ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Jivi 250 IU powder and solvent for solution for injection
Jivi 500 IU powder and solvent for solution for injection
Jivi 1000 IU powder and solvent for solution for injection
Jivi 2000 IU powder and solvent for solution for injection
Jivi 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jivi 250 IU powder and solvent for solution for injection

After reconstitution with the solvent provided, one mL of solution contains approximately 100 IU (250 IU/2.5 mL) of human coagulation factor VIII, damoctocog alfa pegol.

Jivi 500 IU powder and solvent for solution for injection

After reconstitution with the solvent provided, one mL of solution contains approximately 200 IU (500 IU/2.5 mL) of human coagulation factor VIII, damoctocog alfa pegol.

Jivi 1000 IU powder and solvent for solution for injection

After reconstitution with the solvent provided, one mL of solution contains approximately 400 IU (1 000 IU/2.5 mL) of human coagulation factor VIII, damoctocog alfa pegol.

Jivi 2000 IU powder and solvent for solution for injection

After reconstitution with the solvent provided, one mL of solution contains approximately 800 IU (2 000 IU/2.5 mL) of human coagulation factor VIII, damoctocog alfa pegol.

Jivi 3000 IU powder and solvent for solution for injection

After reconstitution with the solvent provided, one mL of solution contains approximately 1 200 IU (3 000 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 10 000 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 dose, 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 6 000 IU.

Special populations

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
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 essentially 'sodium-free'.

4.5 Interactions 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 studies 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) , rare (≥1/10 000 to <1/1 000); very rare (<1/10 000).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Frequency of adverse drug reactions in clinical studies

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 studies 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 national reporting system listed in Appendix V.

4.9 Overdose

There was one case of overdose in the clinical studies. 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 study 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. Haemostasis 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 study 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 (14; 62) IU/kg. 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. Haemostasis 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 years) 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
C_{max} (IU/dL)	163 (14.7) 164 ± 23.8
$t_{½}$ (h)	17.1 (27.1) 17.6 ± 4.26
MRT_{IV} (h)	24.4 (27.5) 25.2 ± 6.19
V_{ss} (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)
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 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 (E 640)
Sodium chloride
Calcium chloride dihydrate (E 509)
Polysorbate 80 (E 433)
Acetic acid, glacial (for pH adjustment) (E 260)

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.

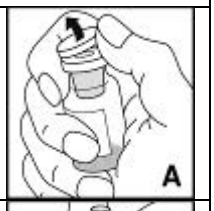
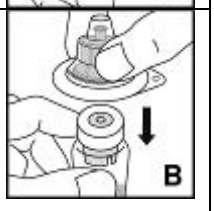
6.6 Special precautions for disposal and other handling

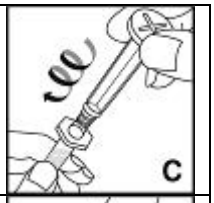
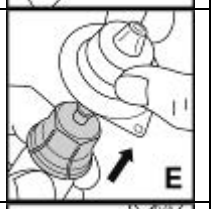
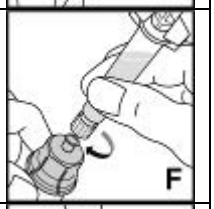
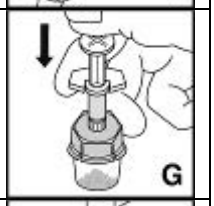
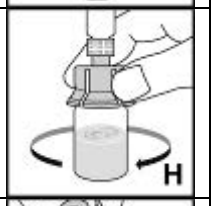
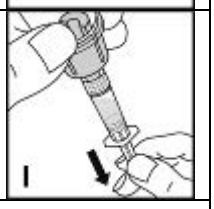
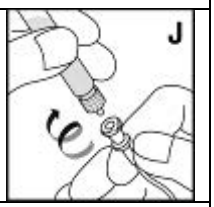
Jivi powder should only be reconstituted with the supplied solvent (2.5 mL water for injections) in the prefilled-syringe and the vial adapter. The medicinal product must be prepared for injection under aseptic conditions. If any component of the package is opened or damaged, do not use this component.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

Detailed instructions for reconstitution and administration of Jivi
You will need alcohol swabs, gauze pads, plasters and tourniquet. These items are not included in the Jivi package.

