▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

JIVI® (DAMOCTOCOG ALFA PEGOL) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

Damoctocog alfa pegol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250, 500, 1000, 2000 or 3000 IU pegylated B-domain deleted recombinant human coagulation factor VIII (PEG-BDD-rFVIII) (INN: damoctocog alfa pegol), presented as sterile, stable, purified dried concentrate.
Each pre-filled syringe contains 2.5 mL of sterile water for injections for reconstitution.

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 List of excipients.

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

Jivi, damoctocog alfa pegol, is a long-acting recombinant Factor VIII concentrate indicated for use in previously treated adults and adolescents (12 years of age and older) with haemophilia A for:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Per-operative management of bleeding (surgical prophylaxis)

Jivi does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.
During the course of treatment, appropriate determination of factor VIII levels (by one-stage clotting or chromogenic assays) is advised to guide the dose to be administered and the frequency of repeated infusions.

Dosage regimen

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 International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one mL of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 1.5% to 2.5% of normal activity.
The clinical effect of factor VIII is the most important element in evaluating the effectiveness of treatment. It may be necessary to adjust the individual dosing at patient level in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected factor VIII levels or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating factor VIII-inhibitor or anti-PEG antibodies in the patient should be suspected (see section 4.4 Special warning and precautions for use).

On demand treatment
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.

The recommended initial dose is 30-40 IU/kg 2x times per week. Based on the patient's bleeding frequency, the regimen may be adjusted to 45-60 IU/kg every 5 days. Jivi can also be individually adjusted to less frequent dosing, e.g. 60 IU/kg every 7 days. Dosing should be based on the individual patient's overall bleeding pattern (see sections 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).

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

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.

Method of administration
Jivi is for intravenous use.

For instructions on reconstitution of the medicinal product before administration, see section Instructions for use/ handling below, see section 6.4 Special precautions for storage and the package leaflet.

Rate of Administration
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).

Each vial of Jivi is labeled with the actual factor VIII potency expressed in IU. The labelled potency is based on the chromogenic assay.
The total recommended maximum dose per infusion is approximately 6000 IU (rounded to vial size)(see Clinical studies; under section 5.1. Pharmacodynamic properties).

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

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

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

Instructions for use/ handling

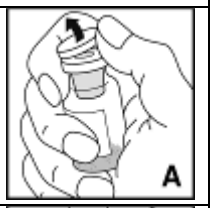
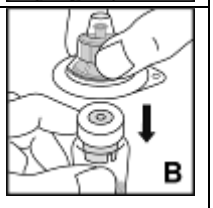
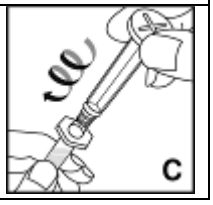
Jivi powder should only be reconstituted with the supplied solvent (2.5 mL water for injections) in the prefilled-syringe and the vial adapter. The medicinal product must be prepared for injection under aseptic conditions. If any component of the package is opened or damaged, do not use this component.

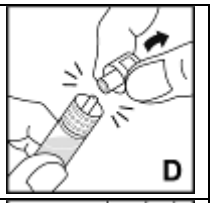
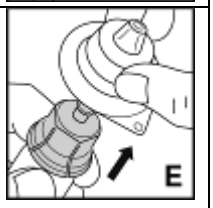
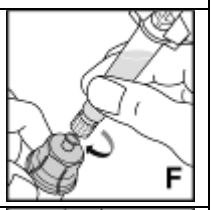
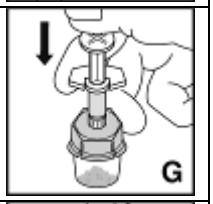
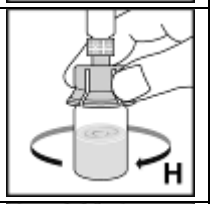
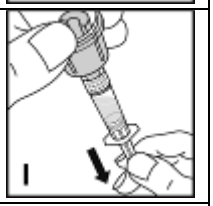
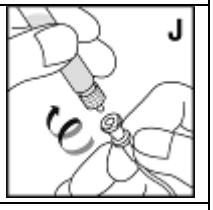
After reconstitution the solution is clear and colourless and then drawn back into the syringe. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

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 (see detailed instructions in the table below).

The product is for single use in one patient only. Discard any residue. Place needles in a sharps container after single-use. Discard all equipment, including any reconstituted Jivi product, in accordance with biohazard procedures.

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 product 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 of water for injections upright. Grasp the plunger rod as per the diagram 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 material is dissolved **(H)**. Do not shake 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 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 product 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 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.

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.
In completed clinical studies with 73 paediatric previously treated patients (PTPs) < 12 years of age (44 PTPs < 6 years, 29 PTPs 6 to < 12 years), adverse reactions due to immune response to PEG were observed in children less than 6 years of age. In 23% of patients in the age group < 6 years of age, loss of drug effect due to neutralizing anti-PEG IgM antibodies during the first 4 exposure days (EDs) was observed. In 7% of the patients < 6 years of age, loss of drug effect was combined with hypersensitivity reactions.

Sodium content

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

Use in the elderly

There is limited experience in patients ≥ 65 years.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interactions of human coagulation factor VIII (rDNA) products with other medicinal products have been reported.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of JIVI on human fertility.

Use in pregnancy – Pregnancy Category B2*

Animal reproduction studies have not been conducted with damoctocog alfa pegol. It is not known whether JIVI poses any risk to the fetus when administered to a pregnant woman. JIVI should be given to a pregnant woman only if clearly needed.

