PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

JIVI®

Antihemophilic Factor (Recombinant, B-domain deleted, PEGylated)

Supplied with Vial Adapter

IV Injection 250, 500, 1000, 2000, 3000 IU/vial

Coagulation Factor FVIII

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Date of Initial Authorization:
OCT 18, 2018

Date of Revision:
AUG 3, 2023

Submission Control No: 265962

RECENT MAJOR LABEL CHANGES

Not Applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]) is indicated in previously treated adults and adolescents (≥12 years of age) with hemophilia A (congenital Factor VIII deficiency) for:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
- Control and prevention of episodic bleeding
- Peri-operative management of bleeding (surgical prophylaxis)

JIVI does not contain von Willebrand factor and is not indicated for the treatment of von Willebrand disease.

Safety and efficacy for previously untreated patients (PUPs) have not been studied.

1.1 Pediatrics

Pediatrics (<12 years of age): The safety and efficacy of JIVI has not been established in pediatric patients less than 12 years of age. JIVI is not indicated for use in children < 12 years of age due to a greater risk for hypersensitivity reactions (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (>65 years of age): Clinical studies of JIVI did not include subjects aged 65 and over. Other reported clinical experience has not identified differences in responses between the elderly and younger patients (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Antihemophilic Factor (Recombinant, B-domain deleted, PEGylated) is contraindicated in patients who have had prior anaphylactic reaction to this drug or its components, or to mouse or hamster protein. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Each vial of JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]) is labelled with the actual Factor VIII potency expressed in International Units (IU). The labelled potency is based on the chromogenic substrate (CS) assay.
- The total recommended maximum dose per infusion is approximately 6000 IU (rounded to vial size) (see 4.2 Recommended Dose and Dosage Adjustment, Prophylaxis treatment).
- Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia.

4.2 Recommended Dose and Dosage Adjustment

The dosage and duration must be individualized according to the patient's needs (weight, severity of disorder of the hemostatic function, the site and extent/severity of the bleeding and the Factor VIII level desired). The clinical effect of Factor VIII is the most important element in evaluating the effectiveness of treatment.

The calculation of the required dosage of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII activity by 2.0% (1.5% to 2.5%) (or IU/dL).

Patients may vary in their pharmacokinetic and clinical response. Dose and frequency should be based on individual response.

The required dose of JIVI is determined using the following formulas:

Equation 1: Calculation of Required Dose

$$Required\ dose\ (IU) = \frac{body\ weight\ (kg) \times desired\ \%\ FVIII\ rise}{expected/observed\ \ recovery}$$

$$Example\ for\ a\ 70\ kg\ adult\text{:}\ \frac{70\ kg\ \times 100\%}{2\%/IU/kg} = 3500\ IU\ required$$

Equation 2: Calculation of Expected % FVIII Increase

$$Expected\ \%\ FVIII\ increase = \frac{(\#\ units\ administered) \times 2\%/\ IU/kg}{body\ weight\ (kg)}$$

$$Example\ for\ a\ 70\ kg\ adult\text{:}\ \frac{1400\ IU \times 2\%/\ IU/kg}{70\ kg} = 40\%$$

On-demand treatment

The dosage necessary to achieve hemostasis depends on the type and severity of the bleeding episode.

In the case of the following hemorrhagic events, the Factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period. Table 1 can be used to guide dosing in bleeding episodes:

Table 1: Guidance for On-Demand Treatment and Control of Bleeding Episodes for Adolescents and Adults

Degree of Hemorrhage/Hemorrhagic Event	Factor VIII Activity Level Required (% or IU/dL)	Recommended Dose (IU/kg)	Frequency of Doses (Hours)	Duration of Therapy
Minor (e.g., early hemarthrosis, minor muscle, oral bleeds)	20-40	10-20	Repeat every 24-48 hours	Until bleeding is resolved
Moderate (e.g., more extensive hemarthorosis, muscle bleeding, or hematoma)	30-60	15-30	Repeat infusion every 24-48 hours	Until bleeding is resolved
Major (e.g., intracranial, intra-abdominal or intrathoracic hemorrhage; gastrointestinal bleeding; central nervous system bleeding; bleeding in the retropharyngeal or retroperitoneal spaces; or iliopsoas sheath, life or limb threatening hemorrhage)	60-100	30-50	Repeat infusion every 8 to 24 hours	Until bleeding is resolved

Perioperative management

A guide for dosing JIVI during surgery (perioperative management) is provided in Table 2. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

Table 2: Guidance for Perioperative Management (during surgery) for Adolescents and Adults

Type of Surgery	Factor VIII Activity Level Required (% or IU/dL)	Recommended Dose (IU/kg)	Frequency of Doses (Hours)	Duration of Therapy (Days)
Minor (e.g., tooth extraction)	30-60 (pre- and post-operative)	15-30	Every 24 hours	At least 1 day, until healing is achieved
Major (e.g., intracranial, intra-abdominal, intrathoracic, or joint replacement surgery)	80-100 (pre- and post-operative)	40-50	Repeat dose every 12-24 hours	Until adequate wound healing, then therapy for at least another 7 days to maintain Factor VIII activity of 30-60% (IU/dL)

Prophylaxis treatment

All treatment decisions for identifying appropriate prophylactic treatment regimens should be guided by clinical judgment based on individual patient characteristics and treatment response (see 14 CLINICAL TRIALS and 10.3 Pharmacokinetics).

The recommended initial regimen is 30-40 IU/kg twice weekly.

Based on the bleeding episodes, the regimen may be adjusted to 45-60 IU/kg every 5 days.

A regimen may be further individually adjusted to more or less frequent dosing.

Treatment monitoring

It is recommended that plasma Factor VIII activity levels of JIVI be measured using chromogenic substrate (CS) assays.

One-stage (OS) assays can be used with reagents and/or kits that have been validated to be compatible with accurate measurement of plasma Factor VIII activity levels of JIVI. For modified long-acting Factor VIII products, it is known that the results are dependent on the reference standard and activated partial thromboplastin time (aPTT) reagent used, resulting in a possible over- or under-estimation of Factor VIII activity. The suitability of the OS assay should be ascertained when selecting the reagents to be used for monitoring Factor VIII activity of JIVI.

Factor VIII activity of JIVI can be accurately measured in plasma using validated CS or OS assays, which was determined in a field study. All CS assays tested were able to accurately detect plasma Factor VIII activity levels of JIVI. For OS assays, aPTT reagents, such as ellagic acid based Actin FSL, as well as silica based SynthasIL and Pathromtin, demonstrated accuracy in measuring activity of JIVI.

4.3 Reconstitution

JIVI powder should only be reconstituted with the supplied diluent (2.5 mL Sterile Water for Injection) using the prefilled syringe. Reconstitution should be performed in accordance with good practices rules, with particular attention to asepsis.

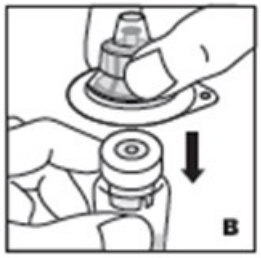
If any component of the package is damaged or already opened, do not use this component. The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the provided Vial Adapter.

Always work on a clean surface and wash your hands before performing the following procedures:

1. Warm both unopened vial and syringe in your hands to a comfortable temperature (do not exceed 37°C, 99°F).

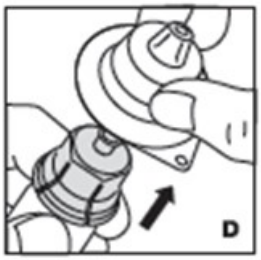
2. Remove protective cap from the vial (A). Disinfect the rubber stopper with alcohol, being careful not to handle the rubber stopper.

3. Place product vial on a firm, non-skid surface. Peel off the paper cover on the Vial Adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.

