AryoSeven™ (recombinant Coagulation factor VIIa)

Health Care Professional Information

Manufactured by:
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Warning: thrombosis

Serious arterial and venous thrombotic events following administration of AryoSeven™ have been reported.
Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive AryoSeven™.
Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis.

1. INDICATIONS AND USAGE

AryoSeven™, Coagulation Factor VIIa (Recombinant), is indicated for:

• Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets.
• Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia

2. DOSAGE AND ADMINISTRATION

For intravenous bolus administration only

2.1 Dose

• Treatment with AryoSeven™ should be initiated under the direction of a qualified healthcare professional experienced in the treatment of bleeding disorders.

• Use hemostasis evaluation to determine the effectiveness of AryoSeven™ and to provide a basis for modification of the AryoSeven™ treatment schedule.

• Coagulation parameters do not necessarily correlate with or predict the effectiveness of AryoSeven™.

Treatment of Acute Bleeding Episodes

AryoSeven™ dosing for the treatment of acute bleeding episodes is provided in Table 1.

Table 1: Dosing for Treatment of Acute Bleeding Episodes

Dose* and Frequency	**Duration of Therapy**	**Additional Information**
Congenital Hemophilia A or B with Inhibitors		
Hemostatic 90 mcg/kg every two hours, adjustable based on severity of bleeding Post-Hemostatic 90 mcg/kg every 3-6 hours for severe bleeds	Until hemostasis is achieved, or until the treatment has been judged to be inadequate After hemostasis is achieved to maintain the hemostatic plug	**The appropriate duration of posthemostatic dosing has not been studied**
Acquired Hemophilia		
70-90 mcg/kg every 2-3 hours	Until hemostasis is achieved	
Congenital Factor VII Deficiency		

15-30 mcg/kg every 4-6 hours	Until hemostasis is achieved	Effective treatment has been achieved with doses as low as 10 micrograms per kg body weight. Adjust dose and frequency of injections to each individual patient
Glanzmann's Thrombasthenia		
90 mcg/kg every 2-6 hours	In severe bleeding episodes requiring systemic hemostatic therapy until hemostasis is achieved	Platelet transfusions are the primary treatment in patients with Glanzmann's Thrombasthenia without refractoriness to platelets or in patients without platelet specific antibodies

* The minimum effective dose has not been determined

Congenital Hemophilia A or B with inhibitors

• Dose and administration interval may be adjusted to the individual patient based on the severity of the bleeding.[1]

• For patients treated for joint or muscle bleeds, a decision on outcome was reached for a majority of patients within eight doses although more doses were required for severe bleeds.

A majority of patients who reported adverse experiences received more than twelve doses. Monitor and minimize the duration of any post-hemostatic dosing.

Perioperative Management

AryoSeven™ dosing for prevention of bleeding in surgical interventions or invasive procedures
(Perioperative management) is provided in Table 2.

Table 2: Dosing for Perioperative Management

Type of Surgery	**Dos e and Frequency**	**Additional Information**
Congenital Hemophilia A or B with Inhibitors		
Minor	Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery Post-surgical: 90 mcg/kg every 2 hours for 48 hours then every 2-6 hours until healing occurs	
Major	Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery Post-surgical: 90 mcg/kg every 2 hours for 5 days then every 4 hours until healing occurs Additional bolus doses should be administered if required	Additional bolus doses should be administered if required
Acquired Hemophilia		

Minor or Major	70-90 mcg/kg immediately before surgery and repeat every 2-3 hours for the duration of the surgery and until hemostasis is achieved*	
Congenital Factor VII Deficiency		
Minor or Major	15-30 mcg/kg immediately before surgery and repeat every 4-6 hours for the duration of the surgery and until hemostasis is achieved	Effective treatment has been achieved with doses as low as 10 micrograms per kg body weight
Glanzmann's Thrombasthenia		
Minor or Major	Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure Post-surgical: 90 mcg/kg every 2-6 hours to prevent post-operative bleeding.	Higher average infused doses (median dose was 100 micrograms per kg (IQR 90-140)) were noted for surgical patients who had clinical refractoriness with or without platelet-specific antibodies compared to those with neither

* The minimum effective dose has not been determined.

