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RECOMBINATE Antihemophilic Factor (Recombinant)

Baxter

Information for Patients
RECOMBINATE
Antihemophilic Factor (Recombinant)

Pronounced: ant-eye-hee-mo-fee-lick factor

Please read this leaflet carefully before using RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF). This leaflet is based on the information provided to your doctor and is a summary of the important information you need to know about your medicine for your factor VIII deficiency. This leaflet does not take the place of talking with your doctor and does not contain all of the information available about RECOMBINATE rAHF. This summary should be used only after you have received instructions from your doctor. If you have any questions after reading this leaflet, ask your doctor or pharmacist.

1. What is RECOMBINATE rAHF?

Factor VIII (also called antihemophilic factor) is the clotting factor that people with hemophilia A are missing. Hemophilia A (classical hemophilia) is a hereditary bleeding disorder that prevents blood from clotting well. All people with hemophilia A are born with the disorder. Frequently, people with hemophilia A have a family history of the disorder. In these cases, it is passed on from mothers, who have a 50% chance with each pregnancy of passing hemophilia A on to their male children. In rare occurrences, females can also exhibit symptoms of the disorder.

RECOMBINATE rAHF is a clotting factor (factor VIII) that helps people with hemophilia A prevent and control bleeding episodes. The factor VIII protein is made in a laboratory by inserting the genetic code (DNA piece) for factor VIII into animal cells, which then produce the human coagulation factor protein. In the manufacture of RECOMBINATE rAHF, the human factor VIII is purified and separated from animal cell components. RECOMBINATE rAHF contains trace amounts of animal proteins. Albumin, a protein purified from human plasma, is included in RECOMBINATE rAHF to make the factor VIII protein more stable. RECOMBINATE rAHF has the same clot promoting effects as factor VIII protein made from human plasma and helps people with hemophilia A prevent and control bleeding episodes.

2. What is RECOMBINATE rAHF used for?

RECOMBINATE rAHF helps prevent and control bleeding in people with hemophilia A (factor VIII deficiency) by temporarily correcting the body's blood clotting process. However, you must carefully follow your doctor's or other health care provider's instructions regarding the dose and schedule for infusing RECOMBINATE rAHF in order for your RECOMBINATE rAHF treatment to work effectively. Adults and children of all ages, including newborns, may use RECOMBINATE rAHF for treatment or prevention of hemophilia A. RECOMBINATE rAHF will not work in treating other clotting disorders.

3. How does RECOMBINATE rAHF work?

RECOMBINATE rAHF temporarily raises the level of factor VIII in the blood to a more normal level, allowing your body's blood clotting process to function better. You must follow your doctor or other health care provider's instructions regarding the dose and schedule for infusing RECOMBINATE rAHF.

4. Who should not use RECOMBINATE rAHF?

You should not use RECOMBINATE rAHF unless your doctor confirms that your clotting disorder is a factor VIII deficiency. Patients with known allergies to mouse, hamster or bovine proteins should talk to their doctor before using this product. Pregnant women should use this product only if clearly needed, since it is not known whether RECOMBINATE rAHF can harm your unborn child. It is also not known if RECOMBINATE rAHF affects a woman's ability to have children. If you are considering becoming pregnant you should talk to your doctor.

5. What is the most important information I need to know about RECOMBINATE rAHF?

Your body may form inhibitors to factor VIII. An inhibitor is an antibody (part of your body's normal immune defenses) that forms against factor VIII and prevents the factor VIII from working properly. These inhibitors can lessen or eliminate your response to factor VIII therapy. This is not an uncommon complication in the treatment of people with hemophilia A. Work with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII. **Contact your doctor if you are not able to prevent or control bleeding episodes with your regular doses of prescribed factor VIII therapy.**

There is a possibility that you could have an allergic reaction to RECOMBINATE rAHF. You should be aware of early signs of allergic reactions. These included: rash, hives, itching, tightness of the chest, difficulty breathing, throat tightness, and low blood pressure. The signs and symptoms of low blood pressure can include a weak pulse, feeling lightheaded or dizzy when you stand, and possible shortness of breath. **If you experience any of these symptoms, stop the infusion immediately and contact your doctor. Severe symptoms, including difficulty breathing and (near) fainting require prompt emergency treatment.**

6. What are the possible side effects of RECOMBINATE rAHF?

The most common side effects are flushing, nausea, fever, chills, mild fatigue, nose bleeds, and hives.

