SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Jivi 2000 IU powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution with the solvent provided, one mL of solution contains approximately 800 IU (2000 IU/2.5 mL) of human coagulation factor VIII, damoctocog alfa pegol.

The potency International Unit (IU) is determined using the European Pharmacopoeia chromogenic assay.

The specific activity of Jivi is approximately 10000 IU/mg protein.

The active substance, damoctocog alfa pegol, is a site specifically PEGylated B-domain deleted recombinant human coagulation factor VIII, produced in baby hamster kidney cells (BHK), with a 60 kDa branched polyethylene-glycol (two 30 kDa PEG) moiety. The molecular weight of the protein is approximately 234 kDa.

Jivi is produced without the addition of any human or animal derived protein in the cell culture process, purification, PEGylation or final formulation.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: solid, white to slightly yellow.

Solvent: clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency).

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to confirm that adequate FVIII levels have been achieved. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

When using an *in vitro* activated partial thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay, which can result in over- or under-estimation of factor VIII activity. It should be noted that there can be significant discrepancies between assay results obtained by specific reagents used in the aPTT-based one stage clotting assay and the chromogenic assay. This is of importance when monitoring the factor VIII activity of Jivi, and when changing laboratory and/or reagents used in the assay. This applies also for modified long acting factor VIII products.
Laboratories intending to measure Jivi activity should check their procedures for accuracy. A field study has indicated that the factor VIII activity of Jivi can be accurately measured in plasma using either a validated chromogenic substrate (CS) assay or a one-stage (OS) clotting assay using specific reagents. For Jivi some silica-based one-stage assays (e.g., APTT-SP, STA-PTT) may underestimate the factor VIII activity of Jivi in plasma samples; some reagents, e.g. with kaolin-based activators, have the potential for overestimation.

The clinical effect of factor VIII is the most important element in evaluating the effectiveness of treatment. It may be necessary to adjust the individual dosing at patient level in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected factor VIII levels or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating factor VIII-inhibitor or anti-PEG antibodies in the patient should be suspected (see section 4.4).

Posology

The dose and duration of substitution therapy depends on the severity of the factor VIII deficiency, the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in IU (relative to an International Standard for factor VIII in plasma).

One IU of factor VIII activity is equivalent to that quantity of factor VIII in one mL of normal human plasma.

On demand treatment

The calculation of the required dose 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 1.5-2.5 % of normal activity.
The required dose of Jivi is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (% or IU/dL) x reciprocal of observed recovery (i.e. 0.5 for recovery of 2.0%).

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness required in the individual case.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Table 1: Guide for dosing in bleeding episodes and surgery for adolescents and adults

Degree of haemorrhage/Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours) / Duration of therapy (days)
Haemorrhage Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat injection every 24-48 hours. At least 1 day, until bleeding episode as indicated by pain is resolved or healing is achieved
More extensive haemarthrosis, muscle bleeding or haematoma	30-60	Repeat injection every 24-48 hours for 3 to 4 days or more until pain and acute disability are resolved.
Life-threatening Haemorrhages	60-100	Repeat injection every 8 to 24 hours until threat is resolved.
Surgery Minor surgery including tooth extraction	30-60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80-100 (pre- and post-operative)	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

All treatment decisions for identifying appropriate prophylactic treatment regimens should be guided by clinical judgement based on individual patient characteristics and treatment response.

For prophylaxis the dose is 45-60 IU/kg every 5 days. Based on patient clinical characteristics the dose can also be 60 IU/kg every 7 days or 30-40 IU/kg two times per week (see sections 5.1 and 5.2).

For overweight patients, the maximum dose per injection for prophylaxis should not be higher than approximately 6000 IU.

Paediatric population
Jivi is not indicated in previously untreated patients and in patients less than 12 years of age.

Adolescent population
On demand and prophylactic treatment dosing in adolescent patients is the same as for adult patients.

Elderly population
There is limited experience in patients ≥ 65 years.

Method of administration

Jivi is for intravenous use.

Jivi should be injected intravenously over a period of 2 to 5 minutes depending on the total volume. The rate of administration should be determined by the patient's comfort level (maximal rate of injection: 2.5 mL/min).