1.	Wash your hands thoroughly using soap and warm water.	
2.	Hold an unopened vial and also a syringe in your hands to warm it to a comfortable temperature (do not exceed 37 °C).	
3.	Remove the protective cap from the vial **(A)**. Wipe the rubber stopper on the vial with an alcohol swab and allow the stopper to air dry before use.	
4.	Place **the powder vial** on a firm, non-slip surface. Peel off the paper cover on the plastic housing of the vial adapter. **Do not remove** the adapter from the plastic housing. Holding the adapter housing, place over the powder vial and firmly press down **(B)**. The adapter will snap over the vial cap. **Do not remove** the adapter housing at this point.	

5.	Hold the pre-filled syringe with solvent upright. Grasp the plunger rod as per the picture and attach the rod by turning it firmly clockwise into the threaded stopper **(C).**	
6.	Holding the syringe by the barrel, snap the syringe cap off the tip **(D)**. Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.	
7.	Now remove and discard the adapter housing **(E)**.	
8.	Attach the pre-filled syringe to the threaded vial adapter by turning clockwise **(F).**	
9.	Inject the solvent by slowly pushing down on the plunger rod **(G)**.	
10.	Swirl vial gently until all the powder is dissolved **(H)**. Do not shake the vial. Be sure that the powder is completely dissolved. Look to check there are no particles or discoloration before you use the solution. Do not use solutions containing visible particles or that are cloudy.	
11.	Hold the vial on the end above the vial adapter and syringe **(I)**. Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the full content of the vial is drawn into the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.	
12.	Apply a tourniquet to your arm.	
13.	Determine the point of injection and clean the skin.	
14.	Puncture the vein and secure the venipuncture set with a plaster.	
15.	Holding the vial adapter in place, remove the syringe from the vial adapter (the adapter should remain attached to the vial). Attach the syringe to the venipuncture set **(J)**. Ensure that no blood enters the syringe	
16.	Remove tourniquet.	
17.	Inject the solution into a vein over 2 to 5 minutes, keeping an eye on the position of the needle. The speed of injection should be based on your comfort, but should not be faster than 2.5 mL per minute.	

18.	If a further dose is needed, use a new syringe with the powder reconstituted as described above.
19.	If no further dose is required, remove the venipuncture set and syringe. Hold a pad firmly over the injection site on your outstretched arm for about 2 minutes. Finally, apply a small pressure dressing to the injection site and consider if a plaster is necessary.
20.	It is recommended that every time you use Jivi, you note down the name and the batch number of the product.
21.	**Do not** throw away any medicines via wastewater or household waste. Ask your pharmacist or physician how to throw away medicines you no longer use. These measures will help protect the environment

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 AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/18/1324/001 – 1 x (Jivi 250 IU)
EU/1/18/1324/002 – 1 x (Jivi 500 IU)
EU/1/18/1324/003 – 1 x (Jivi 1000 IU)
EU/1/18/1324/004 – 1 x (Jivi 2000 IU)
EU/1/18/1324/005 – 1 x (Jivi 3000 IU)
EU/1/18/1324/006 – 30 x (Jivi 250 IU)
EU/1/18/1324/007 – 30 x (Jivi 500 IU)
EU/1/18/1324/008 – 30 x (Jivi 1000 IU)
EU/1/18/1324/009 – 30 x (Jivi 2000 IU)
EU/1/18/1324/010 – 30 x (Jivi 3000 IU)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2018
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Bayer HealthCare LLC
800 Dwight Way
Berkeley
CA
94710
United States

Name and address of the manufacturer responsible for batch release

Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post Authorisation Safety Study (PASS): In order to investigate the potential	Final study protocol

effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a non-interventional post-authorisation safety study according to an agreed protocol.	should be submitted within 3 months after CHMP Opinion. Final study report should be submitted by 31 December 2028

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 250 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 100 IU damoctocog alfa pegol after reconstitution (250 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