7. How do I use RECOMBINATE rAHF?

RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) is injected directly into the blood stream. When you are first starting treatment you must go to a hemophilia treatment center or hospital to receive your infusions. Many people with hemophilia learn to infuse their factor by themselves or with the help of a family member. Your doctor or other health care provider can teach you the proper technique for self-infusion. Once you learn how to self-infuse, you can follow the instructions on the back of this leaflet.

8. How do I know what dose to take of RECOMBINATE rAHF?

Your doctor will prescribe a treatment regimen for you that is based on your body weight, the severity of your hemophilia, and the location and severity of bleeding. Your doctor may periodically need to check laboratory blood test results following infusion of RECOMBINATE rAHF to be sure that the blood level of active factor VIII is high enough to allow satisfactory blood clotting. If your bleeding is not controlled after infusing RECOMBINATE rAHF, contact your doctor immediately.

RECOMBINATE rAHF comes in three different strengths. The strength is designated on the outer box and on the vial label using the following color codes:

Light blue bar: For low potencies between 220-400 IU per vial.

Light pink bar: For medium potencies between 401-800 IU per vial.

Light green bar: For high potencies between 801-1240 IU per vial.

The actual potency for the lot number you are using will also be printed on the outer box and the vial label. Always check the potency printed on the label to make sure you are using the potency prescribed by your doctor. **Always check the expiration date printed on the box.**

Each vial of RECOMBINATE rAHF is for single use only. After you add the diluent to the RECOMBINATE rAHF it should be used within 3 hours. You should not refrigerate RECOMBINATE rAHF after you add the diluent. Any RECOMBINATE rAHF left in the vial at the end of your infusion should be discarded, and the infusion needle and syringe should be properly disposed of.

9. How do I store RECOMBINATE rAHF?

You may store unreconstituted RECOMBINATE rAHF (without the diluent added to it) either in the refrigerator or at normal room temperature (not to exceed 86°F). Once RECOMBINATE rAHF has been stored at room temperature, it should remain so until infused. Do not put room temperature product back in the refrigerator. DO NOT FREEZE.

You should not use the product after the expiration date printed on the box.

10. How can I find out more about Baxter's patient assistance programs?

You can call Baxter to receive more information on patient assistance programs available to you:

Reimbursement Support 1-800-548-4448
Factor Assist (insurance gap program) 1-800-888-4502
Factor Plus (indigent care program) 1-800-548-4448
Patient Notification System 1-888-873-2838
Baxter Customer Service 1-800-423-2090
Hemophilia Galaxy (www.hemophiliagalaxy.com)

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RECOMBINATE
Antihemophilic Factor (Recombinant)

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Description

RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) is a glycoprotein synthesized by a genetically engineered Chinese Hamster Ovary (CHO) cell line. In culture, the CHO cell line secretes recombinant antihemophilic factor (rAHF) into the cell culture medium. The rAHF is purified from the culture medium utilizing a series of chromatography columns. A key step in the purification process is an immunoaffinity chromatography methodology in which a purification matrix, prepared by immobilization of a monoclonal antibody directed to factor VIII, is utilized to selectively isolate the rAHF in the medium. The synthesized rAHF produced by the CHO cells has the same biological effects as Antihemophilic Factor (Human) [AHF (Human)]. Structurally the protein has a similar combination of heterogenous heavy and light chains as found in AHF (Human).

RECOMBINATE rAHF is formulated as a sterile, nonpyrogenic, off-white to faint yellow, lyophilized powder preparation of concentrated recombinant AHF for intravenous injection. RECOMBINATE rAHF is available in single-dose bottles which contain nominally 250, 500 and 1000 International Units per bottle. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximum amounts: 12.5 mg/mL Albumin (Human), 0.20 mg/mL calcium, 1.5 mg/mL polyethylene glycol (3350), 180 mEq/L sodium, 55 mM histidine, 1.5 μg/AHF International Unit (IU) polysorbate-80. Von Willebrand Factor (vWF) is coexpressed with the Antihemophilic Factor (Recombinant) and helps to stabilize it. The final product contains not more than 2 ng vWF/IU rAHF which will not have any clinically relevant effect in patients with von Willebrand's disease. The product contains no preservative.