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reactions to mouse or hamster proteins.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions are possible with Jivi. The medicinal product may contain traces of mouse and hamster proteins. Hypersensitivity reactions could also be related to antibodies against PEG (see paragraph Immune response to polyethylene glycol (PEG)). If symptoms of hypersensitivity occur, patients should be advised to discontinue the use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Symptomatic treatment for hypersensitivity should be instituted as appropriate. In case of anaphylaxis or shock, the current medical standards for treatment should be implemented.

Inhibitors

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia 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. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days (ED) but continues throughout life although the risk is uncommon. Rarely, inhibitors may develop after the first 50 exposure days.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

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.

If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

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 primarily within the first 4 exposure days. Low post-injection factor VIII levels in the absence of detectable factor VIII inhibitors indicate that loss of drug effect is likely due to anti-PEG antibodies; in such cases Jivi should be discontinued and patients switched to a previously effective factor VIII product.

A significant decrease in the risk of an immune response to PEG was observed with an increase in age. This effect may be related to a developmental change in immunity, and although it is difficult to define a clear cut-off age for the change in risk, this phenomenon predominantly occurs in young children with haemophilia.

The implications of any potential risk to affected patients with a hypersensitivity reaction to pegylated proteins are unknown. Data show that in the affected subjects, following discontinuation of Jivi, the anti-PEG IgM antibodies decreased in titre and became undetectable over time . No cross-reactivity of anti-PEG IgM antibodies with other unmodified factor VIII products was observed. All patients could be successfully treated with their previous factor VIII products.

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk.

Catheter-related complications

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

Paediatric population

The listed warnings and precautions apply both to adults and adolescents.
Jivi is not indicated in patients < 12 years of age and in previously untreated patients.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions of human coagulation factor VIII (rDNA) products with other medicinal products have not been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and breast-feeding only if clearly indicated.

Fertility

In the repeat dose systemic toxicity studies in rats and rabbits with Jivi, treatment related effects on male reproductive organs were not seen (see section 5.3). The effect on fertility in humans is unknown.

4.7 Effects on ability to drive and use machines

Jivi has no influence on the ability to drive and use machines

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed and may in some cases progress to severe anaphylaxis (including shock).

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Jivi (see section 5.1). If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialized haemophilia centre be contacted.

The most frequently reported adverse reactions in clinical trials in PTPs were headache, cough and pyrexia.

Tabulated list of adverse reactions

A total of 221 patients constituted the safety population from three pivotal Phase I and III studies [PROTECT VIII], 148 adolescents/adults and 73 paediatric patients < 12 years. In PROTECT VIII, 121 patients continued in the extension study with a median total treatment duration of 3.9 years [range: 0.8-7.0].
In the paediatric study, 59/73 patients < 12 years continued in the extension study. Median (range) total time in study (main study + extension) was 5.8 (1.0-6.6) years with a median of 430 (range 98-671) ED per subject, 39 subjects were treated for =/> 5 years.
The median number of exposure days to Jivi per subject was 237 (min-max.: 1-698) for all subjects in the clinical studies.
Overall, in both studies 75 patients were observed for a treatment duration of more than 5 years.

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Frequency of adverse drug reactions in clinical trials

MedDRA Standard System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	FVIII inhibition	Uncommon (PTPs)[a]
Immune system disorders	Hypersensitivity	common
Psychiatric disorders	Insomnia	common
Nervous system disorders	Headache	very common
	Dizziness	common
	Dysgeusia	uncommon
Vascular disorders	Flushing	uncommon
Respiratory, thoracic and mediastinal disorders	Cough	common
Gastrointestinal disorders	Abdominal pain, Nausea, Vomiting	common
Skin and subcutaneous tissue disorders	Erythema[c], Rash[d]	common
	Pruritus	uncommon
General disorders and administration site conditions	Injection site reactions[b], Pyrexia	common

[a] Frequency is based on studies with all factor VIII products which included patients with severe haemophilia A. PTPs = previously-treated patients
[b] includes injection site pruritus, injection site rash and vessel puncture site pruritus
[c] includes erythema and erythema multiforme
[d] includes rash and rash papular

There was no change in the safety profile during the PROTECT VIII and the paediatric extension studies.