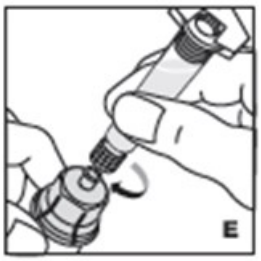


4. Holding the syringe by the barrel, snap the syringe cap off the tip (C). To minimize risk of contamination, **do not touch the syringe tip with your hand or any surface.** Set the syringe aside for further use.

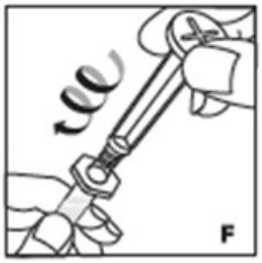
5. Now remove and discard the adapter housing (D).



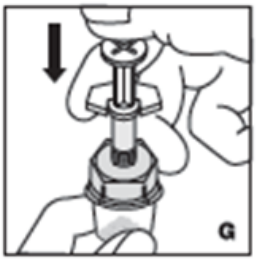
6. Attach the pre-filled syringe to the threaded Vial Adapter by turning clockwise (E).



7. Grasp the plunger rod by the top plate and remove from carton. **Avoid touching the sides and threads of the plunger rod.** Immediately attach the plunger rod by turning it firmly clockwise into the threaded syringe rubber stopper (F).

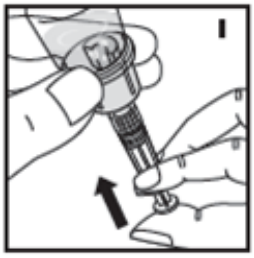


8. Inject the diluent by **slowly** pushing down on the plunger rod (G).



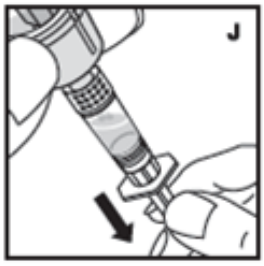
9. Swirl vial gently until all material is dissolved (H). **Do not shake vial.** Be sure that the powder is completely dissolved. **Do not use solutions containing visible particles or that are cloudy.**

10. Push down on the plunger to push all air back into the vial. Then while holding the plunger down, turn the vial with syringe upside-down (invert) so the vial is now above the syringe (I).



11. Withdraw all the solution into the syringe by pulling the plunger rod back slowly and smoothly (J). Tilt the vial to the side and back to make sure all the solution has been drawn toward the large opening in the rubber stopper and into the syringe.

    Remove as much air as possible before removing the syringe from the vial by slowly and carefully pushing the air back into the vial.



12. Detach the syringe with plunger rod from the vial adapter by turning counter-clockwise. Attach the syringe to the administration set provided and inject intravenously (K). NOTE: follow instructions for infusion set provided. The small amount of drug product left in the administration set will not affect your treatment.

If the same patient is to receive more than one bottle, reconstitute each bottle with the diluent syringe provided then combine solutions in a larger syringe (not provided) and administer as usual.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Table 3: Reconstitution of Parenteral Products

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
250 IU	2.5 mL	2.5 mL	100 IU/mL
500 IU	2.5 mL	2.5 mL	200 IU/mL
1000 IU	2.5 mL	2.5 mL	400 IU/mL
2000 IU	2.5 mL	2.5 mL	800 IU/mL
3000 IU	2.5 mL	2.5 mL	1200 IU/mL

4.4 Administration

JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]) with Vial Adapter (with a 15 micrometer filter) is a needleless system that prevents needlestick injuries during reconstitution (see 7 WARNINGS AND PRECAUTIONS, General).

Infuse JIVI intravenously over a period of 1 to 15 minutes, depending on the total volume. Adapt the rate of administration to the response of each individual patient (maximum infusion rate 2.5 mL/min).

- The reconstituted product must be administered intravenously.
- The product must be administered within 3 hours after reconstitution.
- It is recommended to use the administration set provided to minimize losses of product due to adsorption and volume retention.
- JIVI should not be mixed with other medicinal products or solvents.

4.5 Missed Dose

Patients should be advised to proceed immediately with a regular administration of JIVI and continue treatment at regular intervals as required.

Double doses are generally not required to compensate for forgotten individual doses.

5 OVERDOSAGE

No symptoms of overdose have been reported.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Intravenous	Lyophilized powder for injection 250, 500, 1000, 2000, 3000 IU/vial	Calcium chloride, Glycine, Histidine, Polysorbate 80, Sodium chloride, Sucrose

JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]) is a sterile, nonpyrogenic, preservative-free, white to slightly yellow lyophilized powder for reconstitution with water as diluent for intravenous (IV) injection. The product is supplied in single use vials containing dosage strengths of 250,

500, 1000, 2000 and 3000 International Units (IU) in 2.5 mL fill size. For each dosage strength, the actual assayed potency is directly printed on each vial label. The container closure system consists of a 10 mL, Type I glass vial sealed with a bromobutyl grey stopper and an aluminum crimp seal with plastic flip-off cap plus Vial Adapter. The Vial Adapter was designed to connect with the 2.5 mL sterile water for injection (sWFI), prefilled diluent syringe, EP, USP. JIVI is formulated with the following excipients for the final container: 59 mg glycine, 27 mg sucrose, 8.4 mg histidine, 4.7 mg sodium chloride, 1.0 mg calcium chloride dihydrate, and 0.216 mg polysorbate 80. The pH of the reconstituted product is pH of 6.6-7.0.

The specific activity of JIVI is approximately 10,000 IU/mg protein.

7 WARNINGS AND PRECAUTIONS

General

JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]) is intended for the treatment of bleeding disorders as a consequence of a deficiency in coagulation Factor VIII. This deficiency should be confirmed prior to administering JIVI.

Reconstitution, product administration, and handling of the administration set must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted JIVI product in an appropriate container.

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

Hemophilia A patients with cardiovascular risk factors or diseases may have the same risk to develop cardiovascular events as nonhemophilia patients when clotting has been normalized by treatment with Factor VIII.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY for details.

Hypersensitivity Reactions

Hypersensitivity reactions have occurred with JIVI (see Table 5). Early signs of hypersensitivity reactions could progress to anaphylaxis.

Patients should be made aware of potential early signs of hypersensitivity reactions, including chest tightness, dizziness, mild hypotension, nausea, and urticaria during infusion which could progress to anaphylactic reactions. Symptomatic treatment and therapy for hypersensitivity should be instituted as appropriate. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately. In case of anaphylaxis, the current medical standards for treatment should be observed.

Hypersensitivity reactions may also be related to antibodies against PEG [see Immune Response to Polyethylene Glycol (PEG)].

Immune Response to Polyethylene Glycol (PEG)

A clinical immune response associated with anti-PEG antibodies, manifested as symptoms of acute hypersensitivity and/or loss of drug effect has been observed, in the first 4 EDs, primarily in patients <6 years of age (10 out of 44) (see 10 CLINICAL PHARMACOLOGY, Pediatrics:). One patient ≥6 years of age

(1 out of 163) developed a hypersensitivity reaction on the 4th exposure day associated with increase in anti-PEG IgM antibodies. (see Hypersensitivity Reactions; 8 ADVERSE REACTIONS, Immunogenicity; and 10 CLINICAL PHARMACOLOGY, Pediatrics:). This clinical immune response was transient and occurred in the absence of Factor VIII inhibitors and patients were able to resume their previous effective Factor VIII therapy without delay.

In case of clinical suspicion of loss of drug effect, testing for Factor VIII inhibitors (see Inhibitors) and Factor VIII recovery is recommended.

A low post-infusion Factor VIII level in the absence of detectable Factor VIII inhibitors indicates that loss of drug effect is likely due to anti-PEG antibodies. JIVI should be discontinued and patients switched to a previously effective Factor VIII product.

