Part IB Labeling

IB:1 Annotated Package Insert

This section contains the annotated version of the proposed text of the ReFacto package insert. Please note that the list of supporting documentation intentionally does not contain references to Part I, Vol. 2 (Section IC), which consists of expert reports and tabulated summaries concerning the entire dossier.

		Location of Supporting Documentation
ReFacto **Antihemophilic Factor, Recombinant**		
DESCRIPTION		
ReFacto® Antihemophilic Factor (Recombinant) is a purified protein produced by recombinant DNA technology for use in therapy of factor VIII deficiency. ReFacto is a glycoprotein with an approximate molecular mass of 170 kDa consisting of 1438 amino acids. It has an amino acid sequence that is comparable to the 90 + 80 kDa form of factor VIII, and post-translational modifications that are similar to those of the plasma-derived molecule. ReFacto has *in vitro* functional characteristics comparable to those of endogenous factor VIII.	(Ref 1): (Ref 2):	Part II, Vol. 1, Section IIC:1.3 SQ is no longer used to describe ReFacto. Part II, Vol. 2, Section IIC:1.6
ReFacto is produced by a genetically engineered Chinese hamster ovary (CHO) cell line. The CHO cell line secretes B-domain deleted recombinant factor VIII into a defined cell culture medium that contains human serum albumin and recombinant insulin, but does not contain any proteins derived from animal sources. The protein is purified by a	(Ref 3): (Ref 4): (Ref 5): (Ref 6): (Ref 7):	Part II, Vol. 1, Section IIB:1 Part II, Vol. 1, Section IIC:1.3 Part II, Vol. 1, Section IIC:1.5.1 Part II, Vol. 1, Section IIC:1.5.2 Part II, Vol. 2, Section IIC:1.6.8

chromatography purification process that yields a high-purity, active product. The potency expressed in international units (IU) is determined using the European Pharmacopoeial chromogenic assay against the WHO standard. The specific activity of ReFacto is 11,200-15,500 IU per milligram of protein. ReFacto is not purified from human blood and contains no preservatives or added ~~animal or~~ human components in the final formulation.

(Ref 8): Part II, Vol. 4, Sections IIE:1 & IIE:2

ReFacto is formulated as a sterile, nonpyrogenic, lyophilized powder preparation for intravenous (IV) injection. It is available in single-use vials containing the labeled amount of factor VIII activity (IU). Each vial contains nominally 250, 500, or 1000 IU of ReFacto per vial. The formulated product is a clear colorless solution upon reconstitution and contains sodium chloride, sucrose, L-histidine, calcium chloride, and polysorbate 80.

(Ref 9): Part II, Vol. 1, Section IIA:1.1

(Ref 10): Part II, Vol. 1, Sections IIB:1 & IIB:2

CLINICAL PHARMACOLOGY

Factor VIII is the specific clotting factor deficient in patients with hemophilia A (classical hemophilia). The administration of ReFacto® Antihemophilic Factor (Recombinant) increases plasma levels of factor VIII activity and can temporarily correct the *in vitro* coagulation defect in these patients.

(Ref 11): Part IV, Vols. 1-2

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

(Ref 12): Part IV, Vols. 1-2

then converts fibrinogen into fibrin and a clot is formed. Factor VIII activity is greatly reduced in patients with hemophilia A and therefore replacement therapy is necessary.

In a crossover pharmacokinetic study of eighteen (18) previously treated patients **using the chromogenic assay**, the circulating mean half-life for ReFacto was 14.5 ± 5.3 hours (ranged from 7.6-27.7 hours), which was not statistically significantly different from plasma-derived Antihemophilic Factor (Human), (pdAHF), which had a mean half-life of 13.7 ± 3.4 hours (ranged from 8.8-23.7 hours). Mean incremental recovery (K-value) of ReFacto in plasma was 2.4 ± 0.4 IU/dL per IU/kg (ranged from 1.9 - 3.3 IU/dL per IU/kg). This was comparable to the mean incremental recovery observed in plasma for pdAHF which was 2.3 ± 0.3 IU/dL per IU/kg (ranged from 1.7 - 2.9 IU/dL per IU/kg). **Results obtained from this controlled, pharmacokinetic study, which used a central laboratory for the analysis of all plasma samples, showed that the one-stage factor VIII clotting assay gave results which were approximately 50% of the values obtained with the chromogenic assay.**