2.2 Reconstitution

• Follow the procedures below for the preparation and reconstitution of AryoSeven™. For questions regarding reconstitution, please contact patient support at +98-021-22382641.
• Calculate the AryoSeven™ dosage and select the appropriate AryoSeven™ package provided with 1 diluent vial and one lyophilized powder vial.
Reconstitute only with the diluent provided with AryoSeven™.

AryoSeven™ package containing 1 vial of AryoSeven™ powder and 1 vial of diluent.

1. Always use aseptic technique.
2. Bring AryoSeven™ (white, lyophilized powder) and the specified volume of diluent to room temperature, but not above 8°C (46.4 ° F). The specified volume of diluent corresponding to the amount of AryoSeven™ is as follows:
1.2 mg (1200 micrograms) vial + 2.2 mL diluent
3. Remove caps from the AryoSeven™ vials to expose the central portion of the rubber stopper. Cleanse the rubber stoppers with an alcohol swab and allow to dry prior to use.

4. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe. It is recommended to use syringe needles of gauge size 20-26.

5. Insert the needle of the syringe into the diluent vial. Inject air into the vial and withdraw the quantity required for reconstitution.

6. Insert the syringe needle containing the diluent into the AryoSeven™ vial through the center of the rubber stopper, aiming the needle against the side so that the stream of liquid runs down the vial wall (the AryoSeven™ vial does not contain a vacuum). Do not inject the diluent directly on the AryoSeven™ powder.

7. Gently swirl the vial until all the material is dissolved. The reconstituted solution is a clear, colorless solution which may be stored either at room temperature or refrigerated for up to 3 hours after reconstitution. After reconstitution with the specified volume of diluent each vial contains approximately 0.6 mg per mL AryoSeven™ (600 micrograms per mL).

2.3 Administration

For intravenous bolus injection only

• Inspect the reconstituted AryoSeven™ visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is observed.

• Do not freeze reconstituted AryoSeven™ or store it in syringes.

• Administer within 3 hours after reconstitution.

• Do not mix with other infusion solutions.

• Discard any unused solution

Administer AryoSeven™ using the following procedures:

1. Administer as a slow bolus injection over 2 to 5 minutes, depending on the dose administered.

2. If line needs to be flushed before or after AryoSeven™ administration, use 0.9% Sodium Chloride

Injection,

USP.

3. Discard any unused reconstituted AryoSeven™ after 3 hours.

Administer within 3 hours after reconstitution.

Do not mix with other infusion solutions.

Discard any unused solution.

3. DOSAGE FORMS AND STRENGTHS

AryoSeven™ is available as a white lyophilized powder in single-use vials containing 1.2 mg (1200 micrograms) recombinant coagulation Factor VIIa (rFVIIa) per vial.

The diluent for reconstitution of AryoSeven™ is a water for injection. It is a clear colorless water for injection.

After reconstitution with the diluent, the final solution contains approximately 1.2 mg per mL AryoSeven™ (1200 micrograms per mL).

4. CONTRAINDICATIONS

None known.

5. WARNINGS AND PRECAUTIONS

5.1 Thrombosis

• Serious arterial and venous thrombotic events have been reported in clinical trials and Post-marketing surveillance.

• Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or non-activated prothrombin complex concentrates) and uncontrolled post-partum hemorrhage have an increased risk of developing thromboembolic events due to circulating tissue factor (TF) or predisposing coagulopathy.

• Exercise caution when administering AryoSeven™ to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with AryoSeven™ should be weighed against the risk of these complications.

• Monitor patients who receive AryoSeven™ for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, reduce the dose of AryoSeven™ or stop the treatment, depending on the patient's condition.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis have been reported with AryoSeven™. Administer AryoSeven™ only if clearly needed in patients with known hypersensitivity to AryoSeven™ or any of its components, or in patients with known hypersensitivity to mouse, hamster, or bovine proteins.

Should symptoms occur, discontinue AryoSeven™, administer appropriate treatment and weigh the benefit/risks prior to restarting treatment with AryoSeven™.

5.3 Antibody Formation in Factor VII Deficient Patients

Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of AryoSeven™. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not

controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed.

5.4 Laboratory Tests

Serious arterial and venous thrombotic events have been reported in clinical trials and post marketing surveillance.

Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or non-activated prothrombin complex concentrates) and uncontrolled post-partum hemorrhage have an increased risk of developing thromboembolic events due to circulating tissue factor (TF) or predisposing coagulopathy.

Exercise caution when administering AryoSeven™ to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, and post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with AryoSeven™ should be weighed against the risk of these complications.

Monitor patients who receive AryoSeven™ for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, reduce the dose of AryoSeven™ or stop the treatment, depending on the patient's condition.

Laboratory coagulation parameters (PT/INR, aPTT, FVII: C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII: C), may give different results with different reagents.

Treatment with AryoSeven™ has been shown to produce the following characteristics:

PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7- second plateau at a FVII: C level of approximately 5 units per mL. For FVII: C levels > 5 units per mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following AryoSeven™ administration is unknown.

INR: AryoSeven™ has demonstrated the ability to normalize INR. However, INR values have not been shown to directly predict bleeding outcomes, nor has it been possible to demonstrate the impact of AryoSeven™ on bleeding times/volume in models of clinically-induced bleeding

in healthy volunteers who had received Warfarin, when laboratory parameters (PT/INR, aPTT, thromboelastogram) have normalized.

aPTT: While administration of AryoSeven™ shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds.

FVIIa:C: FVIIa:C levels were measured two hours after AryoSeven™ administration of 35 micrograms per kg body weight and 90 micrograms per kg body weight following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 units per mL for the two dose levels, respectively.

5. ADVERSE REACTIONS

Adverse Reactions Significant

1% to 10%:

Cardiovascular: Hypertension (2%), bradycardia (1%), edema (1%), hypotension (1%)

Central nervous system: Fever (4%), headache (1%), pain (1%)

Dermatologic: Pruritus (1%), purpura (1%), rash (1%)

Gastrointestinal: Vomiting (1%)

Hematologic: Plasma fibrinogen decreased (2%), disseminated intravascular coagulation (1%), fibrinolysis increased (1%), prothrombin decreased (1%)

Local: Injection site reaction (1%)

Neuromuscular & skeletal: Arthrosis (1%)

Renal: Abnormal renal function (1%)

Respiratory: Pneumonia (1%)

Miscellaneous: Allergic reactions (1%)

<1% (Limited to important or life-threatening): Anaphylactic shock, angina, angioedema, antibody formation, arterial thrombosis, arterial thrombosis (limb), arthralgia, bowel infarction, cerebral artery occlusion, cerebral infarction and/or ischemia, consumptive coagulopathy, CVA, D-dimer elevation, deep vein thrombosis, fibrin degradation products increased, flushing, hepatic artery thrombosis, hypersensitivity, hypersensitivity reaction, injection site pain, intestinal infarction, I.V. site thrombosis, localized phlebitis, MI, myocardial ischemia, nausea, peripheral ischemia, portal vein thrombosis, pulmonary

embolism, renal artery thrombosis, retinal artery embolism, retinal artery thrombosis, shock, thrombophlebitis, thrombosis, urticaria

6. DRUG INTERACTIONS

• Avoid simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates. The risk of a potential interaction between AryoSeven™ and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies.

• Do not mix AryoSeven™ with infusion solutions.

• Thrombosis may occur if AryoSeven™ is administered concomitantly with Coagulation Factor XIII.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies using AryoSeven™ in pregnant women to determine whether there is a drug-associated risk.

In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of AryoSeven™ in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AryoSeven™ and any potential adverse effects on the breastfed infant from AryoSeven™ or from the underlying maternal condition.

9. OVERDOSAGE

Any case of overdose have not been reported.

10. DESCRIPTION

AryoSeven™, Coagulation Factor VIIa (Recombinant) is a sterile, white lyophilized powder of recombinant human coagulation factor VIIa (rFVIIa) for reconstitution for intravenous injection. The product is supplied as single use vials containing the following:

Contents 1.2 mg Vial

rFVIIa 1200

Sodium chloride

Calcium chloride dihydrate

Glycylglycine

Polysorbate

Mannitol

Sucrose

Methionine

AryoSeven™ also contains trace amounts of proteins derived from the manufacturing and purification processes such as mouse IgG (maximum of 1.2 ng/mg), bovine IgG (maximum of 30 ng/mg), and protein from BHK-cells and media (maximum of 19 ng/mg).

