For the use of a Registered Medical Practitioner or a Hospital only.

Dried Human Antihaemophilic Factor VIII Fraction IP 500 IU

FACTOCEL™ VIII
500 IU

For Intravenous Use Only

DESCRIPTION

FACTOCEL™ VIII is a sterile, lyophilized powder for injection of antihaemophilic Factor VIII. It is prepared from large pools of human plasma obtained from healthy donors. The Factor VIII potency is determined using the Indian pharmacopoeia chromogenic assay. The reconstituted solution of 10 ml containing 500 IU of Factor VIII is intended for intravenous use only.

PRODUCT SAFETY

Collected blood plasma used for manufacturing of FACTOCEL™ VIII, screened for the mandatory infectious diseases. Only on being declared non reactive for HBsAg, HCV, HIV I & II antibodies and negative for HIV I & II, HCV, HBV by NAT the plasma is used for processing.

The manufacturing procedure incorporates two dedicated orthogonal viral clearance steps ensuring viral safety of the product. This includes solvent detergent treatment and dried heat treatment.

The drug product is also tested for viral markers like HBV, HIV & HCV. Multiple chromatography steps have been incorporated for assurance of product safety. The process parameters, characterizations and final product quality are designed such, that they meet the regulatory requirements. FACTOCEL™ VIII contains no preservative and is free from blood group antibodies.

Abbreviation: HBV: Hepatitis B Virus, HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; HBsAg: Hepatitis B surface antigen; NAT: Nucleic Acid Test

COMPOSITION

Each vial contains:

Factor VIII.....500 IU
Sodium Citrate (as stabilizer).....29.0 mg
Calcium Chloride (as stabilizer).....1.8 mg
Aminoacetic Acid (as stabilizer).....NMT 150.0mg
Sodium Chloride (as isotonic agent).....NMT 128.0 mg
Protein.....NMT 40 g/l
Fibrinogen.....NMT 80 % of total protein
Na+.....NMT 200 mM

CLINICAL PHARMACOLOGY

The factor VIII/von Willebrand Factor complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand Factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

INDICATIONS AND USAGE

FACTOCEL™ VIII Injection is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (Congenital Factor VIII deficiency).

DOSAGE AND ADMINISTRATION

FACTOCEL™ VIII should always be administered intravenously only. It should be reconstituted with 10 ml of sterile water for injections. Reconstitution may take 30 minutes. Administer within one hour of reconstitution. If not used within one hour discard remaining solution. Use syringe filter for administration. Do not use if gel or precipitation is observed when reconstituted. After administration, any unused solution and the administration equipment should be discarded.

1 Unit is approximately equal to 1 AHF activity of 1 ml of average normal plasma.

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and other haemostatic disorders. Dosage may vary with individual body weight, age and symptoms.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal; IU/dL) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage / Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours)/Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma.	30-60	Repeat infusion every 12 to 24 hours for 3 to 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60-100	Repeat infusion every 8 to 24 hours until threat resolved.
Surgery		
Minor *Including tooth extraction*	30-60	Every 24 hours, at least 1 day, until healing is achieved.
Major	80-100 (pre- and postoperative)	Repeat infusion every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

Haemophilia A

The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standards for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an international standard for factor VIII in plasma).

One International Unit of factor VIII activity is equivalent to that quantity of factor VIII in one mL of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2.5% of normal activity 2.5 IU/dL. The required dosage is determined using the following formula:

Required units = Body weight (kg) x Desired factor VIII rise (%) (IU/dL) x 0.5

The amount to be administered and the frequency of administration should always be orientated to the clinical effectiveness in the individual case.

Children: The dose for young children with haemophilia A should be calculated on a recovery of 1.5 IU/dL/IU/kg to achieve the same desired levels as in the Table in this section. The equivalent formula is as follows:

Required units = Body weight (kg) x Desired factor VIII rise (%) (IU/dL) x 0.7

Front Side

POSSIBLE SIDE EFFECTS

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur , and may in some cases progress to severe anaphylaxis. Other side effects are back and other pain, dizziness, bradycardia, palpitations, coughing, dysgeusia, drowsiness and blurred vision.