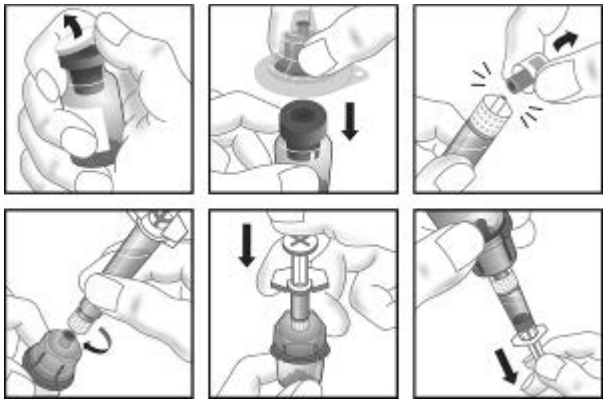
powder and solvent for solution for injection.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/001 – 1 x (Jivi 250 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 250 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 100 IU damoctocog alfa pegol after reconstitution (250 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/006 – 30 x (Jivi 250 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 250 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 100 IU damoctocog alfa pegol after reconstitution (250 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

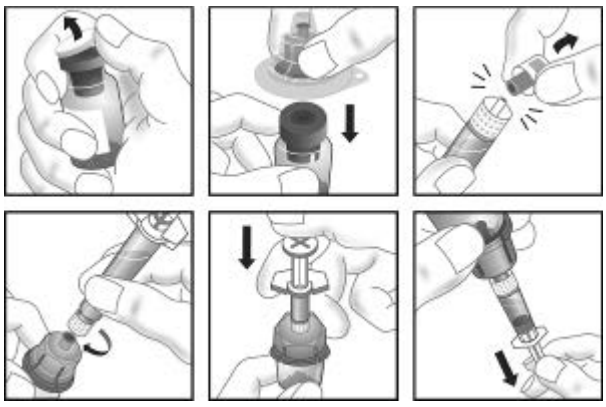
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/006 – 30 x (Jivi 250 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 250

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Jivi 250 IU powder for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU (damoctocog alfa pegol) .

6. OTHER

Bayer-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 500 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 200 IU damoctocog alfa pegol after reconstitution (500 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

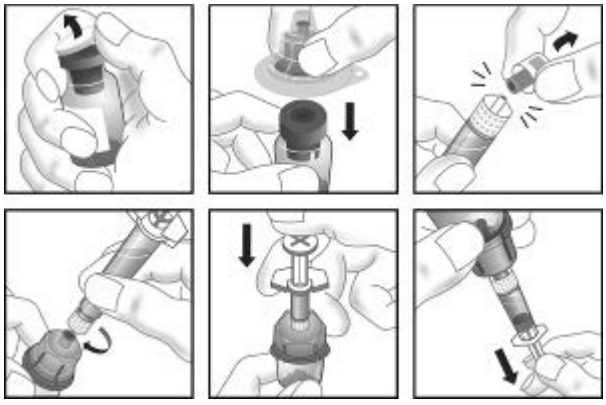
powder and solvent for solution for injection.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/002 – 1 x (Jivi 500 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 500 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 200 IU damoctocog alfa pegol after reconstitution (500 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/007 – 30 x (Jivi 500 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 500 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 200 IU damoctocog alfa pegol after reconstitution (500 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

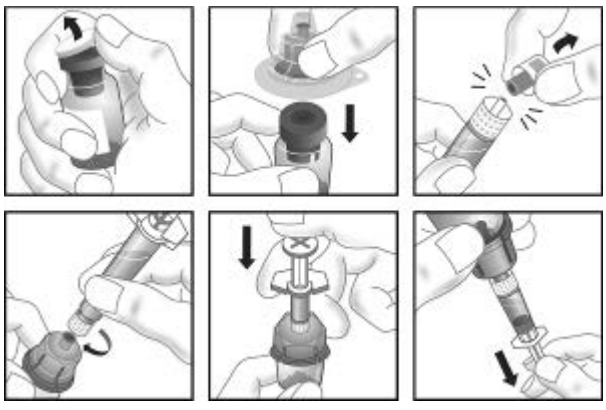
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/007 – 30 x (Jivi 500 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 500

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Jivi 500 IU powder for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU (damoctocog alfa pegol).