The diluent for reconstitution of AryoSeven™ is water for injection and is supplied as a clear colorless solution in a vial. After reconstitution with the appropriate volume of diluent, each vial contains approximately 0.6 mg/mL

AryoSeven™ (corresponding to 600 micrograms/mL). The reconstituted solution is a clear colorless solution with a pH of approximately 6.0 and contains no preservatives.

Recombinant coagulation Factor VIIa (rFVIIa), the active ingredient in AryoSeven™, is a vitamin K dependent glycoprotein consisting of 406 amino acid residues with an approximate molecular mass of 50 kDa). It is structurally similar to endogenous human coagulation factor VIIa.

The gene for human coagulation factor VII (FVII) is cloned and expressed in baby hamster kidney cells (BHK cells). Recombinant FVII is secreted into the culture media (containing newborn calf serum) in its single-chain form and then proteolytically converted by autocatalysis to the active two-chain form, rFVIIa, during a chromatographic purification process. The purification process has been demonstrated to remove exogenous viruses (MuLV, SV40, Pox virus, Reovirus, BEV, IBR virus). No human serum or other proteins are used in the production or formulation of AryoSeven™.

11. CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

AryoSeven™ is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. This process may also occur on the surface of activated platelets.

12. CLINICAL STUDIES

12.1 Hemophilia A or B with Inhibitors

The clinical trial of AryoSeven™ in hemophilia A or B patients have been performed with 66 patients. These patients were all male and aged more than 2 years. There were some inclusion criteria for choosing patients such as no history of arteriovascular disease, more than one episode of bleeding from last month and no administration of Novoseven since last year. These patients were divided in to two groups. 31 patients in AryoSeven™ arm and 35 patients in Novoseven arm treating with 90µg/kg of recombinant factor vii. The primary outcome was reducing pain and improving joint movement on Kavakli global response scoring system. Secondary outcome was increase in plasma FVII: C 20 minutes after the first injection. Treatment safety was analyzed by evaluation of adverse events reported throughout the study period.

A comparison of the Kavakli global response scores after injection and the treatment success rate in terms of achieving to score 6 or higher showed that both groups were comparable in treatment success rates (Table 3). The global treatment response rate was 96.8% in group A and 91.4% in group B. Administration of either AryoSeven™ or Novoseven had comparable effect on controlling pain and joint mobility.

Table 3.Comparison of pain and movement in two different arm according to Kavakli scoring system

	Pain	**AryoSeven™™**	**NovoSeven®**	**P-value***
1 hour	Increase No change Decrease	23 (74.19%) 1 (3.23%) 7 (22.58%)	27 (77.14%) 2 (5.71%) 6 (17.14%)	0.902
3 hours	Increase No change Decrease	21 (67.74%) 1 (3.23%) 9 (29.03%)	18 (51.43%) 0 (0%) 17 (48.57%)	0.164
6 hour	Increase No change Decrease	15 (48.39%) 2 (6.45%) 14 (45.16%)	11 (31.43%) 0 (0%) 24 (68.57%)	0.072
9 hour	Increase No change Decrease	1 (3.23%) 2 (6.45%) 28 (90.3%)	6 (17.14%) 0 (0%) 29 (82.86%)	0.060
	Mobility of bleeding joints	AryoSeven™™	NovoSeven®	P-value*
1 hour	Increase No change Decrease	29 (93.55%) 0 (0%) 2 (6.45%)	32 (91.43%) 1 (2.86%) 2 (5.7%)	1.000
3 hours	Increase No change Decrease	25 (80.65%) 0 (0%) 6 (19.35%)	23 (19.35%) 0 (0%) 12 (34.29%)	0.268
6 hour	Increase No change Decrease	7 (22.58%) 1 (3.23%) 23 (74.19%)	9 (25.71%) 1 (2.86%) 25 (71.43%)	1.000
9 hour	Increase No change Decrease	3 (9.7%) 1 (3.2%) 27 (87.1%)	6 (17.1%) 0 (0%) 29 (82.9%)	0.383

Median (IQR) plasma level of FVII clotting activity (FVII: C) in groups A and B was 103.8 + 38.4 and 98.6 + 26.7 IU/dL before injection, respectively. This results means that there is no difference between AryoSeven™ and Novoseven to increase plasma levels of Fvii.

