FOR THE USE OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR LABORATORY ONLY.

HUMAN C1- ESTERASE INHIBITOR EP 500 IU
(Freeze Dried Powder)
Manufactured from Human Plasma

Celestrase 1

GENERIC NAME
Human C1-Esterase Inhibitor EP 500 IU (Freeze Dried Powder)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each reconstituted vial of Human C1-Esterase Inhibitor contains:
Human C1-Esterase Inhibitor.....500 IU
Total Protein. .....50 - 100 mg
Glycine..... ..85 -115 mg
Sodium Chloride.....70 - 100 mg
Sodium Citrate.....25 - 35 mg
Reconstitute with sterile water for injection. 10 ml

DOSAGE FORM AND STRENGTH
Human C1-Esterase Inhibitor is supplied as a freeze-dried powder for reconstitution with the sterile water for injection in 10 mL vial (containing Human C1-Esterase Inhibitor 500 IU after reconstitution) for intravenous (IV) administration.

CLINICAL PARTICULARS

THERAPEUTIC INDICATION
Human C1-Esterase Inhibitor is indicated for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adult and adolescent patients.

POSOLOGYAND METHOD OF ADMINISTRATION
For intravenous use only.

- The medicine must not be mixed with other medicinal products or administered simultaneously with other intravenous preparation in the same infusion set.
- Ensure that the medicine vial and diluent are at the room temperature before reconstitution. It should be reconstituted with 10 mL of sterile water for injection and administered within eight hours of reconstitution. Do not refrigerate after reconstitution. After administration, any unused solution and the administration equipment should be discarded.
- Store in the original container prior to reconstitution to protect from light.
- The medicine should be at room temperature during administration.
- The medicine should be given as slow intravenous injection following aseptic technique at a rate of approximately 4 mL per minute.
- Appropriately trained patients may self-administer upon recognition of an HAE attack.
- Irrespective of blood group, it can be administered to all recipients.

Dose:
The usual recommended dose of C1 Esterase Inhibitor for the treatment of acute attacks of HAE is 20 International Units (IU) per kg body weight by slow intravenous injection. The second dose of C1 Esterase Inhibitor may be repeated after one hour if the response is not adequate under the guidance of the doctor.

CONTRAINDICATIONS
Human C1 Esterase Inhibitor is contraindicated in individuals who have had anaphylactic or severe systemic reactions to any C1 Esterase Inhibitor products or any ingredients in the formulation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Hypersensitivity
Severe hypersensitivity reactions, including anaphylaxis may occur. Epinephrine and antihistamines should be readily available in case anaphylaxis or an anaphylactic reaction occurs. The signs and symptoms of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing or hypotension during or immediately after the injection. The hypersensitivity symtoms and signs may be confused with HAE attacks. Careful examination and treatment approach is advised. If a severe hypersensitivity reaction occurs, discontinue the medication immediately and institute appropriate therapy as indicated. (See CONTRAINDICATIONS).
Risk of Transmissible Agents in Plasma-derived Preparations
Because Human C1-Esterase Inhibitor is prepared from pooled human plasma, they may carry a risk of transmitting infectious agents, including the causative agents of viral hepatitis and HIV infection, and theoretically may carry a risk of transmitting the causative agent of Creutzfeldt-Jakob disease (CJD) or variant CJD (vCJD).
The risk for transmission of recognized blood-borne viruses is considered to be very low because plasma donors are screened for certain viruses (HBV, HCV, HIV I and II) and viral reduction/inactivation procedures used in Human C1-Esterase Inhibitor production reduce the risk of transmission. Despite such stringent procedures, the risk of transmission can not be fully neglected. Report all infections thought possibly to have been transmitted by Human C1-Esterase Inhibitor to the manufacturer.
Thrombotic Effects
Serious arterial and venous thromboembolic events have been reported at the recommended dose of Human C1-Esterase Inhibitor products. Risk factors may include the presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives or certain androgens, morbid obesity, and immobility. Benefits of treatment of HAE attacks should be weighed against the risks of thromboembolic events in patients with underlying risk factors. Monitor patients with known risk factors for thromboembolic events during and after Human C1-Esterase Inhibitor administration.
Laryngeal Attacks
An acute laryngeal HAE attacks may progress to the airway obstruction. Patients self-administering Human C1-Esterase Inhibitor should be advised to immediately seek medical attention in an appropriate healthcare facility after self-treatment.

DRUGS INTERACTIONS
No drug interaction studies have been conducted.

USE IN SPECIAL POPULATIONS
PREGNANCY
Human C1-Esterase Inhibitor has not been evaluated in pregnant women. Animal reproduction studies have not been conducted with Human C1-Esterase Inhibitor. It is also not known whether it can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Human C1-Esterase Inhibitor should be given to a pregnant woman only if needed with consultation of healthcare professional.
NURSING MOTHERS
Human C1-Esterase Inhibitor has not been evaluated in nursing mothers.
PEDIATRIC USE
Safety and efficacy of Human C1-Esterase Inhibitor have not been established in children. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from older subjects.
GERIATRIC USE
Safety and efficacy of Human C1-Esterase Inhibitor have not been established in elderly patients. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from younger subjects.
EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No information on the effect on the ability to drive and use machines have been known. The patient may also experience the symptoms and signs of HAE. They may jeoparadize the safety while driving. If this happens, they should not drive or use machines until these effects have disappeared.