6. OTHER

Bayer-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 1000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 400 IU damoctocog alfa pegol after reconstitution (1 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

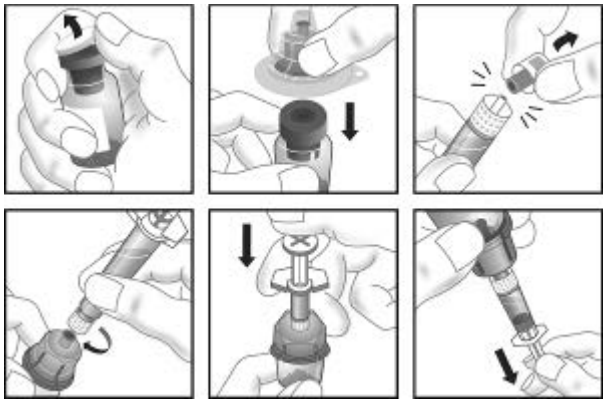
powder and solvent for solution for injection.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/003 – 1 x (Jivi 1000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 1000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 400 IU damoctocog alfa pegol after reconstitution (1 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/008 – 30 x (Jivi 1000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 1000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 400 IU damoctocog alfa pegol after reconstitution (1 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

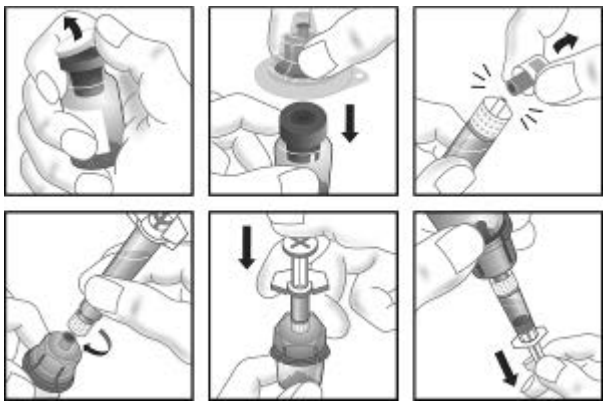
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/008 – 30 x (Jivi 1000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Jivi 1000 IU powder for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 000 IU (damoctocog alfa pegol).

6. OTHER

Bayer-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 2000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 800 IU damoctocog alfa pegol after reconstitution (2 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

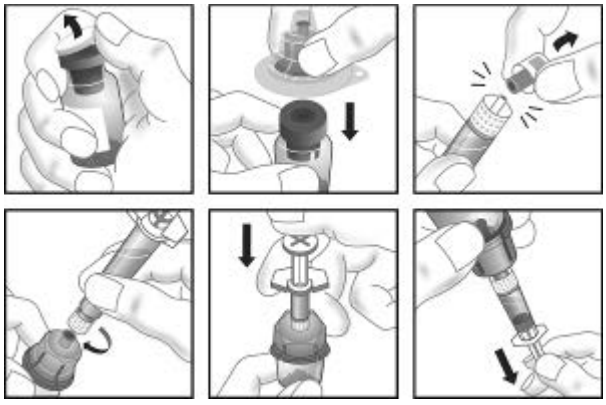
powder and solvent for solution for injection.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/004 -1 x (Jivi 2000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 2000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 800 IU damoctocog alfa pegol after reconstitution (2 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/009 – 30 x (Jivi 2000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 2000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 800 IU damoctocog alfa pegol after reconstitution (2 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

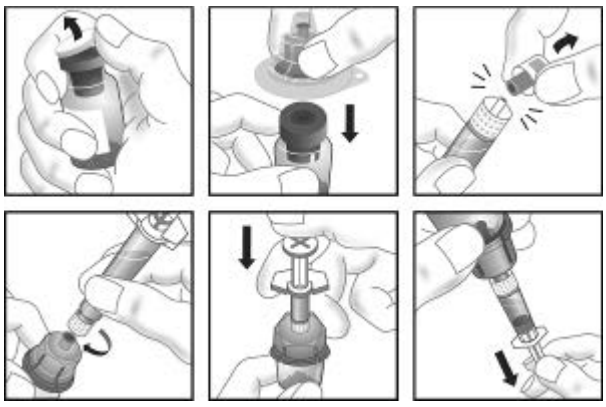
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/009 – 30 x (Jivi 2000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Jivi 2000 IU powder for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 000 IU (damoctocog alfa pegol).