Table 4. Plasma levels of factor VII, 20 min after the first dose of 90 µg/kg, by treatment groups

Factor VII Plasma Level	AryoSeven™™ Arm** (n=31)	NovoSeven® Arm** (n=35)	P-value
20 min post- dosing	731.43±69.55	764.002±85.42	0.772

In conclusion, AryoSeven™ is similar to Novoseven in clinical efficacy, which was evaluated by Kavakli Global Response Scoring System as well as in post-injection FVII clotting activity (FVII: C). The frequency of side effects was also similar. However, the current study was underpowered to detect differences in rare complications between the 2 drugs.

12.2 Congenital Factor VII Deficiency

A multi-center, randomized, double-blind study was performed on 66 patients with congenital factor vii deficiency. The patients were male and female more than 2 years without history of arteriovascular disease and any treatment with Novoseven since 3 months ago. All 66 patients were divided in to two groups, 35 for AryoSeven™ and 31 for Novoseven. They received 30 µg/kg/weekly recombinant factor vii for four weeks as prophylaxis and the levels of factor VII:C was evaluated 20 minutes after each injection**.**

Table 5. Distribution of plasma levels of FVII (20th percentile), 20 min after each weekly dose at 20th percentile

FVII plasma level	**AryoSeven™™ (n=35)**	**NovoSeven® Arm (n=31)**
Week 1	191	175.5
Week 2	155	166
Week 3	177	170

Week 4	172	160.4

Median IQR plasma levels of FVIIa activity (FVII:C) in groups A and B were 1.6 (1.1-14.0) IU/dL and 5.0 (1.1-25.5) IU/dL, respectively, before injection (Table 1). All patients achieved target levels of FVII:C. All patients in both the groups had levels of FVII:C >30 IU/dL, 20 minutes after rFVIIa injection; therefore, there were no treatment failures. The increased levels of FVII:C were comparable between the 2 groups.

The change in frequency of monthly bleeding episodes was also similar between the 2 groups, with a similar reduction compared to the baseline (reduction in median of bleeding frequency during the month of treatment in group A and group B was 1 [IQR: 1-2] per month, P < .626). All the results demonstrated that AryoSeven™ is biosimilar to Novoseven.

13. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AryoSeven™, Coagulation Factor VIIa (Recombinant), is supplied as a white, lyophilized powder in singleuse vials, one vial per carton. The diluent for reconstitution of AryoSeven™ is water for injection in separate vial and is supplied as a clear colorless solution. The amount of rFVIIa in micrograms is stated on the label.

14. PATIENT COUNSELING INFORMATION

- Advise patients to read the patient labeling (Instructions for Use).
- Advise patients about the early signs of hypersensitivity reactions, including hives, urticaria, and tightness of the chest, wheezing, hypotension, and anaphylaxis.
- Advise patients about the signs of thrombosis, including new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness or speech.
- Advise patients to immediately seek medical help if any of the above signs or symptoms occur.
- Advise patients to follow the recommendations in the FDA-approved patient labeling, regarding proper sharps disposal.

Patients can be advised to get in touch with OrchidPharmed Patient Support Center for any question or report any Adverse Drug event.

Phone: +982122382641

24/7 hotline: +989363094949

15. Instructions for Use

AryoSeven™

Coagulation Factor VIIa (Recombinant)

Instructions on how to use AryoSeven™

READ THESE INSTRUCTIONS CAREFULLY BEFORE USING ARYOSEVEN™.

AryoSeven™ is supplied as a powder. Before injection (administration) it must be mixed (Reconstituted) with the liquid diluent supplied in the vial. The liquid diluent water for injection.

The mixed AryoSeven™ must be injected into your vein (intravenous injection).

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads, and bandages.

Don’t use the equipment without proper training from your doctor or nurse.

Always use a clean and germ free (aseptic) technique. It is important that you wash your hands and ensure that the area around you is clean.

Don’t open the equipment until you are ready to us e it.

The equipment is for s ingle us e only.