Manufacturing of RECOMBINATE rAHF is shared by Baxter Healthcare Corporation and Wyeth BioPharma. The recombinant Antihemophilic Factor Concentrate (For Further Manufacturing Use), is produced by Baxter Healthcare Corporation and Wyeth BioPharma (For Further Manufacturing Use) and subsequently formulated and packaged at Baxter Healthcare Corporation.

Each bottle of RECOMBINATE rAHF is labeled with the AHF activity expressed in IU per bottle. Biological potency is determined by an *in vitro* assay which is referenced to the World Health Organization (WHO) International Standard for Factor VIII:C Concentrate.

Clinical Pharmacology

AHF is the specific clotting factor deficient in patients with hemophilia A (classical hemophilia). Hemophilia A is a genetic bleeding disorder characterized by hemorrhages which may occur spontaneously or after minor trauma. The administration of RECOMBINATE rAHF provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect in these patients. Pharmacokinetic studies on sixty-nine (69) patients revealed the circulating mean half-life for rAHF to be 14.6 ± 4.9 hours (n=67), which was not statistically significantly different from plasma-derived **HEMOFIL** M, Antihemophilic Factor (Human), (AHF) (pdAHF). The mean half-life of **HEMOFIL** M AHF was 14.7 ± 5.1 hours (n=61). The actual baseline recovery observed with rAHF was 123.9 ± 47.7 IU/dl (n=23) which is significantly higher than the actual **HEMOFIL** M AHF baseline recovery of 101.7 ± 31.6 IU/dl (n=61). However, the calculated ratio of actual to expected recovery with rAHF (121.2 ± 48.9%) is not different on average from **HEMOFIL** M AHF (123.4 ± 16.4%).

The clinical study of rAHF in previously treated patients (individuals with hemophilia A who had been treated with plasma derived AHF) was based on observations made on a study group of 69 patients. These individuals received cumulative amounts of Factor VIII ranging from 20,914 to 1,383,063 IU over the 48 month study. Patients were given a total of 17,700 infusions totaling 28,090,769 IU rAHF.

These patients were successfully treated for bleeding episodes on a demand basis and also for the prevention of bleeds (prophylaxis). Spontaneous bleeding episodes successfully managed include hemarthroses, soft tissue and muscle bleeds. Management of hemostasis was also evaluated in surgeries. A total of 24 procedures on 13 patients were performed during this study. These included minor (e.g. tooth extraction) and major (e.g. bilateral osteotomies, thoracotomy and liver transplant) procedures. Hemostasis was maintained perioperatively and postoperatively with individualized AHF replacement.

A study of rAHF in previously untreated patients was also performed as part of an ongoing study. The study group was comprised of seventy-nine (79) patients, of whom seventy-six (76) had received at least one infusion of rAHF. To date, this cohort has been given 12,209 infusions totaling over 11,277,043 IU rAHF. Hemostasis was appropriately managed in spontaneous bleeding episodes, intracranial hemorrhage and surgical procedures.

Indications and Usage

The use of RECOMBINATE rAHF is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.[1] RECOMBINATE rAHF is also indicated in the perioperative management of patients with hemophilia A (classical hemophilia).

RECOMBINATE rAHF can be of therapeutic value in patients with acquired AHF inhibitors not exceeding 10 Bethesda Units per mL[2]. In clinical studies with RECOMBINATE rAHF, patients with inhibitors who were entered into the previously treated patient trial and those previously untreated children who have developed inhibitor activity on study, showed clinical hemostatic response when the titer of inhibitor was less than 10 Bethesda Units per mL. However, in such uses, the dosage of RECOMBINATE rAHF should be controlled by frequent laboratory determinations of circulating AHF levels.

RECOMBINATE rAHF is not indicated in von Willebrand's disease.

Contraindications

Known hypersensitivity to mouse, hamster or bovine protein may be a contraindication to the use of Antihemophilic Factor (Recombinant) (see **Precautions**).

Warnings

None.

Precautions

General

Certain components used in the packaging of this product contain natural rubber latex.

Identification of the clotting defect as a Factor VIII deficiency is essential before the administration of RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) is initiated. No benefit may be expected from this product in treating other deficiencies.