6. OTHER

Bayer-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 3000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 1 200 IU damoctocog alfa pegol after reconstitution
(3 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

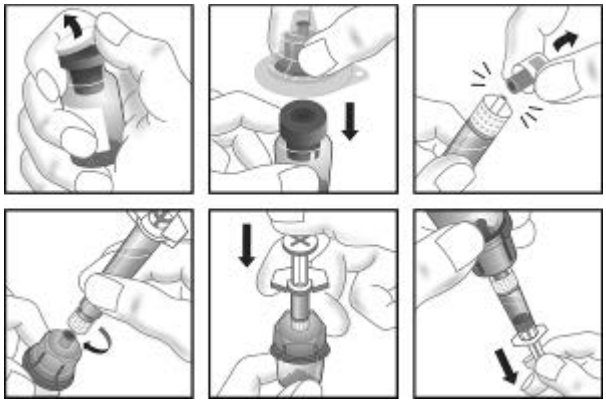
powder and solvent for solution for injection.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/005 – 1 x (Jivi 3000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 3000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 1 200 IU damoctocog alfa pegol after reconstitution
(3 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/010 – 30 x (Jivi 3000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Jivi 3000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains approximately 1 200 IU damoctocog alfa pegol after reconstitution
(3 000 IU / 2.5 mL).

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine (E 640), sodium chloride, calcium chloride dihydrate (E 509), polysorbate 80 (E 433), acetic acid glacial (E 260) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection.

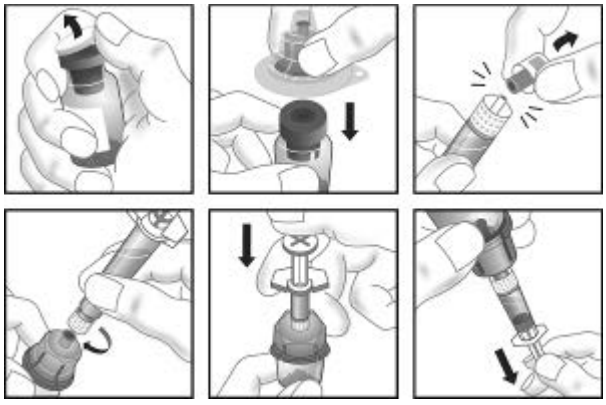
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter and
1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single dose only.
Read the package leaflet before use.
For intravenous use.

For reconstitution using the vial adapter read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 6 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 6 months within the expiry date indicated on the label. Note the new expiry date on the carton.

After reconstitution:
- The product must be used within 3 hours.
- Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Before reconstitution:
- Store in a refrigerator.
- Do not freeze.
- Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1324/010 – 30 x (Jivi 3000 IU)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jivi 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Jivi 3000 IU powder for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 000 IU (damoctocog alfa pegol).

6. OTHER

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Jivi 250 IU powder and solvent for solution for injection
Jivi 500 IU powder and solvent for solution for injection
Jivi 1000 IU powder and solvent for solution for injection
Jivi 2000 IU powder and solvent for solution for injection
Jivi 3000 IU powder and solvent for solution for injection

PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Jivi is and what it is used for

Jivi contains the active substance damoctocog alfa pegol. It is produced by recombinant technology without addition of any human- or animal-derived components in the manufacturing process. Factor VIII is a protein naturally found in the blood that helps to clot it. The protein in damoctocog alfa pegol has been modified (pegylated) to prolong its action in the body.

Jivi is used to **treat and prevent bleeding** in previously treated adults and adolescents aged from 12 years with haemophilia A (hereditary factor VIII deficiency). It is not for use in children younger than 12 years of age.

2. What you need to know before you use Jivi

Do not use Jivi if you are
- allergic to damoctocog alfa pegol or any of the other ingredients of this medicine (listed in section 6).
- allergic to mouse or hamster proteins.