Inhibitors

The formation of neutralizing antibodies (inhibitors) to Factor VIII is a known complication in the management of individuals with hemophilia A. These inhibitors are usually IgG immunoglobulins directed against the Factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified Bethesda assay.

In general, all patients treated with coagulation Factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

Monitoring and Laboratory Tests

Monitor plasma Factor VIII activity by performing a validated test (one-stage assay or chromogenic substrate assay) to confirm the adequate Factor VIII levels have been achieved and maintained (see 4 DOSAGE AND ADMINISTRATION, Treatment monitoring).

Monitor for development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained or if bleeding is not controlled with the expected dose of JIVI. Use Bethesda Units (BU) to report inhibitor titres.

7.1 Special Populations

7.1.1 Pregnant Women

JIVI should be used during pregnancy only if the potential benefit justifies the potential risk. Animal reproduction studies have not been conducted with JIVI. Experience regarding the use of Factor VIII during pregnancy is not available. It is also not known whether JIVI can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity.

7.1.2 Breast-feeding

Based on the very rare occurrence of hemophilia A in women, experience regarding the use of Factor VIII during breast-feeding is not available. Therefore, Factor VIII should be used during lactation only if clearly indicated.

7.1.3 Pediatrics

Pediatrics (<12 years of age): The safety and efficacy of JIVI has not been established in pediatric patients less than 12 years of age. JIVI is not indicated for use in children < 12 years of age due to a greater risk for hypersensitivity reactions. In completed clinical studies with 73 pediatric previously

treated patients (PTPs) < 12 years of age (44 PTPs < 6 years, 29 PTPs 6 to < 12 years), adverse reactions due to an immune response to PEG were observed in children less than 6 years of age. In 23% of subjects in the age group < 6 years of age, loss of drug effect due to neutralizing anti-PEG IgM antibodies during the first 4 exposure days (EDs) was observed. In 7% of the subjects < 6 years of age, loss of drug effect was concurrent with hypersensitivity reactions.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Clinical studies did not include patients over 65 years of age. As with any patient receiving rFVIII, dose selection for an elderly patient should be individualized.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported (≥5%) adverse reactions in clinical trials in PTPs were headache, cough and pyrexia (see Table 5).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

A total of 221 subjects constituted the safety population from three studies. Subjects who received JIVI for perioperative management (n=17) with treatment period of 1 to 3 weeks were excluded from pooled safety analysis but included in analysis for inhibitor development. The median EDs for adults and adolescents (≥ 12 years of age) was 131 EDs (range: 1–309) per subject and the median EDs for subjects < 12 years of age was 53 EDs (range: 1–68) per subject.

Table 5: Adverse Reactions Reported for JIVI

MedDRA Standard System Organ Class Preferred term	**Subjects ≥12 years of age N (%) N=148**	**All Subjects N (%) N = 221**
Gastrointestinal Disorders		
Abdominal pain	5 (3.4%)	9 (4.1%)
Nausea	8 (5.4%)	9 (4.1%)
Vomiting	5 (3.4%)	10 (4.5%)
General Disorders and Administration Site Conditions		
Injection site reactions*	2 (1.4%)	4 (1.8%)
Pyrexia	8 (5.4%)	20 (9.0%)
Immune System Disorders		
Hypersensitivity	3 (2.1%)	8 (3.6%)
Nervous System Disorders		
Dizziness	3 (2.0%)	3 (1.4%)
Dysgeusia	0	1 (0.5%)
Headache	21 (14.2%)	29 (13.1%)
Psychiatric Disorders		
Insomnia	4 (2.7%)	5 (2.3%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	10 (6.8%)	18 (8.1%)
Skin and Subcutaneous Tissue Disorders		
Erythema**	2 (1.4%)	3 (1.4%)
Pruritus	1 (0.7%)	2 (0.9%)
Rash***	3 (2.0%)	9 (4.1%)
Vascular Disorders		
Flushing	1 (0.7%)	1 (0.5%)

* includes Injection site pruritus and Injection site rash

** includes Erythema and Erythema multiforme

*** includes Rash and Rash papular

A total of 121 subjects continued in long-term safety extension studies. The median total time in study (main and extension study) for adults and adolescents (≥ 12 years of age) was 3.9 years (range 0.8 to 7.0 years) and patients accumulated a median of 224 EDs (range 23-698) per subject.

There was no change in the safety profile during the extension study for adults and adolescents (≥ 12 years of age).

Immunogenicity

Immunogenicity was evaluated during clinical trials with JIVI in 158 (including surgery patients) previously treated adolescents (≥12 years of age) and adults diagnosed with severe hemophilia A (FVIII <1%), and ≥150 previous EDs. One trial included 73 pediatric PTPs <12 years of age (refer to 10 CLINICAL PHARMACOLOGY, Pediatrics).

Factor VIII Inhibitors

No *de novo* or confirmed cases of inhibitor against Factor VIII occurred. A single unconfirmed positive result of a low titre of Factor VIII inhibitor (1.7 BU/mL) was reported in one adult patient undergoing surgery.

Anti-PEG Antibodies

Immunogenicity against PEG was evaluated by anti-PEG screening and specific IgM anti-PEG ELISA assays [see 7 WARNINGS AND PRECAUTIONS, Immune Response to Polyethylene Glycol (PEG)]. One patient (19 years of age) with pre-existing asthma, presented at 4 EDs with a clinical hypersensitivity reaction after infusion of JIVI. Subject reported headache, abdominal pain, and shortness of breath, and flushing, all of which resolved following standard asthma treatment. No further medical intervention was required. The event was associated with a transient increase of IgM anti-PEG anti-body titre, which was negative upon retest during follow-up.

No clinical immune response to PEG resulting in loss of drug efficacy or hypersensitivity was observed from the fifth ED through the end of the extension studies.

In the extension study, seven patients were transiently positive for anti-PEG antibodies with low titres at a single visit. One patient was transiently positive for both anti-JIVI and anti-PEG antibodies at a single visit. The detected antibodies had no known clinical significance.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interactions with other drugs, food, herbal products and laboratory tests have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]), a PEGylated form of recombinant antihemophilic factor, temporarily replaces the missing endogenous coagulation Factor VIII needed for effective prevention and control of bleeding episodes in congenital hemophilia A patients (see 10.3 Pharmacokinetics). PEGylation of the A3 domain reduces clearance of Factor VIII resulting in an extended half-life and increased AUC.

10.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in people with hemophilia. Determination of aPTT is a conventional *in vitro* assay for measuring biological activity of Factor VIII. Treatment with JIVI normalizes the aPTT similar to that achieved with plasma-derived Factor VIII. The administration of JIVI increases plasma levels of Factor VIII and can temporarily correct the coagulation defect in hemophilia A patients.

10.3 Pharmacokinetics

In a Phase I multi-centre, non-randomized, open-label, parallel-group design clinical trial, the pharmacokinetics (PK) of JIVI were evaluated and compared to KOGENATE FS following single- and multiple-dose administration in two cohorts of previously treated subjects aged 18 years of age and older with severe hemophilia A. Single doses of JIVI 25 IU/kg and 60 IU/kg, and KOGENATE FS 25 IU/kg and 50 IU/kg were given. PK was also evaluated after dosing with 25 IU/kg given twice weekly and 60 IU/kg given once weekly for 8 weeks. The PK parameters were based on plasma Factor VIII activity measured by the chromogenic substrate (CS) and one-stage clotting (OS) assays.

Compared with KOGENATE FS, JIVI had a reduced clearance that resulted in a ~1.4 fold increase in half-life based on CS assay (N=7; 25 IU/kg: 18.6 h vs. 13.3 h for JIVI and KOGENATE FS, respectively) and dose normalized AUC.