The formation of neutralizing antibodies, inhibitors to factor VIII, is a known complication in the management of individuals with hemophilia A. The reported prevalence of these antibodies in patients receiving plasma derived AHF is 10-20%[3-7, 10-12]. These inhibitors are invariably IgG immunoglobulins, the factor VIII procoagulant inhibitory activity of which is expressed as Bethesda Units (B.U.) per mL of plasma or serum[3-7]. Over the investigational period, none of the 69 previously treated individuals, without an inhibitor at entry into the study, developed an inhibitor. In the previously untreated patient group there were 73 eligible patients with factor VIII levels less than or equal to 2% who received at least one rAHF treatment (median days 100, range 3-821) and who were tested for inhibitor after treatment with RECOMBINATE rAHF. Of this group, 23 individuals developed detectable inhibitor (median days 10, range 3-69) and of these, 8 patients showed a titer greater than 10 B.U. Patients treated with rAHF should be carefully monitored for the development of antibodies to rAHF by appropriate clinical observations and laboratory tests.

Formation of Antibodies to Mouse, Hamster or Bovine Protein

As RECOMBINATE rAHF contains trace amounts of mouse protein (maximum of 0.1 ng/IU rAHF), hamster protein (maximum of 1.5 ng CHO protein/IU rAHF), and bovine protein (maximum of 1 ng BSA/IU rAHF), the remote possibility exists that patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

Information for Patients

The patient and physician should discuss the risks and benefits of this product.

Although allergic type hypersensitivity reactions were not observed in any patient receiving RECOMBINATE rAHF on study, such reactions are theoretically possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician if these symptoms occur.

Laboratory Tests

Although dosage can be estimated by the calculations which follow, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

If the patient's plasma AHF fails to reach expected levels or if bleeding is not controlled after adequate dosage, the presence of inhibitor should be suspected. By performing appropriate laboratory procedures, the presence of an inhibitor can be demonstrated and quantified in terms of AHF International Units neutralized by each mL of plasma or by the total estimated plasma volume. If the inhibitor is present at levels less than 10 Bethesda Units per mL, administration of additional AHF may neutralize the inhibitor. Thereafter, the administration of additional AHF International Units should elicit the predicted response. The control of AHF levels by laboratory assay is necessary in this situation.

Inhibitor titers above 10 Bethesda Units per mL may make hemostasis control with AHF either impossible or impractical because of the very large dose required. In addition, the inhibitor titer may rise following AHF infusion because of an anamnestic response to the AHF antigen.

Carcinogenesis, Mutagenesis, Impairment of Fertility

RECOMBINATE rAHF was tested for mutagenicity at doses considerably exceeding plasma concentrations of rAHF *in vitro* and at doses up to ten times the expected maximum clinical dose *in vivo*, and did not cause reverse mutations, chromosomal aberrations, or an increase in micronuclei in bone marrow polychromatic erythrocytes. Long term studies in animals have not been performed to evaluate carcinogenic potential.

Pediatric Use

RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) is appropriate for use in children of all ages, including the newborn. Safety and efficacy studies have been performed in both previously treated (n=23) and previously untreated (n=75) children. (See **Clinical Pharmacology** and **Precautions).**

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Antihemophilic Factor (Recombinant). It is not known whether Antihemophilic Factor (Recombinant) can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Antihemophilic Factor (Recombinant) should be given to a pregnant woman only if clearly needed.

Adverse Reactions

During the clinical studies conducted in the previously treated patient group, there were 13 infusion related minor adverse reactions reported out of 10,446 infusions (0.12%). One patient experienced flushing and nausea during his first infusion which abated on decreasing the infusion rate. A second patient experienced mild fatigue during and following one infusion and a third patient had a series of eleven nose bleeds with a periodicity associated with the infusions.

The protein in greatest concentration in RECOMBINATE rAHF is Albumin (Human). Reactions associated with intravenous administration of albumin are extremely rare, although nausea, fever, chills or urticaria have been reported. Other allergic reactions could theoretically be encountered in the use of this Antihemophilic Factor preparation. (See **Information for Patients**)

Dosage and Administration

Each bottle of RECOMBINATE rAHF is labeled with the AHF activity expressed in IU per bottle. This potency assignment is referenced to the World Health Organization International Standard for Factor VIII:C Concentrate and is evaluated by appropriate methodology to ensure accuracy of the results.