Warnings and precautions
Talk to your doctor or pharmacist if you have
- tightness in the chest, fall in blood pressure (often shown by feeling dizzy when getting up quickly), itchy nettle-rash, wheezing, feeling sick or faint. These may be signs of a rare severe **sudden allergic reaction** to this medicine. **Stop injecting the product** immediately and get medical help at once if this occurs.
- bleeding that is not being controlled with your usual dose of this medicine. Speak with your doctor immediately if this occurs. You may have developed antibodies against factor VIII (inhibitors) or antibodies against polyethylene glycol (PEG). These make Jivi less effective at preventing and controlling bleeding. Your doctor may carry out tests to confirm this and ensure

that your Jivi dose provides adequate factor VIII levels. Your doctor may switch you back to your previous factor VIII treatment, if needed.
- previously developed factor VIII inhibitors to a different product.
- heart disease or you are at risk of heart disease.
- to use a central venous access device for this medicine. You may be at risk of device-related complications where the catheter is inserted including:
  - local infections
  - bacteria in the blood
  - a blood clot in the blood vessel

Children
Jivi is not for use in children younger than 12 years of age.

Other medicines and Jivi
Jivi is not known to influence or be influenced by other medicines. Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
Jivi has no influence on your ability to drive and use machines.

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

3. How to use Jivi

Treatment with Jivi will be started by a doctor who is experienced in the care of patients with haemophilia A. After suitable training patients or carers may be able to give Jivi at home.
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The dose of factor VIII units is measured in International Units (IU).

Treatment of bleeding
To treat a bleed, your doctor will calculate and adjust your dose and how often it should be given, depending on factors such as:
- your weight
- the severity of your haemophilia A
- where the bleeding is and how serious it is
- whether you have inhibitors and how high their level is
- the factor VIII level that is needed.

Prevention of bleeding
To prevent bleeding your doctor will select an appropriate dose and frequency depending on your need:
- 45–60 IU per kg body weight every 5 days or
- 60 IU per kg body weight every 7 days or
- 30–40 IU per kg body weight two times per week.

Laboratory tests
Laboratory tests at suitable intervals help to ensure you always have adequate factor VIII levels. For major surgery in particular, your blood clotting must be closely monitored.

Duration of treatment
Usually Jivi treatment for haemophilia is needed lifelong.

How Jivi is given
Jivi is injected into a vein over 2 to 5 minutes depending on the total volume and your comfort level. The maximum rate is 2.5 mL per minute. Jivi should be used within 3 hours after reconstitution.

How Jivi is prepared for injection
Use only the components (vial adapter, pre-filled syringe containing solvent and venipuncture set) provided with each package of this medicine. Please contact your doctor if these components cannot be used. Do not use if any component of the package is opened or damaged.

The reconstituted product must be **filtered by using the vial adapter** before injection to remove any possible particles in the solution.

This medicine must **not** be mixed with other injections. Do not use solutions that are cloudy or contain visible particles. Follow the **instructions for use** given by your doctor and provided **at the end of this leaflet.**

If you use more Jivi than you should
Tell your doctor if this occurs. No symptoms of overdose have been reported.

If you forget to use Jivi
Inject your next dose immediately and continue at regular intervals as advised by your doctor.
Do not use a double dose to make up for a forgotten dose**.**

If you stop using Jivi
Do not stop using this medicine without checking with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most **serious** side effects are **allergic reactions** or severe allergic reaction. **Stop injecting Jivi immediately and speak to your doctor at once if such reactions occur.** The following symptoms could be an early warning of these reactions:
- chest tightness/general feeling of being unwell
- burning and stinging at the application site
- nettle–rash, flushing
- a reduction in blood pressure, which may make you feel faint upon standing
- feeling sick (nausea)

For patients who have received previous treatment with factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens your medicine may stop working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately.

The following side effects may occur with this medicine:

Very common (may affect more than 1 in 10 people):
- headache

Common (may affect up to 1 in 10 people):
- stomach pain

- nausea, vomiting
- fever
- allergic reactions (may present as hives, generalized urticaria, tightness of the chest, wheezing, shortness of breath, low blood pressure, for early symptoms see above)
- local reactions at the injection site such as bleeding under the skin, intense itching, swelling, burning sensation, temporary redness
- dizziness
- trouble falling asleep
- cough
- rash, skin reddening

Uncommon (may affect up to 1 in 100 people):
- FVIII inhibition
- taste disturbance
- flushing
- itching

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Jivi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on labels and cartons. The expiry date refers to the last day of that month.

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.