(Ref 13): Part IV, Vols. 1-4
In the original PK report plasma VIII:C values were corrected for the dilution caused by the volume of sodium citrate (0.5 mL) present in the tubes for collection of blood (4.5 mL). It is common practice to calculate the values without correcting for the citrate dilution. Therefore, the half-life, incremental recovery (K-value, IU/dL increase in FVIII:C per IU/kg FVIII given) and in vivo recovery (%) data have been re-calculated without correcting for the citrate dilution using the raw data included in BLA 98-0137.000, PartIV: Vol 4, Appendix I: *Plasma Concentrations of FVIII:C.*

The small variation in half-life occurred due to the reanalysis of the data after elimination of adjustment for citrate dilution, and because in the BLA, dosing was calculated based on actual potency. The recalculations are based on nominal potency.

In two additional clinical studies, pharmacokinetic parameters were evaluated for previously treated patients [PTPs] and previously untreated patients [PUPs]. In PTPs (n=87), ReFacto had a mean incremental recovery of 2.4 ± 0.4 IU/dL per IU/kg (ranged from 1.1-3.8 IU/dL per IU/kg) and an elimination half-life (n=67) of 10.7 ± 2.8 hours. In PUPs (n=45), ReFacto had a lower mean

(Ref 14): Part IV, Vols. 1-2, 5-27
As explained above, half-life and recovery values were recalculated eliminating the adjustment for citrate dilution. Raw data for PTPs is located in BLA 98-0137, Part IV: Vol 11, Appendix K: *Laboratory Efficacy.* Patient numbers 07101, 07102, 07103, 25101, 25102, 25103, and 25202 were not included in the

incremental recovery of 1.7 ± 0.4 IU/dL per IU/kg (ranged from 0.2-2.8 IU/dL per IU/kg) as compared to PTPs. Population pharmacokinetic modeling using data from 44 PUPs led to a mean estimated half-life of ReFacto in PUPs of 8.0 ± 2.2 hours. These parameters did not change over time (12 months) for PTPs or PUPs.

recalculated data set because the data was gathered during studies not described in the BLA. Patient numbers 12109, 12301, 12303, and 14010, not included in the BLA evaluation because of "High pre-injection levels", were included in the recalculated data set.
Raw data for PUPs is located in Part IV: Vol 23, Appendix M: *Pharmacokinetic Determinations and Analysis*. Patient numbers 15931 and 22536 were excluded from the BLA evaluations because of perceived assay deviations, but were included in the recalculated data set. Patient numbers 37331, 42131, and 44131 were excluded from the recalculated data set because the first sample was taken more than 1 hour post-infusion or because of missing dosing information.
See GI FAX to FDA dated 2/25/00.
PK evaluation was not continued beyond 12 months.

In clinical studies of ReFacto involving a total of 218 patients (117 PTPs including 4 who participated in the surgery study only, and 101 PUPs), more than 84 million IU were administered over a period of up to 54 months. The 117 PTPs were given a median of 230 injections (range of 4-1530 injections) over a median of 1200 days (range of 31-1640 days). The 101 PUPs were given a median of 26 injections (range of 1-490 injections) over a median of 830 days (range of 1 - 1298 days). One-hundred-thirteen PTPs and 99 PUPs were evaluated for efficacy in bleeding episodes. The 113 PTPs experienced a median of 54 bleeding episodes and the 99 PUPs experienced a median of 12

BLA 98-0137.015, Vol 2, pg 16, 23, 24, 25, 26, 30, 31, Table 4.1-5

BLA 98-0137.016, Vol 1, pg 69

bleeding episodes. All were treated successfully on an on-demand basis or for the reduction of bleeding episodes except for one PTP and two PUPs who discontinued ReFacto treatment and switched to another product after the development of inhibitors. Bleeding episodes included hemarthroses, and bleeding in soft tissue, muscle, and other anatomical sites.

(Table 10-2), 206, 210.