Compared with KOGENATE FS, JIVI had a reduced clearance that resulted in a 1.5-fold increase in half-life based on OS assay (N=7; 25 IU/kg: 21.4 h vs. 14.1 h for JIVI and KOGENATE FS, respectively) and dose normalized AUC.

The PK profile obtained at week 8, after repeated dosing, was consistent with the PK profile obtained after the first dose. Dose proportional increases in AUC_{norm} and $C_{max,norm}$ were observed between the doses of 25 and 60 IU/kg.

In a Phase II/III study, the PK of JIVI was investigated in 22 PTPs (≥12 years of age) with severe Hemophilia A following administration of single dose 60 IU/kg of JIVI prior to initiation of prophylactic treatment and in 16 subjects after 6 months of prophylaxis treatment with JIVI. The PK data demonstrate that JIVI provides better coverage over the dosing interval with prolonged circulating $t_{½}$ and increased AUC_{norm}.

PK profile obtained in 16 patients, after repeated dosing over 6 months, was consistent with the PK profile after the first dose.

Table 6 summarizes the PK parameters after single dose based on plasma Factor VIII activity measured by the CS assay and OS assay.

Table 6: Pharmacokinetic Parameters (Arithmetic Mean ± SD) for JIVI following a Single Dose based on Chromogenic and One-stage assay

	Chromogenic assay		One-stage assay	
PK Parameters (unit)	25 IU/kg	60 IU/kg[a]	25 IU/kg	60 IU/kg[a]
	n=7	n=29	n=7	n=29
AUC (IU*h/dL)	1640 ± 550	4060 ± 1420	1640 ± 660	4150 ± 1060
C_{max} (IU/dL)	64.2 ± 9.2	167 ± 30	69.4 ± 11.3	213 ± 71
$t_{½}$ (h)	18.6 ± 4.6	17.9 ± 4.0	21.4 ± 13.1	17.4 ± 3.8
MRT_{IV} (h)	26.7 ± 6.6	25.8 ± 5.9	29.0 ± 14.0	24.5 ± 5.4
V_{ss} (mL/kg)	42.8 ± 5.0	39.4 ± 6.3	44.7 ± 5.4	36.0 ± 6.5
CL (mL/h)	142 ± 33	121 ± 53	146 ± 44	114 ± 41
CL (mL/h/kg)	1.68 ± 0.39	1.63 ± 0.52	1.74 ± 0.54	1.52 ± 0.38
Recovery [(IU/dL)/(IU/kg)]	2.13 ± 0.47	2.53 ± 0.43[b]	2.21 ± 0.55	3.25 ± 0.84[b]

AUC: area under the curve; C_{max}: maximum drug concentration in plasma after single dose; $t_{½}$: terminal half-life; MRT_{IV}: mean residence time after an IV administration; V_{SS}: apparent volume distribution at steady-state; CL: clearance

[a] Combined data from Phase 1 and Phase 2/3 study
[b] Recovery value could not be calculated for one subject

Based on data from Phase I and Phase II/III studies in subjects 12-65 years of age given 60 IU/kg of JIVI once weekly, JIVI has a prolonged mean $t_{1/2}$ 17.4 hours (OS assay) and 17.9 hours (CS assay).

In the Phase II/III main study pre-dose (trough) plasma levels were repeatedly collected in all patients at steady-state during prophylactic treatment; the results are presented in Table 7 by treatment regimen for patients ≥12 years.

Table 7: Trough Factor FVIII Levels (Arithmetic Mean ± SD) During Main Study Period in Patients ≥ 12 Years Following Different Prophylactic Treatment Regimens Based on Chromogenic Assay

Treatment Regimen	**2 times per week 30-40 IU/kg**	**Every 5 days 45-60 IU/kg**
Main Study	n=15 (Day 3) n=16 (Day 4)	n=32
Trough (IU/dL)	Day 3: 6.8 ± 3.4 Day 4: 2.9 ± 2.1	2.4 ± 2.3

A population PK model was developed based on measurements (from dense PK sampling and all recovery samples) throughout the 3 clinical studies (N = 206). Table 8 provides PK parameters based on the population PK model.

Table 8: PK Parameters (geometric mean [%CV]) Based on Population PK Estimates, Using Chromogenic Substrate Assay

PK parameter(unit)	12 to <18 years of age N=12	≥ 18 years of age N=133	Total (≥ 12 years) N=145
AUC (IU*h/dL)*	3441 (34.2)	4052 (31.1)	3997 (31.6)
AUC_{norm} (h*kg/dL)	57.4 (32.6)	67.5 (30.6)	66.6 (31.0)
$t_{1/2}$ (h)	16.8 (25.2)	17.4 (28.8)	17.4 (28.4)
V_{SS} (dL/kg)	0.423 (15.5)	0.373 (15.6)	0.376 (15.9)
CL (dL/h/kg)	0.0174 (34.2)	0.0148 (31.1)	0.0150 (31.6)

AUC: area under the curve; AUC_{norm}: AUC normalized; $t_{½}$: terminal half-life; V_{SS}: apparent volume distribution at steady-state; CL: clearance

* AUC calculated for a dose of 60 IU/kg

Incremental Recovery

For PTPs ≥12 years of age, summary statistics of FVIII recovery at start and end of treatment, and overall across all visits were calculated based on the one-stage and chromogenic assays for a total of 132 patients (see Table 9).

Table 9 :Overall Incremental FVIII Recovery [IU/dL per IU/kg]

PROTECT VIII Main study (ITT population)	
Chromogenic assay, N=131	
Median	**2.623**
(Q1; Q3)	(2.333; 3.018)
One-stage assay, N=132	
Median	**2.830**
(Q1; Q3)	(2.427; 3.516)

N = number of patients, (on-demand and prophylaxis, combined)

Note: If a FVIII concentration value is below the lower limit of quantification (LLOQ), a data point with the value of one-half the LLOQ is used for calculation.

Overall FVIII recovery values are calculated across all visits for each patient first, and then across all patients, using valid FVIII pre- and post- infusion levels.

Special Populations and Conditions

Pediatrics:

Pediatrics (<12 years of age): In completed clinical studies with 73 pediatric PTPs (44 PTPs <6 years of age, 29 PTPs 6 to <12 years of age), adverse reactions due to immune response to PEG were observed in some children <≤6 years of age. Loss of drug effect due to neutralizing anti-PEG IgM antibodies during the first 4 EDs was observed in 23% of children <6 years of age. In 7% of the patients, loss of drug effect was combined with hypersensitivity reactions (see 7 WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions). The immune response was transient. No triggers or predictors of the immune response to PEG could be identified.

JIVI is not indicated for use in previously untreated patients (PUPs).

JIVI is not indicated for use in pediatric patients <12 years of age.

Geriatrics:

Geriatrics (>65 years of age): Clinical studies did not include patients over 65 years of age. As with any patient receiving rFVIII, dose selection for an elderly patient should be individualized.

Hepatic Insufficiency:

Dose adjustment for patients with hepatic impairment has not been studied in clinical trials.

Renal Insufficiency:

Dose adjustment for patients with renal impairment has not been studied in clinical trials.

11 STORAGE, STABILITY AND DISPOSAL

JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]) should be stored under refrigeration (2-8°C). Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

Do not use beyond the expiration date indicated on the labels and cartons.

The lyophilized powder may be stored at a temperature up to 25°C for 6 months or up to 30°C for 3 months, such as in home storage situations.

If the product is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The new expiry date should be 6 months (25°C) or 3 months (30°C) from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter. Once product is removed from refrigeration, it cannot be returned to the refrigerator.

After reconstitution, the product should be used immediately (within 3 hours).