This medicine may be stored at room temperature (up to 25 °C) for up to 6 months when you keep it in its outer carton. If you store it at room temperature it expires after 6 months, or the expiry date if this is earlier.
The new expiry date must be noted on the outer carton when the medicine is removed from the refrigerator.

Do not refrigerate the solution after reconstitution. The reconstituted solution must be used within 3 hours.

Do not use this medicine if you notice any particles or the solution is cloudy.

This medicine is for single use only. Any unused solution must be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist or physician how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Jivi contains

- The active substance is PEGylated B-domain deleted recombinant human coagulation factor VIII (damoctocog alfa pegol). Each vial of Jivi contains nominally 250 or 500 or 1 000 or 2 000 or 3 000 IU damoctocog alfa pegol. After reconstitution with the supplied solvent (sterile water for injection), the prepared solutions have the following concentration:

Strength	Concentration after reconstitution approximately
250 IU	(100 IU / mL)
500 IU	(200 IU / mL)
1 000 IU	(400 IU / mL)
2 000 IU	(800 IU / mL)
3 000 IU	(1 200 IU / mL)

- The other ingredients are sucrose, histidine, glycine, sodium chloride (see section 2 "Jivi contains sodium"), calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

What Jivi looks like and contents of the pack

Jivi is provided as a powder and solvent for solution for injection. The powder is dry, and white to slightly yellow. The solvent is a clear liquid. After reconstitution the solution is clear.

Each single pack of Jivi contains:
- a glass vial with powder
- a pre-filled syringe with solvent
- a separate plunger rod
- a vial adapter
- a venipuncture set

Jivi is available in pack sizes of:
– 1 single pack
– 1 multipack with 30 single packs
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11