Content

The package contains:

• Vial with AryoSeven™ powder

• Vial with water for injection

• Sterile alcohol swabs

Overview

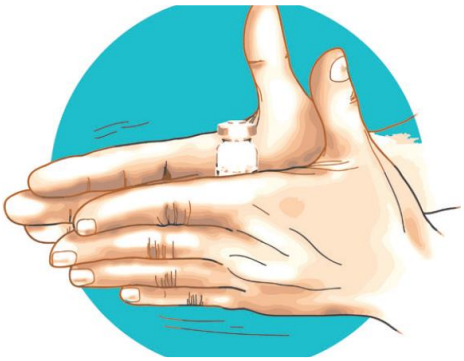
1. Prepare the vial

- Don’t use the equipment if it has been dropped, or if it is damaged. **Use a new package instead.**

- Don’t use the equipment if it is expired. **Use a new package instead. The expiration date is printed on the outer carton and on the vials**
- Don’t dispose of any of the items until after you have injected the mixed solution.

Prepare the vials

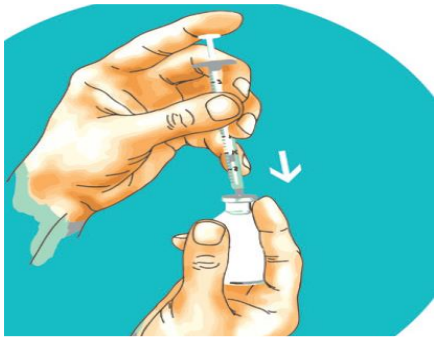
1) Take out the number of AryoSeven™ packages you need from the refrigerator. Check the expiry date.
2) Check the name and the color of the package, to make sure it contains the correct product.
3) Wash your hands and dry them properly using a clean towel or air dry.
4) Take powder vial and diluent vial between your palms to reach body temperature.



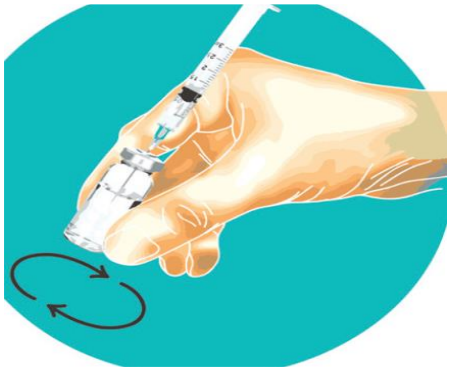
5) Swipe powder vial and diluent vial caps with sterile alcohol swab and let them dry. Then, be careful for any accidental touching these parts.

6) Prepare the appropriate syringe and put the needle inside the diluent vial and drain the solvent.

7) Enter the solvent in to powder vial carefully by pushing the diluent to the vial walls. (Do not push the solvent to powder directly)



8) For better solution, shake the vial like a circle slowly.



AryoSeven™ is recommended to be used immediately after it is mixed.

If you cannot use the mixed AryoSeven™ solution immediately, it can be kept in the vial, still with the vial at refrigerated for no longer than 3 hours.

Do not freeze mixed AryoSeven™ solution or store it in syringes.

Keep mixed AryoSeven™ solution out of direct light.

Inject the mixed solution

AryoSeven™ is now ready to inject into your vein.

• Do not mix AryoSeven™ with any other intravenous infusions or medications.

• Inject the mixed solution slowly over 2 to 5 minutes as instructed by your doctor or nurse.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or subcutaneous port:

• Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and central venous access device in consultation with your doctor or nurse.

• Injecting into a CVAD may require using a sterile 10 mL plastic syringe for withdrawal of the mixed solution and injection.

• If necessary, use 0.9% Sodium Chloride Injection, USP to flush the CVAD line before or after AryoSeven™ injection.

The peel-off label found on the AryoSeven™ vial can be used to record the lot number.

Disposal

After injection, safely dispose of the syringe with the infusion set, the vial with the vial adapter, any unused AryoSeven™ and other waste materials as instructed by your doctor or nurse.

Don’t throw it out with the ordinary household trash.

Patients can be advised to get in touch with OrchidPharmed Patient Support Center for any question or report any Adverse Drug event.

Phone: +982122382641

24/7 hotline: +989363094949