SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal product:

1.1 Product name

U-TRYP 100,000 I.U.
[Ulinastatin for Injection 100,000 I.U. (Lyophilized)]

1.2 Strength

100,000 IU.

1.3 Pharmaceutical dosage form

Lyophilized

2. Qualitative and Quantitative compositions

Pack Size: 5 ml Vial

Ingredient	Specification	Quantity/Vial	Justification for the use of ingredient
Ulinastatin	J.P.	100,000 I.U.	Active Pharmaceutical Ingredient
Mannitol	B.P.	80.0 mg	Bulking Agent
Sucrose	B.P.	20.0 mg	Stabilizer
Di-Sodium Hydrogen Phosphate Dihydrate	B.P.	4.256 mg	Maintaining pH
Sodium Chloride	B.P.	18 mg	Maintaining ionic strength
Phosphoric Acid	B.P.	q.s. for pH Adjustment	pH Adjustment

B.P.: British Pharmacopoeia

J.P.: Japanese Pharmacopoeia

I.H.: In-House

3. Pharmaceutical form:

Freeze Dried Powder for Injection.

4. Clinical particulars:

4.1 Therapeutic Indications:

1. Severe Sepsis:

Sepsis is defined as the presence (suspected or proven) of infection together with systemic inflammatory response syndrome (SIRS). 'Severe sepsis' is defined as sepsis associated with evidence of organ dysfunction, tissue hypoperfusion or hypotension. The pathological mechanism involves the release of pro-inflammatory cytokines like TNF α, Interleukins (IL) 1, 6, 8 and chemokines. These cytokines can act directly to affect organ function or they may act indirectly through secondary mediators. These can also cause the release of tissue-factor by endothelial cells leading to fibrin deposition and disseminated intravascular coagulation (DIC). There is a continuum of clinical manifestations from SIRS to sepsis to severe sepsis to septic shock to Multiple Organ Dysfunction Syndrome (MODS). [1-3].

The most common cause for severe sepsis is bacterial infection; the most commonly affected sites being the respiratory tract, abdomen and urinary tract. Severe sepsis can also be caused by viruses (e.g. influenza, dengue), parasites (e.g. falciparum malaria) and fungi (e.g. Candida). Additionally, noninfectious conditions, such as burns and trauma can also lead to severe sepsis. [2-4] Common predisposing factors are very young or old age, diabetes mellitus, cirrhosis, weakened immune systems due to HIV, cancer or treatment with cytotoxic drugs/radiation, immunosuppressive drugs (e.g. corticosteroids) and invasive devices. The documented incidence of sepsis worldwide is 1.8 million cases annually with an estimated 20,000 deaths per day. [5] Severe sepsis is reported to account for around 15% of ICU admissions at tertiary hospitals in India; and despite treatment, mortality is reported in more than 50% of the patients. [6] Ulinastatin acts by reducing the pro-inflammatory process and promotes homeostasis, resulting in reduction in mortality and new organ dysfunctions.

2. 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. [7]

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. [8] Acute pancreatitis carries an overall mortality rate of 10%-15%; the severe disease exists in around 20% with mortality approaching 30%-40%. [9] 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

For both severe sepsis and mild and severe acute pancreatitis:

Reconstitute 1 to 2 vials of 100,000 I.U. of Ulinastatin in 100ml of 0.9% Normal Saline or 5% Dextrose and administer 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.

Method of Reconstitution:

Preferred Diluents or Infusion Fluid: 0.9% Normal Saline or Dextrose 5%.

1. Add 5 ml of the diluent slowly to the vial, directing the needle point to the wall of the vial, Abolish residual vacuum by briefly loosening the needle from the syringe.
2. Tilt and roll the vial gently. Swirl the contents gently to effect dissolution. Do not shake to avoid foaming.
3. Once the powder is completely dissolved, transfer the content of the vial into 100 ml of the infusion fluid.
4. Administer Ulinastatin immediately after reconstitution.

4.3 Contra-indications

Hypersensitivity to the drug.

4.4 Special warning and precautions for use

1. Ulinastatin should be administered with caution if patient has a history of allergy.
2. Ulinastatin should be avoided in pregnant & lactating women.
3. Ulinastatin can NOT replace and should only be used as an adjuvant to standard treatment (antimicrobials, fluids, vasoactive agents, ventilation etc.) for severe sepsis.
4. The safe dosage for children is NOT determined yet.

4.5 Interaction with other drugs , other forms of interactions:

No drug interactions have been reported or noted.

4.6 Use in 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 operate machine

No effects on ability to drive and use machines have been observed.

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 Overdoses

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 [12, 13]. No specific antidote is recommended in case of accidental overdose.

5. Pharmacological properties :

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.

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.

6. Pharmaceutical particulars :

6.1 List of Excipients:

Excipients	**Pharmacopoeial claim**
Mannitol	B.P.
Sucrose	B.P.
Di-Sodium Hydrogen Phosphate Dihydrate	B.P.
Sodium Chloride	B.P.
Phosphoric Acid	B.P.
Water for Injection	B.P.

B.P. : British Pharmacopoeia

6.2 Incompatibilities:

Not Applicable

6.3 Shelf-life:

24 months from the date of manufacturing.

6.4 Special precaution for storage:

Store at 2º C – 8ºC. Protect from light. Do not freeze.

6.5 Nature and contents of container:

U-TRYP 100,000 I.U. [Ulinastatin for Injection 100,000 I.U. (Lyophilized)] is available as white to light yellow powdered cake which is supplied in 5 ml clear, colourless, USP Type I (Neutral borosilicate) tubular glass vial with concave bottom in a carton along with a pack insert.

7. Marketing authorization holder :

Bharat Serums & Vaccines Ltd.
17th Floor, Hoechst House,
Nariman Point,
Mumbai – 400 021
India.

8. Marketing authorization number :

Not Applicable

9. Date of first authorization / renewal of authorization :

Not Applicable

10. Date of revision of the text :

Not Applicable