The expected *in vivo* peak increase in AHF level expressed as IU/dL of plasma or % (percent) of normal can be estimated by multiplying the dose administered per kg body weight (IU/kg) by two. This calculation is based on the clinical findings of Abildgaard *et al*[8] and is supported by the data generated by 419 clinical pharmacokinetic studies with rAHF in 67 patients over time. This pharmacokinetic data demonstrated a peak recovery point above the pre-infusion baseline of approximately 2.0 IU/dL per IU/kg body weight.

Example (Assuming patient's baseline AHF level is at <1%):

(1) A dose of 1750 IU AHF administered to a 70 kg patient, *i.e.* 25 IU/kg (1750/70), should be expected to cause a peak post-infusion AHF increase of 25 x 2 = 50 IU/dL (50% of normal).

(2) A peak level of 70% is required in a 40 kg child. In this situation the dose would be 70/2 x 40 = 1400 IU.

Recommended Dosage Schedule

Physician supervision of the dosage is required. The following dosage schedule may be used as a guide.

Hemorrhage		
Degree of hemorrhage	**Required peak post-infusion AHF activity in the blood (as % of normal or IU/dL plasma)**	**Frequency of infusion**
Early hemarthrosis or muscle bleed or oral bleed	20-40	Begin infusion every 12 to 24 hours for one-three days until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleed, or hematoma	30-60	Repeat infusion every 12 to 24 hours for usually three days or more until pain and disability are resolved.
Life threatening bleeds such as head injury, throat bleed, severe abdominal pain	60-100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Type of operation		
Minor surgery, including tooth extraction	60-80	A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases.
Major surgery	80-100 (pre-and post-operative)	Repeat infusion every 8 to 24 hours depending on state of healing.

The careful control of the substitution therapy is especially important in cases of major surgery or life threatening hemorrhages. Although dosage can be estimated by the calculations above, it is strongly recommended that whenever possible, appropriate laboratory tests including serial AHF assays be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

Other dosage regimens have been proposed such as that of Schimpf, *et al*, which describes continuous maintenance therapy.[9]

Reconstitution: Use Aseptic Technique

1. Bring RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) (dry concentrate) and Sterile Water for Injection, USP, (diluent) to room temperature.
2. Remove caps from concentrate and diluent bottles.
3. Cleanse stoppers with germicidal solution and allow to dry prior to use.
4. Remove protective covering from one end of double-ended needle and insert exposed needle through the center of the stopper.
5. Remove protective covering from other end of double-ended needle. Invert diluent bottle over the upright RECOMBINATE rAHF bottle, then rapidly insert free end of the needle through the RECOMBINATE rAHF bottle stopper at its center. The vacuum in the bottle will draw in the diluent.
6. Disconnect the two bottles by removing needle from diluent bottle stopper, then remove needle from RECOMBINATE rAHF bottle. Swirl gently until all material is dissolved. Be sure that RECOMBINATE rAHF is completely dissolved, otherwise active material will be removed by the filter needle.

NOTE: Do not refrigerate after reconstitution. (See **Administration)**

Administration: Use Aseptic Technique

Administer at room temperature.

RECOMBINATE rAHF should be administered not more than 3 hours after reconstitution.

Intravenous Syringe Injection

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. A colorless to faint yellow appearance is acceptable for RECOMBINATE rAHF.

Plastic syringes are recommended for use with this product since proteins such as AHF tend to stick to the surface of all-glass syringes.

1. Attach filter needle to a disposable syringe and draw back plunger to admit air into the syringe.
2. Insert the needle into reconstituted RECOMBINATE rAHF.
3. Inject air into bottle and then withdraw the reconstituted material into the syringe.
4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under **Rate of Administration**.
5. If a patient is to receive more than one bottle of RECOMBINATE rAHF, the contents of multiple bottles may be drawn into the same syringe by drawing up each bottle through a separate unused filter needle. Filter needles are intended to filter the contents of a single bottle of RECOMBINATE rAHF only.

Rate of Administration

Preparations of RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) can be administered at a rate of up to 10 mL per minute with no significant reactions.

The pulse rate should be determined before and during administration of RECOMBINATE rAHF. Should a significant increase in pulse rate occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

How Supplied

RECOMBINATE rAHF is available in three different strengths in single-dose bottles. The strength is designated on the outer box and on the vial label using the following color codes:

Light blue bar: For low potencies between 220-400 IU per vial (NDC 0944-2938-01)
Light pink bar: For medium potencies between 401-800 IU per vial (NDC 0944-2938-02)
Light green bar: For high potencies between 801-1240 IU per vial (NDC 0944-2938-03)

RECOMBINATE rAHF is packaged with 10 mL of Sterile Water for Injection, USP, a double-ended needle, a filter needle, one physician insert and one patient insert.