Lietuva
UAB Bayer
Tel. +37 05 23 36 868

България
Байер България ЕООД
Тел.: +359-(0)2-424 72 80

Česká republika
Bayer s.r.o.
Tel: +420 266 101 111

Danmark
Bayer A/S
Tlf: +45 45 23 50 00

Deutschland
Bayer Vital GmbH
Tel: +49 (0)214-30 513 48

Eesti
Bayer OÜ
Tel: +372 655 8565

Ελλάδα
Bayer Ελλάς ABEE
Τηλ: +30-210-61 87 500

España
Bayer Hispania S.L.
Tel: +34-93-495 65 00

France
Bayer HealthCare
Tél (N° vert): +33-(0)800 87 54 54

Hrvatska
Bayer d.o.o.
Tel: +385-(0)1-6599 900

Ireland
Bayer Limited
Tel: +353 1 216 3300

Ísland
Icepharma hf.
Sími: +354 540 8 000

Italia
Bayer S.p.A.
Tel: +39 02 397 8 1

Κύπρος
NOVAGEM Limited
Τηλ: +357 22 48 38 58

Latvija
SIA Bayer
Tel: +371 67 84 55 63

Luxembourg/Luxemburg
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11

Magyarország
Bayer Hungária KFT
Tel:+36 14 87-41 00

Malta
Alfred Gera and Sons Ltd.
Tel: +35 621 44 62 05

Nederland
Bayer B.V.
Tel: +31-23–799 1000

Norge
Bayer AS
Tlf: +47 23 13 05 00

Österreich
Bayer Austria Ges.m.b.H.
Tel: +43-(0)1-711 46-0

Polska
Bayer Sp. z o.o.
Tel: +48 22 572 35 00

Portugal
Bayer Portugal, Lda.
Tel: +351 21 416 42 00

România
SC Bayer SRL
Tel: +40 21 529 59 00

Slovenija
Bayer d. o. o.
Tel: +386 (0)1 58 14 400

Slovenská republika
Bayer spol. s r.o.
Tel. +421 2 59 21 31 11

Suomi/Finland
Bayer Oy
Puh/Tel: +358- 20 785 21

Sverige
Bayer AB
Tel: +46 (0) 8 580 223 00

United Kingdom (Northern Ireland)
Bayer AG
Tel: +44-(0)118 206 3 000

This leaflet was last revised in

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu

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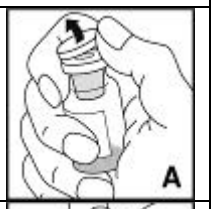
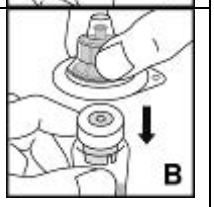
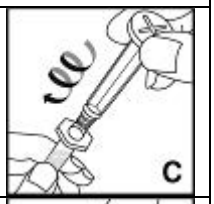
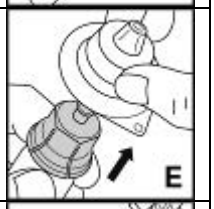
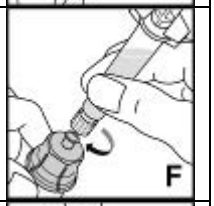
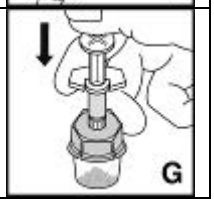
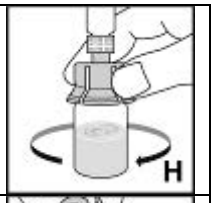
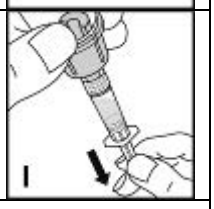
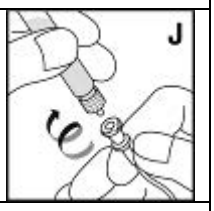
Detailed instructions for reconstitution and administration of Jivi
You will need alcohol swabs, gauze pads, plasters and tourniquet. These items are not included in the Jivi package.

1.	Wash your hands thoroughly using soap and warm water.	
2.	Hold an unopened vial and also a syringe in your hands to warm it to a comfortable temperature (do not exceed 37 °C).	
3.	Remove the protective cap from the vial **(A)**. Wipe the rubber stopper on the vial with an alcohol swab and allow the stopper to air dry before use.	
4.	Place **the powder vial** on a firm, non-slip surface. Peel off the paper cover on the plastic housing of the vial adapter. **Do not remove** the adapter from the plastic housing. Holding the adapter housing, place over the powder vial and firmly press down **(B)**. The adapter will snap over the vial cap. **Do not remove** the adapter housing at this point.	
5.	Hold the pre-filled syringe with solvent upright. Grasp the plunger rod as per the picture and attach the rod by turning it firmly clockwise into the threaded stopper **(C).**	
6.	Holding the syringe by the barrel, snap the syringe cap off the tip **(D)**. Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.	
7.	Now remove and discard the adapter housing **(E)**.	
8.	Attach the pre-filled syringe to the threaded vial adapter by turning clockwise **(F).**	
9.	Inject the solvent by slowly pushing down on the plunger rod **(G)**.	

10.	Swirl vial gently until all the powder is dissolved **(H)**. Do not shake the vial. Be sure that the powder is completely dissolved. Look to check there are no particles or discoloration before you use the solution. Do not use solutions containing visible particles or that are cloudy.	
11.	Hold the vial on the end above the vial adapter and syringe **(I)**. Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the full content of the vial is drawn into the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.	
12.	Apply a tourniquet to your arm.	
13.	Determine the point of injection and clean the skin.	
14.	Puncture the vein and secure the venipuncture set with a plaster.	
15.	Holding the vial adapter in place, remove the syringe from the vial adapter (the adapter should remain attached to the vial). Attach the syringe to the venipuncture set **(J)**. Ensure that no blood enters the syringe	
16.	Remove tourniquet.	
17.	Inject the solution into a vein over 2 to 5 minutes, keeping an eye on the position of the needle. The speed of injection should be based on your comfort, but should not be faster than 2.5 mL per minute.	
18.	If a further dose is needed, use a new syringe with the powder reconstituted as described above.	
19.	If no further dose is required, remove the venipuncture set and syringe. Hold a pad firmly over the injection site on your outstretched arm for about 2 minutes. Finally, apply a small pressure dressing to the injection site and consider if a plaster is necessary.	
20.	It is recommended that every time you use Jivi, you note down the name and the batch number of the product.	
21.	**Do not** throw away any medicines via wastewater or household waste. Ask your pharmacist or physician how to throw away medicines you no longer use. These measures will help protect the environment	