Description of selected adverse reactions

Immunogenicity
Immunogenicity was evaluated during clinical trials with Jivi in 159 (including surgery patients) previously treated adolescents (≥ 12 years of age) and adults diagnosed with severe haemophilia A (FVIII:C < 1%), and ≥ 150 previous exposure days.

FVIII 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 with development of specific IgM anti-PEG antibodies was observed in one patient. The immune response was accompanied by a clinical hypersensitivity reaction after 4 injections of Jivi. Antibodies to PEG disappeared after discontinuation of Jivi. No clinical immune response to PEG resulting in loss of drug efficacy or hypersensitivity was observed from the 5th ED through the end of the extension studies.

Paediatric population
In completed clinical studies with 73 paediatric PTPs < 12 years (44 PTPs < 6 years, 29 PTPs 6 - <12 years), adverse reactions due to immune response to PEG were observed in children less than 6 years of age. In 10 of 44 patients (23%) in the age group of younger than 6 years of age loss of drug effect due to neutralising anti-PEG antibodies during the first 4 exposure days was observed. In 3 of 44 patients (7%), loss of drug effect was combined with hypersensitivity reactions (see section 4.4). No triggers or predictors of the immune response to PEG could be identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There was one case of overdose in the clinical trials. No adverse events were reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics: blood coagulation factor VIII,
ATC code: B02BD02.

Mechanism of action

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a patient with haemophilia, factor VIII binds to patient's von Willebrand factor. 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 then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels or absence of factor VIII:C that results in bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Damoctocog alfa pegol is a PEGylated form of rFVIII. Site-specific PEGylation reduces clearance of factor VIII resulting in an extended half-life while maintaining the normal functions of the B-domain deleted rFVIII molecule (see section 5.2). Damoctocog alfa pegol does not contain von Willebrand factor.

Clinical efficacy and safety

Clinical studies

A total of 232 previously treated patients with severe haemophilia A have been exposed in the clinical trial program which included one phase I study and two phase II/III studies. One-hundred and fifty nine (159) subjects were ≥ 12 years of age,

Phase II/III (PROTECT VIII): The pharmacokinetics, safety and efficacy of Jivi for on demand treatment, prophylaxis with three regimens (two times per week 30-40 IU/kg, every 5-days 45-60 IU/kg and every 7-days 60 IU/kg) and haemostasis during major surgeries were evaluated in a multi-national, open-label, uncontrolled, partially randomized study which was performed in compliance with the agreed Paediatric Investigation Plan. An extension study included patients completing the main study. The primary efficacy variable was annualized bleed rate (ABR).

One hundred and thirty four male PTPs received at least one injection of Jivi (including 13 subjects aged 12 to 17 years of age) for prophylaxis (n=114) or on-demand treatment (n=20) for a period of 36 weeks. A total of 121 subjects received treatment during the extension study, 107 subjects received prophylaxis and 14 subjects on-demand treatment. Thirty-six subjects received prophylaxis treatment for >5 years up to 7.0 years. Total median (range) time in study was 3.9 years (0.8 – 7.0 years) in all 121 patients. Hemostasis during 20 major surgeries in 17 patients was evaluated in the surgery part.

Phase III (Paediatric): Pharmacokinetics, safety, and efficacy of Jivi for three prophylaxis regimens (twice weekly, every 5 and every 7 days) and treatment of breakthrough bleeds were evaluated in a multi-national, uncontrolled, open-label trial in 73 paediatric patients (< 12 years of age) during a period of 50 EDs and at least 6 months. This study has been performed in compliance with the agreed Paediatric Investigation Plan. Sixty one subjects (83.6%) completed the main study and 59 patients continued in the optional extension study with a total median time in study of 5.8 years (range 1.0-6.6 years).

Prophylactic treatment in subjects ≥12 years

During the main study period subjects were assigned to prophylaxis 2x/week (n=24), or randomized to every 5 days (n=43) or every 7 days (n=43) or received on-demand treatment (n=20) with Jivi. Ninety nine of 110 patients (90%) remained on the assigned regimen. Eleven patients in the every 7 days arm increased frequency. The median dose for all prophylaxis regimens was 46.9 IU/kg/injection. The median (Q1; Q3) ABR during prophylaxis was 2.09 (0.0; 6.1) for all bleeds and 0.0 (0.0; 4.2) for spontaneous bleeds as compared to 23.4 (18; 37) total bleeds in the on-demand group. Forty-two out of 110 in the prophylaxis arms (38.2%) experienced no bleeding episode.