BLA 98-0137.028

Clinical Study Report, May 6, 1999, PTP, PUP, Surgery Safety Experience Update, submitted in BLA 98-0137.015 May 13, 1999.
IND 5348.090, submitted January 31, 2000

ReFacto has been studied in short-term routine prophylaxis. In uncontrolled clinical trials, an average dose of 27±10 IU/kg in PTPs (n=77) and an average dose of 57±20 IU/kg in PUPs (n=17) was given repeatedly at variable intervals longer than 2 weeks. In 64 patients who had both "on demand" and prophylactic periods during their time on study, the mean rate of spontaneous musculoskeletal bleeding episodes was less during periods of routine prophylaxis. There were an average of 10 bleeding episodes per year during the prophylactic periods compared to an average of 37 bleeding episodes per year during the "on demand" periods. The clinical trial experience with routine prophylaxis in PUPs is limited (n=17). These non-randomized trial results should be interpreted with caution, as the investigators exercised their own discretion in deciding when and in whom prophylaxis was to be initiated and terminated.

See revised Table 1-1 appended to BLA 98-0137.036.

Management of hemostasis was evaluated in the surgical setting where 28 surgical procedures have been performed in 25 patients. The average preoperative dose in PTPs was 59 IU/kg. Procedures included orthopedic procedures, inguinal

(Ref 16): Part IV, Vols 1-2, 5-17, 28-38

Typo corrected in BLA 98-0137.005

hernia repair, epidural hematoma evacuation, transposition ulnar nerve, and other minor procedures (e.g., venous access catheter placement and explantation, toenail removal). Circulatory factor VIII levels targeted to restore and maintain hemostasis were achieved. While the one-stage clotting assay was used most frequently in the surgical setting (24 versus 4 surgeries), hemostasis was maintained throughout the surgical period regardless of which assay was used. Hemostatic efficacy was rated as excellent or good in all procedures.

BLA 98-0137.005

Part IV, Vol 1, pg 252

The occurrence of neutralizing antibody (inhibitors) is well known in the treatment of patients with hemophilia A[1,2,3]. Thirty out of 101 PUPs (30%) developed an inhibitor: 16 out of 101 (16%) with a high titer (≥ 5 B. U.) (11 of the 16 patients had peak values ≥10 BU/mL) and 14 out of 101(14%) with a low titer (< 5 B. U.). In this study the incidence of inhibitor development to factor VIII using ReFacto is similar to that reported for other factor VIII products[1,2,3,5].

(Ref 17): Part IV, Vols. 1-38

Clinical Study Report, May 6, 1999, PTP, PUP, Surgery Safety Experience Update, pg.2. Submitted in BLA 98-0137.015 May 13, 1999.

One of 113 PTPs (0.9%) developed a low titer inhibitor after 107 exposure days with ReFacto. In this study the incidence of inhibitor development to factor VIII using ReFacto is similar to that reported for other factor VIII products[4].

(Ref 18): Part IV, Vols. 1-2, 28-38
BLA 98-0137.015 Clinical Study Report, May 6, 1999, PTP, PUP, Surgery Safety Experience Update, pg.2.

INDICATIONS AND USAGE

ReFacto® Antihemophilic Factor (Recombinant) is indicated for the control and prevention of hemorrhagic episodes and for surgical prophylaxis in patients

(Ref 19): Part IV, Vols. 1-38

with hemophilia A (congenital factor VIII deficiency or classic hemophilia).

ReFacto is indicated for short-term routine prophylaxis to reduce the frequency of spontaneous bleeding episodes. The effect of regular routine prophylaxis on long-term morbidity and mortality is unknown.

ReFacto can be of a significant therapeutic value for treatment of Hemophilia A in certain patients with inhibitors to factor VIII[6]. In clinical studies of ReFacto, patients who developed inhibitors on study continued to manifest a clinical response when inhibitor titers were < 10 BU/mL. When an inhibitor is present, the dosage requirement of factor VIII is variable. The dosage can be determined only by a clinical response and by monitoring of circulating factor VIII levels after treatment (see **DOSAGE and ADMINISTRATION**).

ReFacto does not contain von Willebrand factor and therefore is not indicated in von Willebrand's disease.

CONTRAINDICATIONS

Known hypersensitivity to mouse, hamster, or bovine proteins may be a contraindication to the use of ReFacto® Antihemophilic Factor (Recombinant).

WARNINGS

As with any intravenous protein product, allergic type hypersensitivity reactions are 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 physicians if these symptoms occur.

PRECAUTIONS

General

(Ref 20): Part IV, Vols. 1-38

Activity-neutralizing antibodies (inhibitors) have been detected in patients receiving factor VIII-containing products. There is no evidence that ReFacto® Antihemophilic Factor (Recombinant) is associated with a higher-than-historical incidence of inhibitors. As with all coagulation factor VIII products, patients should be monitored for the development of inhibitors that should be titrated in Bethesda Units using appropriate biological testing.