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Antihemophilic Factor (Recombinant, B-domain deleted, PEGylated)

Chemical name: Antihemophilic Factor (Recombinant), PEGylated

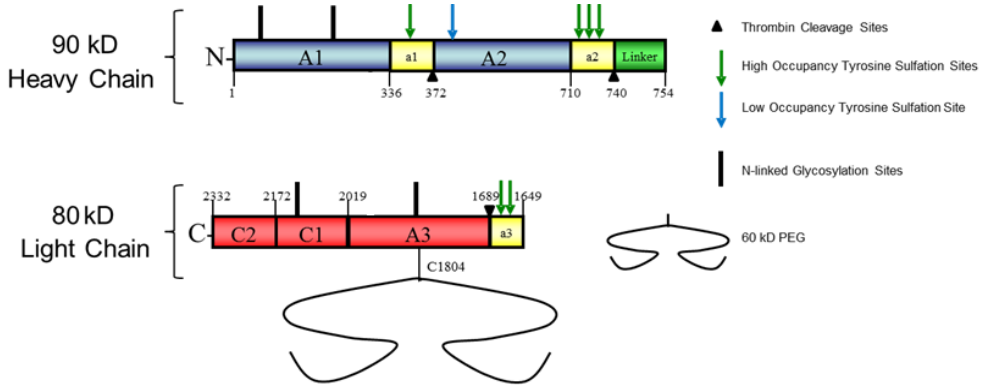
Molecular formula and molecular mass:

$C_{3895}H_{5939}N_{1029}O_{1140}S_{29}$ for the heavy chain (excludes signal peptide but includes the linker peptide)

$C_{3550}H_{5401}N_{955}O_{1026}S_{34}$ for the light chain

The average molecular weight of Antihemophilic Factor (Recombinant, B-domain deleted, PEGylated) is approximately 234 kDa.

Structural formula:



Physicochemical properties: Antihemophilic Factor (Recombinant, B-domain deleted, PEGylated) Drug Product is white to slightly yellow solid before reconstitution and clear colourless liquid after reconstitution with water for injection. The reconstituted Drug Product has a nominal pH of 6.8.

Product Characteristics

JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]) is a B-domain deleted (BDD) recombinant human coagulation FVIII molecule which is site-specifically conjugated with polyethylene glycol to prolong its half-life (therapeutic activity) in circulation while retaining full biological coagulant activity. JIVI is produced by site-specific conjugation of the BDD-rFVIII variant K1804C at the cysteine amino acid position 1804 (within the A3 domain) with a single maleimide-derivatized, 60 kilodalton (kDa) branched PEG (two 30 kDa PEG) moiety. The A3 domain was selected for conjugation to provide a consistent coagulation activity, high PEGylation efficiency, and to conceal an epitope region for inhibitors. The BDD-rFVIII variant corresponds to amino acids 1-754 and 1649-2332 of human blood coagulation Factor VIII with a heavy-chain (A1 and A2 domains) and a light-chain (A3, C1 and C2 domains) heterodimer (linked by a metal bridge).

The molecular weight of the protein is approximately 234 kDa based on the calculated average molecular weight of the BDD-rFVIII variant of 165 kDa, plus glycosylation (~4 kDa), and the average molecular weight of the single maleimide-derivatized 60 kDa branched PEG moiety. Functional characterization of JIVI shows comparable mechanism of action to that of rFVIII product with a prolonged plasma half-life (see 10.3 Pharmacokinetics).

The active protein (or starting molecule), prior to conjugation is a recombinant BDD rFVIII produced by recombinant DNA technology in Baby Hamster Kidney (BHK) cells and the conjugated protein is prepared without the addition of any human- or animal- derived protein. This applies to the cell culture process, purification, site-specific PEGylation and final formulation. The manufacturing process of JIVI involves propagation of the recombinant production cell line with the harvest isolation process consisting of continuous filtration of tissue culture fluid and anion exchange chromatography on a membrane adsorber capsule.

Viral Inactivation

The process intermediate is purified from process- and product-related impurities using a series of chromatography and filtration steps including 20 nm viral filtration, prior to conjugation to the 60 kDa maleimide PEG moiety. The mono-PEGylated JIVI active molecule is separated from product-related species by chromatography and then formulated by ultrafiltration. The cell culture, PEGylation, purification process and formulation used in the manufacture of JIVI do not use any additives of human or animal origins.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Previously treated adults and adolescents (≥12 years of age) with hemophilia A

The pharmacokinetics, safety and efficacy of JIVI (Antihemophilic Factor [Recombinant, B-domain deleted, PEGylated]) for on demand treatment, perioperative management of bleeding and routine prophylaxis in subjects with severe hemophilia A was evaluated in a clinical study (PROTECT VIII). Immunocompetent male subjects with severe hemophilia A (Factor VIII activity <1%) and no history of Factor VIII inhibitors were eligible for the trial.

Table 10: Summary of Patient Demographics for Clinical Trial in On demand Treatment, Peri-operative Management of Bleeding and Prophylaxis

Study #	Trial Design	Dosage, route of administration, and duration	Study subjects (n)	Median Age (Range) (years)	Sex
Study 1 (PROTECT VIII)	Multi-national, open-label, uncontrolled, partially randomized	Part A: On-demand arm: • Dose as indicated based on location and severity of bleeds (max. 60 IU/kg), 36 weeks	20	48 (22-61)	male
		Prophylaxis arm: • Run-in phase (10 weeks): 2 times per week at 25 IU/kg • Partially randomized phase (week 10-36): 2 times per week at 30-40 IU/kg, every 5 days at 45-60 IU/kg, every 7 days at 60 IU/kg	114	33 (12-62)	
		Part B: Peri-operation, 3 weeks	16	42 (13-61)	
		Optional: Extension Part A patients to accumulate at least 100 EDs	121	36 (12-62)	
		Part B	7	37 (13-61)	

Study 1 (PROTECT VIII): A multi-national, open-label, uncontrolled, partially randomized study in adolescents and adults (age 12 to 65 years of age) PTPs (≥150 EDs). Part A of the study evaluated the pharmacokinetics (single dose of 60 IU/kg), safety and efficacy of JIVI for on-demand treatment and routine prophylaxis with three regimens. Safety and efficacy of JIVI in hemostasis during major surgical procedures was evaluated in Part B. The main study duration (Part A) was 36 weeks. An optional extension study included patients completing Part A to accumulate at least 100 EDs. The primary efficacy variable was annualized bleed rate (ABR).

In Part A of this study, a total of 134 PTPs (including 13 subjects aged 12 to 17 years) received at least one infusion of JIVI and 132 subjects were evaluable for efficacy (see Table 11). One hundred and twenty-six (126) (94%) subjects completed the main study (prophylaxis group: N=108; on-demand group; N=18). The median time in the main study for the prophylaxis arms was 255 days with 59 EDs.

A total of 121 subjects continued treatment in the extension study (107 subjects received prophylaxis; 14 subjects continued on-demand treatment), for a median of 3.2 years (range 0.1 – 6.3 years). Thirty-six (36) subjects were treated for a total of ≥ 5 years. One hundred and ten (110) subjects were treated for at least 100 EDs.

Table 11: Overview of Study 1 (PROTECT VIII – Part A Main) for Adolescent and Adult PTPs (≥12 Years of Age)

	PROTECT VIII – Part A Main N=134	
	On demand (N=20)	**Prophylaxis[a] (N=112)**
Previous Factor VIII treatment type: n (%) **On-Demand (episodic)** **Prophylaxis**	 20 (100.0%) 0 (0%)	 23 (20.5%) 89 (79.5%)
# of Target joints at baseline: (mean; SD)	2.5 ± 2.1	1.5 ± 1.5
Joint hemorrhage history (mean #; SD of joint bleeds during 12 months prior study)	23.6 ± 18.8	9.5 ± 15.2

[a] Comprises all prophylaxis regimens (week 10-36); 2 subjects dropped out after single infusion, 2 additional patients dropped out during run-in without efficacy data.