During the extension study (median duration of 3.2 years, range 0.1-6.3 years), 23 patients were treated 2x/week, 33 patients every 5-days, 23 patients every 7 days during total time in

the extension study and 28 patients changed treatment regimen. The median dose for prophylaxis was 47.8 IU/kg. The overall median (Q1; Q3) total ABR was 1.49 (0.4; 4.8) and 0.75 (0.0; 2.9) for spontaneous bleeds in the combined prophylaxis groups and total ABR was 34.1 in the on-demand group.
Of note, ABR is not comparable between different factor concentrates and between different clinical studies.

Treatment of bleeding

Of the 702 bleeding events treated with Jivi during the main study, 636 (90.6%) were treated with 1 or 2 injections, thereof 81.1% with 1 injection. The median (range) dose per injection was 31.7 IU/kg (14; 62). During the extension 1902 bleeds were treated with Jivi and 94.0% were controlled with 1 or 2 injections, thereof 84.9% with 1 injection. The median (range) dose was 37.9 (15; 64) IU/kg/injection.

Perioperative Management

A total of 20 major surgical procedures were performed and assessed in 17 patients. The median total dose for major surgeries was 219 IU/kg (range: 50-1500 IU/kg, including postoperative period up to 3 weeks). Perioperative haemostatic efficacy was rated as good or excellent during all major surgeries.
Additional 34 minor surgeries were performed in 19 patients. Hemostasis was assessed as good or excellent in all available cases.

Paediatric population < 12 years of age

The use of Jivi in children below 12 years is not indicated (see section 4.2, for information on paediatric use).
A total of 73 previously treated paediatric patients (44 subjects < 6 years and 29 subjects 6 to <12 years) received prophylaxis treatment twice weekly, every 5 days or every 7 days in the phase III study. For 53 patients who completed the main study, the median (Q1; Q3) annualised bleeding rate was 2.87 (1.1; 6.1) and the spontaneous ABR was 0.0 (0.0; 2.6). For treatment of bleeds, 84.4 % of the bleeds were resolved with 1 injection, and 91.9% of the bleeds were resolved with 1 or 2 injections.
11 patients in the age group < 6 years dropped out due to an immune response to PEG associated with loss of efficacy and/or hypersensitivity reaction during the first four ED.
For 59 patients who continued in the extension study the overall median (Q1; Q3) ABR during the extension period was 1.64 (0.5; 3.1). For 30 patients ≥ 12 years at the end of the extension study, the median (Q1; Q3) ABR was 1.76 (0.5; 3.3).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of Jivi was compared to that of factor VIII in a crossover Phase I study. PK was also evaluated in 22 subjects (≥12 yrs) and in 16 of these subjects after 6 months of prophylaxis treatment in the Phase II/III study.

The PK data (based on chromogenic assay) indicated that Jivi has a reduced clearance (CL), resulting in a terminal half-life that is 1.4-fold longer and a dose normalized AUC which is 1.4-fold higher, as compared to the comparative factor VIII product.

Dose proportional increases were observed between the doses of 25 and 60 IU/kg indicating dose linearity between 25 IU/kg and 60 IU/kg.

Table 3 summarizes the PK parameters after single dose of 60 IU/kg from the Phase II/III study where PK was evaluated in 22 subjects. Repeated PK measurements did not indicate any relevant changes in PK characteristics after long-term treatment.

Table 3: Pharmacokinetic parameters (geometric mean (%CV) and arithmetic mean (±SD)) for Jivi following a single 60 IU/kg dose based on chromogenic assay.