UNDESIRABLE EFFECTS
Because clinical studies are conducted under widely varying conditions and postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.
Adverse reactions reported with the use of Human C1-Esterase Inhibitor include hypersensitivity/anaphylactic reactions, injection-site pain, injection-site redness, chills, and fever. The most common adverse reaction reported was dysgeusia. The most serious adverse reaction reported was an increase in the severity of pain associated with HAE.
Thromboembolic events including both arterial and venous thrombosis, multiple pulmonary microemboli, and thrombosis have been reported with the use of Human C1-Esterase Inhibitor following treatment of HAE and during off-label use during cardiac surgery.

OVERDOSE
The thrombosis has been reported after doses exceeding 20 IU/kg body weight of Human C1-Esterase Inhibitor when used off-label in newborns and young children with congenital heart anomalies during or after cardiac surgery under extracorporeal circulation.
The maximum dose administered in clinical studies in hereditary angioedema was 20 IU/kg body weight. In case of overdose, further infusion should be halted and medical supervision is suggested along with symptomatic management.

PHARMACOLOGICAL PROPERTIES
MECHANISM OF ACTION
C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins). C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade. Administration of Human C1-Esterase Inhibitor to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients.

PHARMACODYNAMIC PROPERTIES
HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.
The plasma concentration of C1 esterase inhibitor in healthy volunteers is approximately 270 mg/L. Human C1-Esterase Inhibitor replacement in the patients with deficiency will replace the missing protein from the cascade of events leading to control of HAE.

PHARMACOKINETIC PROPERTIES
The product specific information is not available. The pharmacokinetics of Human C1-Esterase Inhibitor were evaluated in an open-label, uncontrolled, study in 35 adults with either mild or severe HAE. All subjects received a single intravenous injection of Human C1-Esterase Inhibitor ranging from 500 IU to 1500 IU. The baseline adjusted pharmacokinetic parameters observed in adults are as follows: area under the curve (AUC0-t) was 12.8±6.7 hr x IU/mL (3.9-34.7) based on a 15 IU/kg dose; clearance was 1.44 ± 0.67 mL/hr/kg (0.43-3.85); and half-life was 18.4 ± 3.5 hours (7.4-22.8).
Studies have not been conducted to evaluate the pharmacokinetics of Human C1-Esterase Inhibitor in special patient populations identified by gender, race, geriatric age, or the presence of renal or hepatic impairment.

NONCLINICAL PROPERTIES
ANIMAL TOXICOLOGY OR PHARMACOLOGY
Being human plasma-derived proteins, safety testing in animals is not particularly relevant to correlate the safety of use in man. Moreover, as these human plasma proteins are more immunogenic to animals than humans, reliability and productivity of pre-clinical testing further diminish.
In animals, single-dose toxicity testing is of little relevance and does not permit the evaluation of toxic and lethal doses or a dose-effect relationship. Repeated dose toxicity testing is impractical due to the development of antibodies to heterogeneous protein in animal models.

DESCRIPTION
Human C1-Esterase Inhibitor is a human plasma-derived, sterile preparation for intravenous use. It is prepared from the human plasma obtained from the healthy donors. The potency of C1 esterase inhibitor is expressed in International Units (IU), which is related to the current World Health Organization standard for C1 esterase inhibitor products. Irrespective of blood group, it can be transferred to all recipients.

PRODUCT SAFETY
All plasma used in the manufacturing of Human C1-Esterase Inhibitor, screened for the mandatory infectious diseases. Only on being declared non reactive to HBsAg, HIV I & II antibodies, antibodies against HCV and negative for HIV I & II, HCV, HBV by NAT, the plasma is used for processing.
Additionally, the manufacturing procedure incorporates solvent detergent treatment and virus retentive filtration which inactivates/removes any leftover viruses if present. After manufacturing, the product is tested as per specifications and indicates the product is non-reactive from viruses like HIV I and II, HBsAg, and HCV. Multiple steps have been applied to product safety assurance; there is a very remote probability that unknown infectious agents may be present in these products. The process parameters, characterizations, and final product quality are designed such, that they meet the regulatory requirements.
Abbreviation: HAE: hereditary angioedema; HIV: Human Immunodeficiency Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HBsAg: Hepatitis B surface antigen.

PHARMACEUTICAL PARTICULARS
INCOMPATIBILITIES
In the absence of compatibility studies, this medicine must not be mixed with other medicinal products.

HOW SUPPLIED
Human C1-Esterase Inhibitor is supplied as lyophilized powder in a vacuum-sealed single-use glass vial that contains 500 IU per vial to be reconstituted with 10 mL of sterile water for injection.

STORAGE AND HANDING INSTRUCTIONS
Store between +2°C to +8°C.
Partially used vials should be discarded.
Do not freeze.
Before use, visually inspect the medicine. The solution must be clear or slightly opalescent and colorless or pale yellow. Do not use if the solution is cloudy or has deposits.
Keep out of reach and sight of children.
Store in the original container to protect from light.
Do not use it after expiry date mentioned on vial and carton.

EXPIRY
Two years from the date of manufacture. Do not use after expiry date

Report suspected adverse reaction at: Hemofluidsafety@intaspharma.com
Date of preparation: 21-Apr-2021

Manufactured and Marketed by:
INTAS
INTAS PHARMACEUTICALS LTD.
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