AryoSeven™ 1.2 mg (60 KIU)

WARNINGS
Despite the increment of the thrombotic adverse events risk after treatment with ***AryoSeven*™** is considered low, but is not definitely known. Patients with predisposing coagulopathy (DIC, septicemia, crush injury, etc.) may have an increased risk of developing thrombotic events.

1. NAME OF THE PRODUCT

***AryoSeven*™** 1.2 mg (60 KIU) - powder with a solvent to prepare injectable solution.

2. PHARMACEUTICAL FORM AND COMPOSITION

***AryoSeven*™** is a powder with solvent to prepare injectable solution containing 1.2 mg eptacog alfa (activated) per vial (corresponds to 60 KIU/vial).
Eptacog alfa (activated) is recombinant coagulation factor VIIa (rFVIIa) produced by genetic engineering from baby hamster kidney cells (BHK Cells).
After reconstitution the product contains 0.6 mg/ml eptacog alfa (activated).

3. CLINICAL CHARACTERISTICS

3.1 Indications

***AryoSeven*™** is indicated for the treatment and prevention from bleeding episodes in those undergoing surgery or invasive procedures in the following patients:
• In patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU)
• In patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration
• In patients with acquired haemophilia
• In patients with congenital FVII deficiency
• In patients with Glanzmann's thrombasthenia with antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

3.2 Method of administration

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

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

Dose
***AryoSeven*™** should be administered as immediately as possible after the start of a bleeding episode. The initial dose is 90µg per kg intravenously bolus injection.
The treatment could vary according to the severity of the hemorrhage, the invasive procedures or surgery.

Dosing in children
While children have faster clearance than adults so higher doses of rFVIIa may be needed to achieve similar plasma concentrations as in adults.

Dose interval
The dose interval is 2 - 3 hours to obtain haemostasis, but it can be increased consecutively to every 4, 6, 8 or12 hours once effective haemostasis is achieved.

Mild to moderate bleeding episodes and home therapy
Early intervention is effective in the treatment of mild to moderate joint, muscle and mucocutaneous bleeds. Two dosing regimens are recommended:
1) Two to three injections of 90µg per kg administered at three-hour intervals if further treatment is required, one additional dose of 90µg per kg can be administered
2) One single injection of 270µg per kg

The duration of the home therapy should not exceed 24 hours.
There is no clinical experience with administration of a single dose of 270µg per kg in elderly patients.

Serious bleeding episodes
An initial dose of 90µg per kg is recommended to administer on the way to the hospital. The following dose varies according to the type and severity of the hemorrhage. At the beginning, the dose interval should be every 2 hours until clinical improvement is observed and it can be increased to 3 hours for 1-2 days. Thereafter, the dose interval can be increased to every 4, 6, 8 or 12 hours for as long as treatment is judged as being indicated. The treatment in major bleeding episodes is performed for 2 - 3 weeks or extended beyond this if clinically justified.

Invasive procedure/surgery
The dose of 90µg per kg should be given immediately before the intervention. It should be repeated after 2 hours and then at 2-3 hour intervals for the first 24-48 hours depending on the intervention performed and the clinical status of the patient. In major surgery, the dose should be continued at 2-4 hour intervals for 6-7 days. Then, the dose interval may be increased to 6-8 hours for another 2 weeks of treatment. Patients undergoing major surgery may be treated for up to 2-3 weeks until healing has obtained.

II. Acquired Haemophilia

Dose and dose interval
***AryoSeven*™** should be administered as immediately as possible after the start of a bleeding episode. The Initial dose is 90µg per kg intravenously bolous injection.
The treatment duration and interval between injections could vary according to the severity of the hemorrhage, the invasive procedures or the surgery being performed.
The initial dose interval should be 2-3 hours. The dose interval can be increased consecutively to every 4, 6, 8 or 12 hours for as long as treatment is determined to be indicated once haemostasis has been accessed.

III. Factor VII deficiency

Dose and dose interval
The recommended dose range for all kinds of treatment and prevention of bleeding is 15-30 µg per kg every 4-6 hours until haemostasis is achieved. Dose and frequency of injections should be adapted to each individual.

IV. Glanzmann's thrombasthenia

Dose and dose interval

The recommended dose for all kinds of treatment and prevention of bleeding is 90 µg (range 80 - 120 µg) per kg at intervals of two hours (1.5 - 2.5 hours). At least three doses should be administered to secure effective Haemostasis. The recommended route of administration is bolus injection because the efficacy may be impaired by continuous infusion.

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
- DIC

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 rFVIIa activity fails 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 indicate no adverse effects of rFVIIa on pregnancy or on the health of the fetus/new-born child, but as a cautionary measure, it is preferable to avoid using ***AryoSeven™*** during pregnancy because no relevant epidemiological data are available up to now.

Lactation
It is unknown whether rFVIIa is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with ***AryoSeven™*** should be judged between the benefit of breast-feeding to the child and the benefit of ***AryoSeven™*** therapy to the woman.

3.8 Undesirable effects
The frequencies of both serious and non-serious adverse drug reactions are listed by system organ classes in the table below.

Blood and the lymphatic system disorders	
*Rare	– DIC (Disseminated Intravascular Coagulation) and related laboratory findings including elevated levels of D-dimer and decreased levels of AT – Coagulopathy.
Vascular disorders	
Rare	– Arterial thromboembolic events (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia). – Angina pectoris
**Uncommon	– Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)
Skin and subcutaneous disorders	
Uncommon Not known	– Rash (including allergic dermatitis and rash erythematous) – Pruritus and urticaria – Flushing – Angioedema
Gastrointestinal disorders	
Rare	– Nausea.
Nervous system disorders	
Rare	– Headache.
Immune system disorders	
Rare Not known	– Hypersensitivity – Anaphylactic reaction.

General disorders and administration site conditions	
Uncommon Rare	– Therapeutic response decreased – Pyrexia – Injection site reaction including injection site pain.
Investigations	
Rare	– Increased fibrin degradation products – Increase in alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin

*Rare: (> 1/10,000, <1/1,000) **Uncommon: (> 1/1,000, < 1/100)

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 VIIa 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 VIIa 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, Glycylglycine, 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 poly propylene 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 discolouration 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.

6. MANUFACTURING BY:

AryoGen Biopharma Co.
No: 140, Corner Tajbakhsh Street, 24th Km Makhsous Road, Tehran, Iran.