0.3 mg	-	B.P.	Bacteriostatic
Sucrose	60.0 mg	-	B.P.	Stabilizer
Disodium Hydrogen Phosphate Dihydrate	1.1 mg	-	B.P.	Buffer component
Tween 80	0.1 mg	-	B.P.	Stabilizer (Prevents formation of protein aggregates)
Phosphoric Acid	q.s.	-	B.P.	For pH adjustment
Water for Injection	q.s.	-	B.P.	Vehicle

*with 10% Overages

3. PHARMACEUTICAL FORM

Clear, colorless solution

4. Clinical particulars

4.1 Therapeutic indications

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. 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.

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%.

Mild and Severe Acute Pancreatitis:

Acute pancreatitis is an acute inflammatory process of the pancreas initiated by the intrapancreatic activation of proteases like trypsin and subsequent autodigestion of the pancreas. The trypsin may activate other pathways, such as complement, coagulation or fibrinolysis, extending the process outside the gland. Occasionally SIRS may develop, mediated by cytokines and pancreatic enzymes released in to general circulation that may affect distant organs, giving rise to organ failure, shock or metabolic alterations which may further progress to MODS.

Biliary stones and alcohol abuse are responsible for 70% to 75% of cases. The disease is classified as mild when there is localized oedema and inflammation, whereas the severe disease is associated with pancreatic and peripancreatic complications like necrosis, abscess or pseudocyst and/or remote organ failure. The diagnosis of acute pancreatitis requires two of the following three features: upper abdominal pain of acute onset often radiating through to the back, serum amylase or lipase activity greater than 3 times normal, and findings on cross-sectional abdominal imaging consistent with acute pancreatitis. Acute pancreatitis carries an overall mortality rate of 10%-15%; the severe disease exists in around 20% with mortality approaching 30%-40%. Ulinastatin, by inhibiting the activity of proteases, exerts localized as well as generalized anti-inflammatory effect, resulting in reduction in mortality and new organ dysfunctions.

4.2 Posology and method of administration

Administer 1 to 2 vials of 100,000 I.U. of Ulinastatin (Reconstituted in 100 ml of Dextrose 5% or 100 ml 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.

4.3 Contraindications

U-Tryp is contra-indicted in patients who have shown hypersensitivity to Ulinastatin or any other component included in the formulation

4.4 Special warnings and precautions for use

Warnings:

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

Precautions:

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

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions have been reported or noted.

4.6 Pregnancy and Lactation

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.

Ulinastatin is not used for nursing women in principle. If used, breast feeding should be stopped.

4.7 Effects on ability to drive and use machines

U – Tryp can influence the ability to drive and use machines due to visual disturbances and dizziness.

4.8 Undesirable effects

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.

4.9 Overdose

Safety of Ulinastatin in humans is supported by a number of clinical studies, available in published literature, in which the subjects were exposed to varying doses of Ulinastatin.

Doses as high as 900,000 IU/day for 3 days and 200,000 I.U. weekly for 3 months leading to cumulative doses of 2,700,000 I.U. and 2,400,000 I.U., respectively have been used without any safety concerns. No specific antidote is recommended in case of accidental overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Protease inhibitor, ATC code: B02AB05

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.

5.2 Pharmacokinetic properties

- 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.
- hours after the administration, 24% of Ulinastatin is discharged in urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- m- Cresol
- Sucrose
- Disodium Hydrogen Phosphate Dihydrate
- Tween 80
- Phosphoric Acid

6.2 Incompatibilities

None Reported

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Storage temperature 2°C to 8°C. Protect from light.

Any unused portion should be discarded.

6.5 Nature and contents of container

Pack size: 1 vial x 5 ml

Clear colorless solution packed in USP Type I glass vial. Each vial is then packed in carton along with pack insert.

6.6 Special precautions for disposal

Not applicable

7. APPLICANT/MANUFACTURER

Applicant:

Bharat Serums & Vaccines Ltd.

3rd Floor, Liberty Tower, Plot No. K-10,
Behind Reliable Plaza, Kalwa Industrial Estate, Airoli,
Navi Mumbai 400708

Manufactured by:

Bharat Serums and Vaccines Limited.

Plot No. K-27, Anand Nagar, Jambivili Village,
Additional M.I.D.C., Ambernath East- 421506,
Maharashtra State, India.