The treatment of breakthrough bleeds and perioperative management were at the investigator's discretion based on standard of care.

Efficacy in Routine Prophylaxis

In Study 1 (PROTECT VIII), one hundred and ten (110) subjects received JIVI for prophylaxis during main efficacy period (week 10-36). Of these, total of 107 subjects participated in an optional extension study.

All (N = 110) subjects in the prophylaxis treatment arms began treatment with twice weekly infusions of 25 IU/kg for 10 weeks (run-in phase). Eighty-eight percent of subjects (97 of 110) experienced ≤1 breakthrough bleeds during run-in phase and qualified for randomization (1:1) to an extended dosing interval of either every 5 days or once-weekly for an additional 26 weeks (Week 10-36; [26 weeks, approx. 6.5 months]). Subjects (N = 43) assigned to the every 5 day treatment regimen began treatment with a dose of 45 IU/kg (up to 60 IU/kg). Forty-three (43) subjects assigned to the every 7 day treatment regimen were treated with a fixed dose of 60 IU/kg (maximum total dose approximately 6000 IU, rounded to full vials). Eleven (11) subjects eligible for randomization remained on the 2 times per week treatment because the limit in the randomization groups was reached. Subjects (N = 13) ineligible for randomization, experienced ≥2 spontaneous bleed during 10 week run-in phase continued on 2 times per week dosing frequency (30-40 IU/kg) for the additional 26 weeks.

The compliance for prophylaxis treatment was nearly 100% for all regimens.

Prophylaxis dose per treatment regimen is summarized in Table 12. In the main part of the study (Week 10-36), the majority (99/110 [90 %]) of subjects did not change their treatment regimens. All subjects in the every 5-day regimen (43/43) and 2 times per week regimens (24/24) remained in their assigned treatment arm until Week 36.

During the extension study, most patients continued their treatment regimen of the main study. Twenty-three (23) patients were treated 2 times per week, 33 patients every 5-days, 23 patients every 7 days, and 28 patients changed treatment regimens (variable frequency). The median prophylaxis dose per infusion was 47.8 IU/kg. Patients treated 2 times per week and every 5 days reported a median

prophylaxis dose per infusion (range) of 37.5 IU/kg (27-43 IU/kg) and 46.2 IU/kg (41-60 IU/kg), respectively, and a mean (±SD) total annual dose (IU/kg/year) of 3881.82 (±711.51) and 3648.80 (±500.84), respectively.

Table 12: Prophylaxis Treatment Adolescents and Adults – Treatment Exposure

PROTECT VIII Main Study (Part A)[a] (Week 10-36)			
Patients per regimen (n)	**2 times per week 30-40 IU/kg**		**Every 5 days 45-60 IU/kg**
	Eligible for randomization[b] N=11	**Ineligible for randomization**[c] N=13	N=43
Median prophylaxis dose/infusion (range)	30.6 IU/kg (29-41 IU/kg)	39.2 IU/kg (33-42 IU/kg)	45.3 IU/kg (39-58 IU/kg)
Total dose (IU/kg/year) (Mean ± SD)	3341.1 ± 381.7	4497.8 ± 653.4	3671.8 ± 637.3

a Main efficacy period, 26 week treatment periods
b Eligible for randomization - Subjects completed the run-in phase after the every 5- and 7-day arms were filled; remained in the 2 times per week arm
c Ineligible for randomization - Subjects with ≥ 2 spontaneous bleeds during the first 10 weeks.

The ABR was calculated based on the time treated in the assigned treatment regimen (see Table 13).

During the 26-week treatment period, the median ABR was 2.09 for all prophylaxis groups combined. Forty-two (42) subjects (38.2%) in the prophylaxis arms had no bleeds during the 26-week period. For subjects in the on-demand group, median ABR was 23.42. The ABR was significantly lower ($p<0.0001$) with each of the prophylaxis compared to on-demand treatment as calculated by the negative binomial regression model. The ABR by regimen is summarized in Table 13.

The median ABR in the every 7 days treatment arm was 3.85 for the ITT population. Twenty-six percent of subjects in this arm experienced bleeding and moved to more frequent dosing during Part A of Study 1.

During the extension study, the overall median (Q1; Q3) total ABR was 1.49 in the combined prophylaxis groups and 34.1 (20.3; 36.6) in the on-demand group. The median (Q1; Q3) total and joint ABR was 1.6 (0.8; 3.6) and 0.7 (0; 1.7) in the 2 times per week treatment arm, respectively, and 1.2 (0; 4.6) and 1.0 (0; 3.7) in the every 5 day treatment arm, respectively.

Table 13: ABR (median [Q1, Q3]) in Adults and Adolescents by Treatment Regimen, PROTECT VIII Main Study

PROTECT VIII Main Study (Week 10-36)				
N = number of patients	**2times per week 30-40 IU/kg**		**Every 5 days 45-60 IU/kg**	**On-demand[a]**
	Eligible for randomization N=11	**Ineligible for randomization N = 13**	**N=43**	**N=20**
ABR Median (Q1; Q3)				
All Bleeds	1.93 (0.0; 5.24)	4.11 (2.0; 10.6)	1.93 (0.0; 4.23)	24.1 (17.8; 37.3)
Spontaneous Bleeds	0.0 (0.0; 1.93)	3.87 (0.0; 4.11)	0.0 (0.0; 3.99)	14.3 (7.3; 22.7)
Joint Bleeds	1.93 (0.0;5.24)	4.01 (1.98; 8.03)	1.86 (0.0; 3.99)	16.3 (11.6; 30.3)
Subjects with Zero Bleeding Episodes % (n)	45.5% (5)	15.4% (2)	44.2% (19)	0 (0)

a The treatment period for on-demand was Weeks 0-36.

Efficacy in Control of Bleeding Episodes

A total of 386 bleeding episodes were treated with JIVI during Week 0 to 36 in the on-demand arm and 316 in all prophylaxis groups combined.

The majority of bleeds were successfully treated with 1 or 2 infusions in approximately 90% of the subjects in both the on-demand and prophylaxis groups (see Table 14). The median time interval between 1st and 2nd infusion was 1 day. The subjects' assessment of response to treatment in the electronic patient diary (EPD) (ie, adequacy of hemostasis for treatment of bleeds based on a 4-point scale: excellent, good, moderate, poor) was available for 693 of 702 bleeding episodes during the main study, and rated as either good or excellent in 73.3% of treatment, 23.4% were rated as moderate and 3.3% as poor.

During the extension study, in the on-demand arm (N=14) and combined prophylaxis arms (N=107), 1086 and 816 bleeds were treated with JIVI, with 95.1% and 92.4% of bleeds being treated with 1 or 2 infusions, respectively. The response to treatment of bleeds was assessed as "Excellent" or "Good" for 81.1% and 85.2% of bleeds in the on-demand and combined prophylactic arms, respectively.

Table 14: On-demand Treatment and Control of Bleeding Episodes

Characteristics of Bleeding Episodes	PROTECT VIII Main Study	
	On Demand N = 20	Total Prophylaxis N = 112
Total number of bleeds treated	386	316
% of bleeds treated with		
1 infusion	307 (79.5%)	262 (82.9%)
1 or 2 infusions	352 (91.2%)	284 (89.9%)
≥ 3 infusions	34 (8.8%)	32 (10.1%)
Response to treatment of bleeds assessed as "Excellent" or "Good": n/total (%)	252 (65.8%)	256 (82.6%)

Excellent: Abrupt pain relief and/or improvement in signs of bleeding with no additional infusion administered
Good: Definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one infusion for complete resolution
Moderate: Probable or slight improvement, with at least one additional infusion for complete resolution
Poor: No improvement or condition worsened.