Formation of Antibodies to Mouse and Hamster Protein

As Antihemophilic Factor (Recombinant), ReFacto contains trace amounts of mouse protein (maximum of 5 ng/1000 IU) and hamster protein (maximum of 30 ng/1000 IU), the remote possibility exists that patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

Carcinogenicity, Mutagenicity, Impairment of Fertility

(Ref 21): Part III, Vol. 1, Section IIID

(Ref 22): Part III, Vol. 3, Kabi Pharmacia Report 9296824

ReFacto® Antihemophilic Factor (Recombinant) has been shown to be nonmutagenic in the mouse micronucleus

assay. No other mutagenicity studies and no investigations on carcinogenesis or impairment of fertility have been conducted.

Pregnancy Category C

Animal reproduction and lactation studies have not been conducted with ReFacto® Antihemophilic Factor (Recombinant). It is not known whether ReFacto can affect reproductive capacity or cause fetal harm when given to pregnant women. ReFacto should be administered to pregnant and lactating women only if clearly indicated.

Pediatric Use (Ref 23): Part IV, Vols. 1-38

ReFacto® Antihemophilic Factor (Recombinant) is appropriate for use in children of all ages, including newborns. Safety and efficacy studies have been performed both in previously treated children and adolescents (N=22, ages 8-15 years) and in previously untreated neonates, infants, and children (N=101, ages 0-52 months) (see **Clinical Pharmacology and Precautions**).

BLA 98-0137.015, Appendix E.

Age = 15 years and under.

Geriatric Use

Clinical studies of ReFacto did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. As with any patient receiving ReFacto, dose selection for an elderly patient should be individualized

Proposed language is based on FDA standard language from 21 CFR 201.57. Last sentence is replaced with language proposed by GI as more appropriate for ReFacto.

ADVERSE REACTIONS (Ref 24): Part IV: Vols. 1-38

As with the intravenous administration of any protein product, the following reactions may be observed after administration: headache, fever, chills, flushing, nausea, vomiting, lethargy, or manifestations of allergic reactions. During clinical studies with ReFacto® Antihemophilic Factor (Recombinant), 77 adverse reactions in 43 of 218 patients (20%) probably or possibly-related to therapy were reported for 64,363 infusions (0.12%). These were anaphylaxis (1), dyspnea (6), urticaria (1), nausea (11), headache (4), vasodilation (5), dizziness (4), permanent venous access catheter complications (3), asthenia (3), fever (3), taste perversion [altered taste] (3), bleeding/hematoma (3), infected hematoma (1), anorexia (2), diarrhea (2), injection site reaction (2), somnolence (2), rash (2), pruritus (2), angina pectoris (1), tachycardia (1), perspiration increased (1), chills (1), increased amino transferase (1), increased bilirubin (1), pain in finger (1), muscle weakness (1), CPK increase (1), cold sensation (1), eye disorder-vision abnormal (1), coughing (1), myalgia (1), gastroenteritis (1), abdominal pain (1), acne (1), and forehead bruises (1). If any adverse reaction takes place that is thought to be related to administration of ReFacto, the rate of infusion should be decreased or stopped.

In addition, inhibitor development is a known adverse event associated with the treatment of patients with hemophilia A (See CLINICAL PHARMACOLOGY).

A total of 182 adverse reactions in 54 of 218 patients (25%) who received 32,013 infusions (0.6%) were reported by the investigator to have an "unlikely" or "not

BLA 98-0137.015 Vol. 2, pg. 87

Terminology revised:
Fatigue = asthenia
Paresthesia = vasodilation (incorrectly coded)
Gastritis = abdominal pain
Moniliasis = not related, deleted
Slight CK-MB elevation = CPK increase

Revised numbers based on updates to the July 1998 data set. See BB-IND 5348.090: Annual report submitted January 31, 2000.

Vesiculobullous rash has been coded as rash. Actual description is "single pimple at injection site".

BLA 98-0137.029, submitted

assessable" relationship to ReFacto administration. The study sponsor considered that the events may be of possible or of unknown relationship to therapy because of the temporal relationship to the infusion and/or the frequency of the event for a given patient and/or because insufficient information was available to assign another causality. In this category, 25 patients experienced the following 38 events which are different from the events described above: pain (10), rhinitis (10), vomiting (4), insomnia (3), constipation (2), pharyngitis (2), flushing (1), palpitation (1), sinusitis (1), gastritis (1), dyspepsia (1), hypotension (1), and URI (1).

