**3.2 Method of administration**

Treatment should be supervised by a physician experienced in the treatment of haemophilia and/or bleeding disorders.

1. **Haemophilia A or B with inhibitors** or expected to have a high anamnestic response

2. **Factor VII deficiency**

3. **Factor VII deficiency**

4. **Glanzmann’s thrombasthenia**

5. **Acquired Haemophilia**

**3.3 Laboratory tests for treatment monitoring**

There is no requirement for monitoring of rFVIIa therapy. Severity of bleeding condition and clinical response to rFVIIa must guide dosing requirements. (PT) and (aPTT) have been decreased after administration of rFVIIa; however, no correlation has been demonstrated between (PT) and (aPTT) and clinical efficacy of rFVIIa.

**3.4 Contraindications**

Hypersensitivity to the active substance, or to any of the excipients, or to mouse, hamster or bovine protein.

**3.5 Special warnings and precautions for use**

Where tissue factor may be expressed more extensively (DIC, septicemia, crush injury, etc.), treatment with rFVIIa may be a potential risk for development thrombotic events or induction of Disseminated Intravascular Coagulation (DIC). Caution should be considered according to thromboembolic complications, when rFVIIa is administered in such conditions as following:

- Liver disease
- Post-operative
- Neonates
- Coronary heart disease
- Risk of thromboembolic phenomena

In each of these situations, the potential benefit of treatment with **AryoSeven™** should be judged against the complications risk. As **AryoSeven™** may contain trace amounts of residual culture proteins (hamster and bovine serum proteins), so it is possible to develop hypersensitivity to these proteins. In such cases treatment with antihistamines I.V should be considered.

If anaphylactic reactions occur, the administration should be discontinued immediately. Patients should be informed of the early signs of hypersensitivity reactions and should be advised to contact the physician if such symptoms occur.

**AryoSeven™** should be administered in hospital in case of severe bleeds, or if not possible in close collaboration with a physician.

Before and after administration of **AryoSeven™**, factor VII deficient patients should be monitored for prothrombin time and factor VII coagulant activity. If the prothrombin activity falls to reach the expected level or bleeding is not controlled after treatment, the analysis for antibodies against rFVIIa should be performed.

**3.6 Interaction with other medicinal products**

The risk of a potential interaction between **AryoSeven™** and coagulation factor concentrates is unknown.

Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided. Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and **AryoSeven™** treatment is however limited.

**3.7 Pregnancy and lactation**

**Pregnancy**

There are some data on a limited number of exposed pregnancies within approved indications which
Inhibitory antibody formation

There have been no reports of antibodies against rFVIIa in patients with haemophilia A or B. In patients with factor VII deficiency, formation of antibodies against rFVIIa is the only adverse drug reaction reported (frequency: ≥1/100 to <1/10).

Risk factors that may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived factor VII, severe mutation of FVII gene, and overdose of rFVIIa were present. Patients with factor VII deficiency treated with AryoSeven™ should be monitored for factor VII antibodies.

4. PHARMACOLOGICAL INFORMATION

4.1 Pharmacodynamic

AryoSeven™ contains activated recombinant coagulation factor VII (rFVIIa). The mechanism of action includes the binding of factor Vlla to exposed tissue factor. This complex activates factor IX into factor IXa and factor X into factor Xa, leading to the initial conversion of small amounts of prothrombin into thrombin. Thrombin leads to the activation of platelets and factors V and VIII at the site of injury and to the formation of the haemostatic plug by converting fibrinogen into fibrin. Pharmacological doses of rFVIIa activate factor X directly on the surface of activated platelets, localized to the site of injury, independently of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin independently of tissue factor. Accordingly, the pharmacodynamic effect of factor Vlla gives rise to an increased local formation of factor Xa, thrombin and fibrin.

A theoretical risk for the development of systemic activation of the coagulation system in patients suffering from underlying diseases predisposing them to DIC cannot be totally excluded.

5. PHARMACEUTICAL CHARACTERISTIC

5.1 List of excipients

Powder: Sodium chloride, Calcium chloride dihydrate, Glycyglycine, Polysorbate 80, Mannitol

Solvent: Water for injections

5.2 Incompatibilities

AryoSeven™ must not be mixed with infusion solutions or be given in a drip.

5.3 Shelf life

The shelf life is 2 years for the product packed for sale. After reconstitution, chemical and physical stability has been demonstrated for 24 hours at 25°C. The product should be used immediately. If not used immediately, storage time and storage conditions prior to use are the responsibility of the user, and would not be longer than 24 hours at 2°C - 8°C unless reconstitution has occurred in controlled and validated aseptic conditions.

5.4 Special precautions for storage

– Store AryoSeven™ at (2°C - 8°C)
– Store in original package in order to protect from light
– Do not freeze in order to prevent damage to the solvent vial.

5.5 Nature and contents of container

Vials for AryoSeven™:

USP Type I glass vials has been used as the primary packaging material and container of AryoSeven™ Drug product (lyophilized powder). This type is also used for the USP sterile water for injection (as solvent) accompanied the vial of powder. These two vials are packaged with patient information leaflet besides them. Stability studies have shown there is no incompatibility between container materials and formulation ingredients and demonstrated packaging materials have no impact on the stability of the dosage form. Vials have been sealed with grey bromobutyl rubber stoppers and covered with aluminum caps and polypropylene preserver on the top.

5.6 Special precautions for disposal and other handling

Always use an aseptic technique

Reconstitution

• Bring the AryoSeven™ powder and water vials to room temperature (but not above 37°C). Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with the alcohol-swabs and allow them to dry before use.
• Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial.
• Drive the syringe tightly onto the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.
• Hold the syringe with the water vial upside down and pull the plunger to draw the water into the syringe.
• Remove the empty water vial by tipping the syringe.
• Click the syringe onto the powder vial. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the water into the powder vial. Make sure not to aim the stream of water directly at the AryoSeven™ powder as this will cause foaming.
• Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming. AryoSeven™ reconstituted solution is colourless and should be inspected visually for particulate matter and discoloration prior to administration.

Do not store reconstituted AryoSeven™ in plastic syringes.

It is recommended to use AryoSeven™ immediately after reconstitution.

Administration

– Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.

• Unscrew the empty vial.
• AryoSeven™ is now ready for injection. Locate a suitable site, and slowly inject AryoSeven™ into a vein over a period of 2 - 5 minutes without removing the needle from the injection site.

Safely dispose of the syringe, vials, infusion set and any unused product. Any unused product or waste material should be disposed of in accordance with local requirements.