Perioperative Management

A total of 17 subjects successfully completed 20 major surgeries in Part B using JIVI for hemostasis. Fourteen major surgeries were orthopedic joint surgeries (3 arthroplasties, 6 joint replacements and 3 synovectomies, 2 other joint procedures). For all 20 major surgeries, treatment with JIVI provided 'good' or 'excellent' hemostatic control. The initial JIVI pre-surgery doses administered ranged between 2500 and 5000 IU. The median total dose per surgery was 16,250 IU (218.8 IU/kg) with a median of 35.1 IU/kg/infusion.

A total of 34 minor surgeries performed in 19 subjects were reported during Part A of the main or extension study. More than half of these surgeries were dental procedures. No subjects required blood transfusions. The adequacy of hemostasis during minor surgeries was assessed as either "good" or "excellent" in all reported cases. No hemostasis-related complications were reported.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

The single-dose, and repeated-dose nonclinical systemic toxicity studies in rats and rabbits did not identify any adverse effects related to JIVI or PEG.

Single dose studies in rats with the radiolabeled PEG moiety showed that there was no indication of retention or irreversible binding of radioactivity in the animal body. Specifically, no residual radioactivity was detected in the brain, indicating that the radio-labelled PEG compound did not cross the blood brain barrier. PEG 60 kDa moiety when tested alone did not show any toxicity after acute or repeated administration over 4 weeks in rats and rabbits at high doses. Excretion of the 60 KDa PEG moiety of JIVI via urine and feces was demonstrated in rats.

No adverse effects were observed in immune-deficient rats intravenously injected with JIVI (40–1200 IU/kg/injection), twice weekly for 26 weeks in a chronic study. No evidence of accumulation of the PEG component of JIVI was detected by immunohistochemical staining in the brain (including the choroid plexus), spleen, or kidneys in animals sacrificed at 13 and 26 weeks. PEG was not detected in the cerebrospinal fluid.

No indication of any local intolerance was seen at the IV injection sites in rats and rabbits.

Genotoxicity:

Genotoxicity studies conducted with the PEG 60 kDa component of JIVI showed no indication of genotoxicity.

Carcinogenicity:

No carcinogenicity studies were conducted. Due to its mechanism of action limited to the coagulation cascade. In general PEG molecules of various sizes, and Factor VIII products are not genotoxic, have been used in patients for many years, and have not shown any indication of a carcinogenic potential.

Reproductive and Developmental Toxicology:

Embryo-fetal development has not been assessed in animals since the patient population is mainly male.

Reproductive organs were evaluated by histology in the systemic toxicity studies. No effect on male and female reproductive organs was seen in repeated administration toxicity studies.

Juvenile Toxicity:

Studies in juvenile animals (rat) did not identify age specific effects.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

JIVI®

Antihemophilic Factor (Recombinant, B-domain deleted, PEGylated)

Read this carefully before you start taking **JIVI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **JIVI**.

What is JIVI used for?

JIVI is for the treatment of hemophilia A in previously treated patients (PTPs) 12 years of age and older. JIVI can be used to:

- Prevent bleeding before it happens
- Stop a bleeding episode that has already began.

JIVI is not for the treatment of von Willebrand disease.

JIVI is not for use in children < 12 years of age and in previously untreated patients.

How does JIVI work?

- In people without hemophilia A, a protein called Factor VIII is produced naturally by the body to help the blood form clots and stop bleeding.
- People with hemophilia A do not have enough Factor VIII in their bodies. When they are injured, they may bleed internally, which can lead to damage in muscles and joints.
- JIVI is a medicine containing clotting Factor VIII. It is very similar to the Factor VIII that occurs naturally in human blood. JIVI raises the level of Factor VIII in the blood to help prevent bleeding (prophylaxis) or stop it when it happens. JIVI is given directly into the blood through an injection in a vein.
- JIVI is prepared by recombinant technology. It has a component called polyethylene glycol (PEG), which helps JIVI to remain active in the body longer (have a longer half-life).
- JIVI is made without addition of any human- or animal-derived components in the manufacturing process.

What are the ingredients in JIVI?

Medicinal ingredients: Antihemophilic Factor (Recombinant, B-domain deleted, PEGylated)

Non-medicinal ingredients: Calcium chloride, Histidine, Glycine, Polysorbate 80, Sodium chloride, Sucrose

JIVI comes in the following dosage forms:

JIVI is available in single-use vials that contain nominally 250, 500, 1000, 2000, or 3000 International Units (IU) per vial. After reconstitution with the supplied diluent (sterile water for injection), the prepared solution for injection will have the following concentration:

Vial Size	Approximate Concentration After Reconstitution
250 IU	100 IU/mL
500 IU	200 IU/mL
1000 IU	400 IU/mL
2000 IU	800 IU/mL
3000 IU	1200 IU/mL

Do not use JIVI if:

- you are allergic (hypersensitive) to JIVI, or to any of the other ingredients of JIVI
- you have had allergic reactions to mouse or hamster protein

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take JIVI. Talk about any health conditions or problems you may have, including if you:

- are allergic to mouse or hamster protein.

Other warnings you should know about:

Allergic reactions to JIVI have occurred.

If you experience tightness in the chest, feel dizzy, sick or faint, or experience dizziness upon standing, you may be experiencing a rare severe sudden allergic reaction (a so-called anaphylactic reaction) to JIVI. If this occurs, stop administration of the product immediately and seek medical advice.

Your doctor may carry out tests to ensure that your current dose of JIVI provides adequate Factor VIII levels.

- If your bleeding is not being controlled with your usual dose of JIVI, consult your doctor immediately. Your body may have formed molecules known as Factor VIII inhibitors and your doctor may carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood and are a natural part of the body's defense system. Your doctor may consider other treatment options.
- Antibodies to PEG may block the activity of JIVI, making it less effective to prevent and control bleeding. Your doctor may switch you to your previous Factor VIII treatment without delay.

When frequent injections are required, your healthcare professional may propose to have a device (called a catheter) surgically placed under the skin to facilitate access to the bloodstream. This device may result in an infection. Inform your healthcare provider if you have a catheter-related infection.

Tell your healthcare provider if you have been told you have heart disease or are at risk for heart disease.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with JIVI:

- No interactions with other medicines are known.

How to take JIVI:

JIVI is given by injection into the bloodstream (intravenously).

JIVI should be injected intravenously over a period of 1 to 15 minutes depending on the total volume. The rate of administration depends on your comfort level. The maximum infusion rate is 2.5 mL/min.

Administer reconstituted JIVI as soon as possible. If not, store at room temperature for no longer than 3 hours.

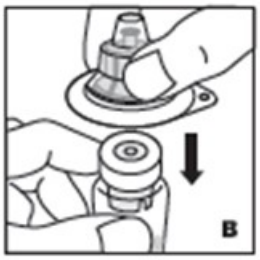
You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices (Vial Adapter, pre-filled syringe containing diluent and administration set) for reconstitution and administration that are provided with each carton of JIVI. If a device package is opened or damaged, do not use this medical device. If these devices cannot be used, please contact your healthcare provider. If you have any questions about JIVI, contact Bayer at 1-800-265-7382 or canada.medinfo@bayer.com.

JIVI must not be mixed with other medicinal products or solvents. Follow the directions given by your doctor closely and use the instructions below as a guide:

1. Warm both unopened vial and syringe in your hands to a comfortable temperature (do not exceed 37°C, 99°F).

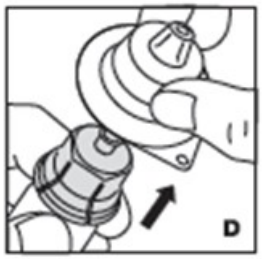
2. Remove protective cap from the vial (A). Disinfect the rubber stopper with alcohol, being careful not to handle the rubber stopper.