November 17, 1999, Questions 1 and 3.

Other adverse experiences that were reported during the clinical trials, but which were assessed by both the investigator and the sponsor as "unlikely" to be related to ReFacto administration included: dyspnea (3), rash (2), pruritus (1), neuropathy (1), arm weakness (1), ~~possible hepatitis A seroconversion (1-2)~~, and thrombophlebitis of upper arm (1).

BB-IND 5348.090 Annual Report submitted 1/31/00.

DOSAGE AND ADMINISTRATION

[The reference that immediately follows applies to the entire "Dosage and Administration" section]

Treatment with ReFacto® Antihemophilic Factor (Recombinant) should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.

(Ref 25): Part IV, Vols. 1-38

Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Doses administered should be titrated to the patient's clinical response.

In the presence of an inhibitor, higher doses may be required.

One international unit (IU) of factor VIII activity corresponds approximately to the quantity of factor VIII in one mL of normal human plasma. The calculation of the required dosage of factor VIII is based upon the empirical finding that, on average, 1 IU of factor VIII per kg body weight raises the plasma factor VIII activity by approximately 2 IU/dL per IU/kg administered. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 IU/kg per IU/dL

Corrected units.

The following chart can be used to guide dosing in bleeding episodes and surgery:

Type of Hemorrhage	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (h)/ Duration of Therapy (d)
Minor		
Early hemarthrosis, minor muscle or oral bleeds	20–40	Repeat every 12 to 24 hours as necessary until resolved. At least 1 day, depending upon the severity of the hemorrhage.
Moderate		
Hemorrhages into muscles. Mild trauma capitis. Minor operations including tooth extraction. Hemorrhages into the oral cavity.	30–60	Repeat infusion every 12–24 hours for 3–4 days or until adequate local hemostasis is achieved. For tooth extraction a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient.
Major		
Gastrointestinal bleeding. Intracranial, intraabdominal or intrathoracic hemorrhages. Fractures. Major operations	60–100	Repeat infusion every 8–24 hours until threat is resolved or in the case of surgery, until adequate local hemostasis is achieved.

Precise monitoring of the replacement therapy by means of coagulation analysis (plasma factor VIII activity) is recommended, particularly for surgical intervention.

Paragraph bolded at FDA request.

Product is labeled on the basis of the chromogenic assay. The available clinical trial data suggest either the one-stage clotting assay or the chromogenic assay may be used to help follow patients clinically. Most clinical trial subjects were monitored with the one-stage clotting assay. It must be noted that the one-stage clotting assay yields results which are lower than the values obtained with the chromogenic assay (see **CLINICAL PHARMACOLOGY**).

BLA 98-0137.028

For short-term routine prophylaxis to prevent or reduce the frequency of spontaneous musculoskeletal hemorrhage in patients with hemophilia A, ReFacto should be given at least twice a week. In some cases, especially pediatric patients, shorter dosage intervals or higher doses may be necessary.
Pharmacokinetic/pharmacodynamic modeling, based on pharmacokinetic data from 185 infusions in 102 PTPs, predicts that routine prophylactic dosing 3 times per week may be associated with a lower bleeding risk than with dosing twice weekly. No randomized comparison of different doses or frequency regimens of ReFacto for routine prophylaxis has been performed. In clinical studies in PTPs (ages 8-73 years) and PUPs (ages 9-52 months), the mean dose used for routine prophylaxis was 27 ± 10 IU/kg and 57 ± 20 IU/kg, respectively.

Patients using ReFacto should be monitored for the development of factor VIII inhibitors. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. If the inhibitor is present at levels less than 10

Bethesda Units per mL, administration of additional antihemophilic factor may neutralize the inhibitor.

ReFacto is administered by IV infusion after reconstitution of the lyophilized powder with Sodium Chloride Diluent (provided).

INSTRUCTIONS FOR USE

Patients should follow the specific reconstitution and administration procedures provided by their physicians. The procedures below are provided as general guidelines for the reconstitution and administration of ReFacto.

Clarification of instructions

Reconstitution

Always wash your hands before performing the following procedures. Aseptic technique should be used during the reconstitution procedure.