Storage

RECOMBINATE rAHF can be stored under refrigeration [2° - 8°C (36° - 46°F)] or at room temperature, not to exceed 30°C (86°F). Avoid freezing to prevent damage to the diluent bottle. Do not use beyond the expiration date printed on the box.

References

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To enroll in the confidential, industry-wide Patient Notification System, call 1-888-UPDATE U (1-888-873-2838).

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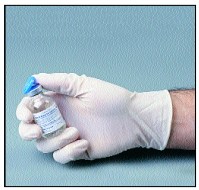
RECOMBINATE
Antihemophilic Factor (Recombinant)
(For intravenous use only)

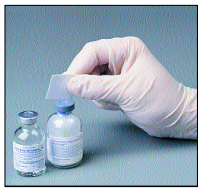
1

In a quiet place, prepare a clean surface. Let the bottle with the FVIII concentrate and the Sterile Water for Injection (diluent) warm up to room temperature.



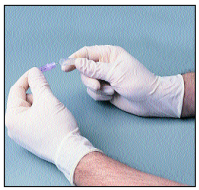
2

After washing your hands and putting on sterile gloves, remove caps from the concentrate and diluent bottles to expose the centers of the rubber stoppers.



3

Disinfect the stoppers with an alcohol swab or other suitable solution suggested by your doctor or hemophilia center.

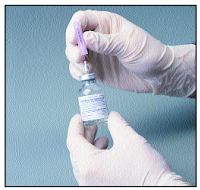


4

Remove the protective covering from one end of the double-ended transfer needle.

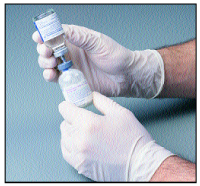
5

Insert the exposed short part of the needle through the diluent stopper.



6

Remove the protective covering from the other end of the double-ended transfer needle.

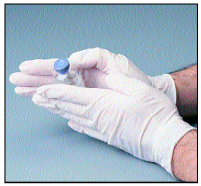


7

Insert the free end of the needle through the concentrate bottle stopper at its center. The vacuum in the bottle will draw in the diluent. Invert the diluent bottle over the upright concentrate bottle.

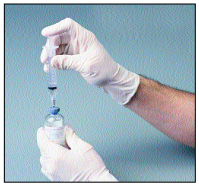
8

Disconnect the two bottles by removing the needle from the diluent bottle stopper, then remove the needle from the concentrate bottle. Do not recap the needle! Place the needle in a hard-walled Sharps container for proper disposal.



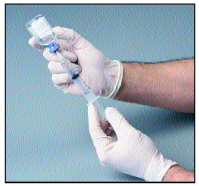
9

Gently roll the vial between palms until all material is dissolved. **Do not shake.** Check to make sure the product is completely dissolved.



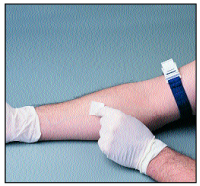
10

Attach filter needle to a disposable syringe and draw back the plunger to allow air into the syringe. Insert the needle into the reconstituted FVIII concentrate. Inject air into the bottle.



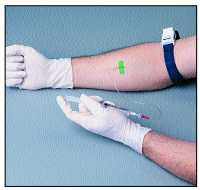
11

Withdraw the solution into the syringe.



12

Prepare the injection site by wiping with an alcohol swab or other suitable solution suggested by your doctor or hemophilia center.



13

Do not infuse the product any faster than 10 mL per minute. Use a winged infusion set if available. After infusion, apply pressure with sterile gauze to the infusion site for 3 minutes. Do not recap the needle after infusion. Place it with the used syringe in a hard-walled Sharps container for proper disposal.

14

After infusion, remove peel-off label from the concentrate bottle and place it in your factor log. Clean up any spilled blood with freshly prepared 10% bleach solution or soap and water.

IMPORTANT: Contact your doctor or local Hemophilia Treatment Center if you experience any problems. These instructions are intended as a visual aid only for those patients who have been instructed by their doctor or hemophilia center on the proper way to self-infuse the product. If you have not been taught by your doctor, do not attempt to self-infuse.