3. Place product vial on a firm, non-skid surface. Peel off the paper cover on the Vial Adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.

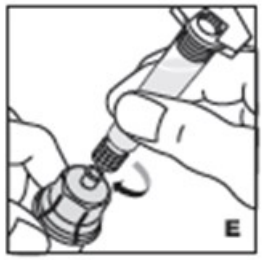


4. Holding the syringe by the barrel, snap the syringe cap off the tip (C). **Do not touch the syringe tip with your hand or any surface.** Set the syringe aside for further use.

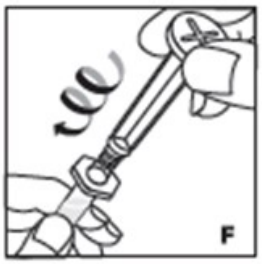
5. Now remove and discard the adapter housing (D).



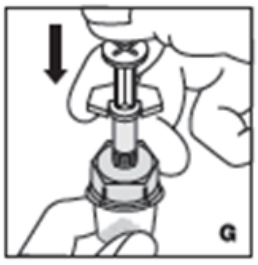
6. Attach the pre-filled syringe to the threaded Vial Adapter by turning clockwise (E).



7. Grasp the plunger rod by the top plate and remove from carton. **Avoid touching the sides and threads of the plunger rod.** Immediately attach the plunger rod by turning it firmly clockwise into the threaded syringe rubber stopper (F).

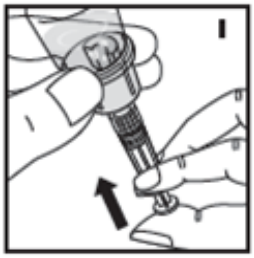


8. Inject the diluent by **slowly** pushing down on the plunger rod (G).



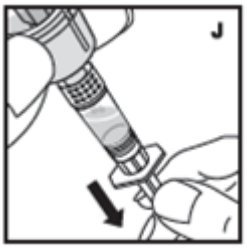
9. Swirl vial gently until all material is dissolved (H). **Do not shake vial.** Be sure that the powder is completely dissolved. **Do not use solutions containing visible particles or that are cloudy.**

10. Push down on the plunger to push all air back into the vial. Then while holding the plunger down, turn the vial with syringe upside-down (invert) so the vial is now above the syringe (I).

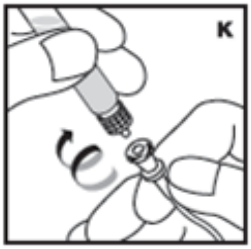


11. Withdraw all the solution into the syringe by pulling the plunger rod back slowly and smoothly (J). Tilt the vial to the side and back to make sure all the solution has been drawn toward the large opening in the rubber stopper and into the syringe.

    Remove as much air as possible before removing the syringe from the vial by slowly and carefully pushing the air back into the vial.



12. Detach the syringe with plunger rod from the vial adapter by turning counter-clockwise. Attach the syringe to the administration set provided and inject intravenously (K). NOTE: follow instructions for infusion set provided. The small amount of drug product left in the administration set will not affect your treatment.



If the same patient is to receive more than one bottle, reconstitute each bottle with the diluent syringe provided then combine solutions in a larger syringe (not provided) and administer as usual.

Visually inspect the reconstituted JIVI solution for particulate matter and change in colour before administration. JIVI should be clear and colourless. Do not use JIVI if you see particles or if the solution is cloudy.

Documentation

It is recommended that every time you use JIVI, you note down the name and batch number of the product.

Usual dose:

<u>Prevention of bleeding (prophylaxis)</u>

JIVI can be used to increase Factor VIII levels in your body to help prevent bleeding before it happens, and to protect joints.

The recommended initial regimen is 30-40 IU/kg twice weekly. Based on bleeding episodes, the regimen can be adjusted to 45-60 IU/kg every 5 days. A regimen may be further individually adjusted to more or less frequent dosing.

Because everyone is different, your doctor will individualize your JIVI regimen to meet your specific needs. To get the most out of your treatment, be sure to administer JIVI at the dose and frequency prescribed by your doctor.

Treatment of bleeding

How much JIVI you should use and how often you should use it depends on many factors, including your weight, the severity of your hemophilia, where the bleed is and how serious it is, whether you have inhibitors and the level of inhibitors your blood, and the Factor VIII level that is needed.

Your doctor will calculate the dose of JIVI and how frequently you should use it to get the necessary level of Factor VIII activity in your blood. He/she should always adjust the amount of JIVI to be administered and the frequency of administration according to your individual needs. Under certain circumstances larger amounts than those calculated may be required, especially for the initial dose.

Laboratory Test

After treatment, it is strongly recommended that appropriate laboratory tests be performed on your plasma at suitable intervals to ensure that adequate Factor VIII levels have been reached and are maintained. For major surgery in particular, close monitoring of the treatment by means of coagulation analysis must be carried out.

If bleeding is not controlled

If the Factor VIII level in your plasma fails to reach expected levels, or if bleeding is not controlled after adequate dose, you may have developed Factor VIII inhibitors. This must be checked by an experienced doctor.

If you feel the effect of JIVI is too strong or too weak, talk to your doctor.

Patients with inhibitors

If you have been told by your doctor that you have developed Factor VIII inhibitors, you may need to use a larger amount of JIVI to control bleeding.

Do not increase your dose of JIVI you use to control your bleeding without consulting your doctor.

Duration of treatment

Your doctor will tell you, how often and at what intervals JIVI is to be administered.

Usually, replacement therapy with JIVI is a life-time treatment.

Overdose:

No symptoms of overdose with recombinant human coagulation Factor VIII have been reported.

If you think you, or a person you are caring for, have taken too much JIVI, contact your healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- Proceed with your next dose immediately and continue at regular intervals as advised by your doctor.
- **Do not** take a double dose to make up for a forgotten dose.

What are possible side effects from using JIVI?

These are not all the possible side effects you may have when taking JIVI. If you experience any side effects not listed here, tell your healthcare professional.

Very common (may affect 10% of patients or more)

- headache

Common (may affect more than 1% and less than 10% of patients)

- hypersensitivity reactions including tightness of the chest/general feeling of being unwell, dizziness and nausea and mildly reduced blood pressure, which may make you feel faint upon standing. Severe allergic reactions or anaphylactic shock (an uncommon, severe allergic reaction affecting blood pressure and breathing) have not been reported during clinical trials with JIVI.
- stomach pain/discomfort
- vomiting
- fever
- cough
- local reactions where you injected the medication
- dizziness
- trouble falling asleep
- rash/itchy rash

Uncommon (may affect more than 0.1% and less than 1% of patients)

- dysgeusia (odd taste)
- hives
- flushing (redness of the face)

Serious side effects and what to do about them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Hypersensitivity reactions including tightness of the chest/general feeling of being unwell, dizziness and nausea and mildly reduced blood pressure, which may make you feel faint upon standing.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use beyond the expiration date indicated on the labels and cartons.

Store in a refrigerator (2-8°C). **Do not** freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

You may store the product when kept in its outer carton at room temperature up to 25°C for 6 months or up to 30°C for 3 months. Once the product is removed from refrigeration, it cannot be returned to the refrigerator.

If the product is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The new expiry date should be 6 months (25°C) or 3 months (30°C) from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter.

The reconstituted solution should be used immediately (within 3 hours). This product is for single use only. Any unused solution must be discarded.

Keep out of reach and sight of children.

If you want more information about JIVI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.bayer.ca or by calling Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

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Last Revised AUG 3, 2023