Parameters (units)	Jivi Patients ≥12 years n=22
AUC (IU*h/dL)	3710 (33.8) 3900 ± 1280
AUC, norm (h*kg/dL)	62.5 (33.7) 65.7 ± 21.4
Cmax (IU/dL)	163 (14.7) 164 ± 23.8
t½ (h)	17.1 (27.1) 17.6 ± 4.26
MRTIV (h)	24.4 (27.5) 25.2 ± 6.19
Vss (dL/kg)	0.391 (16.3) 0.396 ± 0.0631
CL (dL/h/kg)	0.0160 (33.7) 0.0168 ± 0.00553

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

Incremental recovery was determined in 131 patients at several time points. The median (Q1; Q3) recovery was 2.6 (2.3; 3.0) by chromogenic assay.

A population PK model was developed based on all available factor VIII measurements (from dense PK sampling and all recovery samples) throughout the 3 clinical studies allowing calculation of PK parameters for subjects in the various studies. The table 4 below provides PK parameters based on the population PK model.

Table 4: PK parameters (geometric mean [%CV]) based on population PK model, using chromogenic assay.

PK parameter(unit)	12-<18 years N=12	≥ 18 years N=133	Total (≥ 12 years) N=145
AUC (IU.h/dL)*	3341 (34.2)	4052 (31.1)	3997 (31.6)
AUCnorm (kg.h/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)
Vss (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 calculated for a dose of 60 IU/kg

5.3 Preclinical safety data

Jivi was evaluated in pharmacology, single and repeated dose as well as juvenile toxicity studies in rats and rabbits. In a long-term, 6-months chronic toxicity study no indication of PEG accumulation or other effects related to administration of Jivi were seen. In addition 4 weeks toxicity studies with the PEG moiety of Jivi were conducted in two species. The PEG-linker moiety was also tested in a standard set of in vivo and in vitro genotoxicity studies and they did not indicate a potential for genotoxicity. These studies did not reveal any safety concerns for humans.

Single dose studies in rats with the radio-labelled 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 compound did not cross the blood brain barrier. In distribution and excretion studies in rats, the 60 kDa PEG moiety of Jivi was shown to be widely distributed to and eliminated from organs and tissues, and excreted in urine (68.4% up to day 231 after administration) and faeces (13.8% up to day 168 after administration).

No long-term studies in animals to evaluate the carcinogenic potential of Jivi, or studies to determine the effects of Jivi on reproduction have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Histidine
Glycine
Sodium chloride
Calcium chloride dihydrate
Polysorbate 80
Acetic acid, glacial (for pH adjustment)

Solvent
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Only the components provided in the package should be used for reconstitution and injection because treatment failure can occur as a consequence of factor VIII adsorption to the internal surfaces of some injection equipment.

6.3 Shelf life

Unopened vial

2 years.

Reconstituted solution

The chemical and physical in-use stability after reconstitution has been demonstrated for 3 hours at room temperature. Do not refrigerate after reconstitution.

From a microbiological point of view the product should be used immediately after reconstitution. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

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

Within its overall shelf life of 2 years, the product (when kept in its outer carton) may be stored at up to 25 °C for a limited period of 6 months. The end date of the 6 month storage period at a temperature up to 25 °C should be recorded on the product carton. This date should never exceed the expiry date printed on the outer carton. At the end of this period the product should not be put back in the refrigerator, but should be used or discarded.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each single package of Jivi contains:

- one vial with powder (10 mL clear type 1 glass vial with grey bromobutyl rubber blend stopper and aluminium seal)
- one pre-filled syringe with 2.5 mL solvent (clear type 1 glass cylinder syringe with grey bromobutyl rubber blend stopper)
- one syringe plunger rod
- one vial adapter (with integrated filter)

- one venipuncture set

Pack sizes

~ 1 single pack.

~ 1 multipack with 30 single packs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Detailed instructions for preparation and administration are contained in the package leaflet provided with Jivi.

Jivi powder should only be reconstituted with the supplied solvent (2.5 mL water for injections) in the prefilled-syringe and the vial adapter. The medicinal product must be prepared for injection under aseptic conditions. If any component of the package is opened or damaged, do not use this component.

After reconstitution the solution is clear and colourless and then drawn back into the syringe. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration

The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the vial adapter.

Jivi is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer plc

400 South Oak Way

Reading

RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00010/0683

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/06/2023

10 DATE OF REVISION OF THE TEXT

23/06/2023