ReFacto® Antihemophilic Factor (Recombinant) is administered by intravenous (IV) infusion after reconstitution with the supplied Sodium Chloride Diluent.

1. Allow the vials of lyophilized ReFacto and diluent to reach room temperature.

2. Remove the plastic flip-top caps from the ReFacto vial and the diluent vial to expose the central portions of the rubber stoppers.

3. Wipe the tops of both vials with the alcohol swab provided, or use another antiseptic solution, and allow to dry.

4. Remove the transparent protective cover from the short end of the sterile double-ended needle and insert that end into the diluent vial at the center of the stopper.

Clarification of reconstitution instructions.

5. Remove the colored protective cover from the long end of the sterile double-ended needle. Invert the diluent vial and, to minimize leakage, quickly insert the long end of the needle through the center of the stopper of the upright ReFacto vial.

   Note: Point the double-ended needle toward the wall of the ReFacto vial to prevent excessive foaming.

6. The vacuum will draw the diluent into the ReFacto vial.

7. Once the transfer is complete, remove the double-ended needle from the ReFacto vial, and properly discard the needle with the diluent vial.

   OSHA requirement not to instruct user to recap needles.

   Note: If the diluent does not transfer completely into the ReFacto vial, DO NOT USE the contents of the vial. Note that it is acceptable for a small amount of fluid to remain in the solvent vial after transfer.

8. Gently rotate the vial to dissolve the powder.

9. The final solution should be inspected visually for particulate matter before administration. The solution should appear clear and colorless.

ReFacto should be administered within 3 hours after reconstitution. The reconstituted solution may be stored at room temperature prior to administration.

Administration (Intravenous Injection)

ReFacto® Antihemophilic Factor (Recombinant) should be administered using a single sterile disposable plastic syringe. In addition, the

solution should be withdrawn from the vial using the sterile filter needle.

1. Using aseptic technique, attach the sterile filter needle to the sterile disposable syringe. Pull back the syringe plunger to the 5 mL mark.

2. Insert the filter needle into the stopper of the ReFacto vial. Push plunger forward to inject air into the vial.

3. Invert the vial and withdraw the reconstituted solution into the syringe.

4. Remove and discard the filter needle.

   Note: If you use more than one vial of ReFacto, the contents of multiple vials may be drawn into the same syringe through a separate, unused filter needle.

5. Attach the syringe to the luer end of the infusion set tubing and perform venipuncture as instructed by your physician.

After reconstitution, ReFacto should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.

Dispose of all unused solution, empty vials, and used needles and syringes in an appropriate container for throwing away waste that might hurt others if not handled properly.

Storage

Product as packaged for sale: ReFacto® Antihemophilic Factor (Recombinant) should be stored under refrigeration at a temperature of 2 to 8 °C (36 to 46 °F). ReFacto may also be stored at

(Ref 26): Part II, Vol. 4, Section IIF

room temperature not to exceed 25 °C (77 °F) for up to 3 months. Freezing should be avoided to prevent damage to the diluent vial. During storage, avoid prolonged exposure of ReFacto® vial to light. Do not use ReFacto after the expiry date on the label.

Product after reconstitution: The product does not contain a preservative and should be used within 3 hours.

How Supplied

ReFacto® Antihemophilic Factor (Recombinant) is supplied in single-use vials which contain nominally 250, 500, or 1000 IU per vial (NDC 58394-007-01, 58394-006-01, 58394-005-01, respectively) with sterile diluent, sterile double-ended needle for reconstitution, sterile filter needle for withdrawal, sterile infusion set, and two (2) alcohol swabs. Actual factor VIII activity in IU is stated on the label of each vial.

REFERENCES

Copies of these four references are located in Part IV, Vol. 38, Appendix R

1. Ehrenforth S, Kreuz W, Scharrer I, et al. Incidence of development of factor VIII and factor IX inhibitors in hemophiliacs. Lancet. 1992;339:594-598.

2. Bray GL, Gomperts ED, Courter S, et al. A multicenter study of recombinant factor VIII (Recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. Blood. 1994;83(9):2428-2435.

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purified FVIII concentrate. Lancet 1990; 335:1403.

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6. Kessler CM. An Introduction to Factor VIII Inhibitors: The Detection and Quantitation. American Journal of Medicine 91 1991, (Supplement 5A): 1S-5S.

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