On rare occasions, fever has been observed. Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases it is recommended that a specialized haemophilia centre be contacted.

USE IN SPECIAL POPULATION

Pregnancy and Lactation

The safety of administration to pregnant women has not been established. The possibility of human parvovirus B19 infection risk cannot be eliminated when administered. Since the fetus could develop disorders (miscarriage, hydrops fetalis, fetal defect) when infected, the drug must be administered to patients who are pregnant or with possibility of pregnancy only when the benefits of the treatment outweigh the possible risks.

Geriatric

Since the physiological function of the elderly is generally decreased, the condition of the patient should be observed and administered with caution.

CONTRAINDICATION

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS AND WARNINGS

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. The product contains traces of human proteins other than factor VIII and vWF. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician. In case of shock, the current medical standards for shock-treatment should be observed.

As this drug is produced from human blood plasma, at the present level of scientific technology the risk of infection by blood borne virus or other kinds of infectious agent Creutzfeldt-Jakob disease (CJD) cannot be eliminated. Accordingly, appropriate vaccinations such as hepatitis B vaccination also Along with hepatitis A vaccination are recommended to hemophilic patients or those with very low immune functions. When medicating, doctors should monitor periodically for any sign of infection. Since human blood is used as the source of the drug the possibility of infection cannot be entirely excluded. In this reason doctors must fully explain the risks and minimize the administration to patients after careful review of the necessity.

General precautions

1) The progress after administration must be observed sufficiently since the possibility of viral infection, such as non-hepatitis A and non-hepatitis B virus, cannot be excluded. Appropriate treatment should be used when hepatopathy occurs.

2) Careful administration and observation of the progress are required in repeated administration with intervals as anaphylaxis may occur.

3) Careful administration and observation of the progress are required In repeated administration as inhibitors to coagulation factor may develop in patients' plasma.

4) Plasma fibrinogen concentration may elevate excessively after administration as FACTOCEL™ VIII Injection contains fibrinogen.

5) FACTOCEL™ VIII Injection contains anti-A and B blood type antibodies. If high dose injection is administered to patients of blood type A, B and AB, it may cause hemolytic anemia.

6) The progress after administration must be observed sufficiently since the possibility of infection cannot be excluded as it is difficult to completely inactivate or eliminate human parvovirus B19 in the plasma derivatives produced under the current manufacturing process.

7) Along with the necessity of this drug in the treatment of the disease, it should also be explained to the patient that the risk of infection derived from human blood cannot be excluded completely, although certain safety measures are applied in the production process of this drug in order to prevent infection.

Special warnings

1) Patients with immunoglobulin A (IgA) deficiency (Hypersensitivity may occur in patients with anti-IgA antibody.)

2) Patients with hemolytic or hemorrhagic anemia (There is a possibility of human parvovirus B19 infection. In case of infection, acute systemic responses may occur along with fever and severe acute anemia.)

3) Patients with immunodeficiency or Immunodepression (There is a possibility of human parvovirus B19 infection. In case of infection, prolonged anemia may occur.)

DRUG INTERACTION

No pharmacologic interactions of factor VIII with other medicinal products are currently known.

PACKING UNIT

FACTOCEL™ VIII Injection is supplied in sterile, lyophilized powdered form in a single dose vial.

SHELF LIFE

24 months from the manufacturing date.
Do not use after expiry date.

STORAGE CONDITION

Store between 2°C and 8°C in an airtight container, protect from light.

WARNING

Do not freeze.
Report suspected adverse reaction at: Hemofluidsafety@intaspharma.com
Date of preparation : 18-Apr-2020

Manufactured and Marketed by:
INTAS
INTAS PHARMACEUTICALS LTD.
Plot No. 496/1/A&B, Sarkhej-Bavla Highway,
Village: Matoda, Taluka: Sanand,
Ahmedabad-382213, Gujarat, (INDIA)

AW-044-02

Back Side