Use in lactation

The safety of JIVI for use in lactating women has not been established. It is not known if JIVI or its metabolites (including the PEG component) are excreted in human milk. Healthcare professionals should balance the potential risks and only prescribe JIVI to a breastfeeding woman if clearly needed

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**Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.*

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (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 Pharmacodynamic properties). If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialized haemophilia centre be contacted.

The most frequently reported adverse reactions in clinical trials in previously treated patients (PTPs) were headache, cough and pyrexia.

Tabulated list of adverse reactions

A total of 221 patients constituted the safety population from three pivotal Phase I and III studies [PROTECT VIII], 148 adolescents/adults and 73 paediatric patients < 12 years. In PROTECT VIII, 121 patients continued in the extension study with a median total treatment duration of 3.9 years [range: 0.8-7.0].
In the paediatric study, 59/73 patients < 12 years continued in the extension study. Median (range) total time in study (main study + extension) was 5.8 (1.0-6.6) years with a median of 430 (range 98-671) ED per subject, 39 subjects were treated for =/> 5 years. The median number of exposure days to Jivi per subject was 237 (min-max: 1-698) for all subjects in the clinical studies.
Overall, in both studies 75 patients were observed for a treatment duration of more than 5 years. The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse Reactions reported for Jivi in pivotal trials

MedDRA Standard System Organ Class Preferred term	All Subjects n (%) n=221	Subjects ≥12 years of age n (%) n=148
Gastrointestinal Disorders		
Abdominal pain	9 (4%)	5 (3%)
Nausea	9 (4%)	8 (5%)
Vomiting	10 (5%)	5 (3%)
General Disorders and Administration Site Conditions		
Injection site reactions[a]	4 (2%)	2 (1%)
Pyrexia (fever)	20 (9%)	8 (5%)
Immune System Disorders		
Hypersensitivity	8 (4%)	3 (2%)
Nervous System Disorders		
Dizziness	3 (1%)	3 (2%)
Dysgeusia (distorted sense of taste)	1 (1%)	0
Headache	29 (13%)	21 (14%)
Psychiatric Disorders		
Insomnia	5 (2%)	4 (3%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	18 (8%)	10 (7%)
Skin and Subcutaneous Tissue Disorders		
Erythema[b] (redness)	3 (1%)	2 (1%)
Pruritus (itching)	2 (1%)	1 (1%)
Rash[c]	9 (4%)	3 (2%)
VascularDisorders		
Flushing	1 (1%)	1 (1%)

[a] Includes Injection site pruritus and Injection site rash
[b] Includes Erythema and Erythema multiforme
[c] Includes Rash and Rash papular

Description of selected adverse reactions

Immunogenicity

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

FVIII inhibitors

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

Anti-PEG antibodies
Immunogenicity against PEG with development of specific IgM anti-PEG antibodies was observed in one patient. The immune response was accompanied by a clinical hypersensitivity reaction after 4 injections of Jivi. Antibodies to PEG disappeared after discontinuation of Jivi. No clinical immune response to PEG resulting in loss of drug efficacy or hypersensitivity was observed from the 5th ED through the end of the extension studies.
Paediatric population
In completed clinical studies with 73 paediatric PTPs < 12 years (44 PTPs < 6 years, 29 PTPs 6-< 12 years), adverse reactions due to immune response to PEG were observed in children less than 6 years of age. In 10 of 44 patients (23%) in the age group of younger than 6 years of age loss of drug effect due to neutralising anti-PEG antibodies during the first 4 exposure days was observed. In 3 of 44 patients (7%), loss of drug effect was combined with hypersensitivity reactions (see section 4.4 Special warnings and precautions for use). No triggers or predictors of the immune response to PEG could be identified.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 X-chromosomal 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 B-domain deleted recombinant human coagulation factor VIII (PEG-BDD-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 Pharmacokinetic properties). Damoctocog alfa pegol does not contain von Willebrand factor.

Clinical trials

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

Phase II/III (PROTECT VIII): The pharmacokinetics, safety and efficacy of Jivi for on demand treatment, prophylaxis with three regimens (two times per week 30-40 IU/kg, every 5-days 45-60 IU/kg and every 7-days 60 IU/kg) and haemostasis during major surgeries were evaluated in a multi-national, open-label, uncontrolled, partially randomized study. An extension study included patients completing the main study. The primary efficacy variable was annualized bleed rate (ABR). 134 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. 36 subjects received prophylaxis treatment for > 5 years up to 7.0 years. Total median (range) time in study was 3.9 years (0.8 – 7.0 years) in all 121 patients. Hemostasis during 20 major surgeries in 17 patients was evaluated in the surgery part.

Prophylactic treatment in subjects ≥12 years
All patients in the prophylaxis arms started with 2x/week at a dose of 25 IU/kg for 10 weeks. Thereafter, only patients with ≤ 1 breakthrough (spontaneous, no identified trauma) joint and/ or muscle bleeds qualified for random assignment to the less frequent dosing regimens. Those with 2 or more breakthrough bleeds were not randomized (2x/ week 'failed' group), and remained on the twice-weekly treatment at hogher doses (30-40 IU/kg). Treatment then continued for a further 26 weeks. Patients then had the option of continuing in the study extension.
After the 10 week 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. 99 of 110 patients (90%) remained on the assigned regimen. 11 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. 42 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. 20 patients needed to increase their dose frequency during the extension study, 13/37 (35%) patients in the every 7 days arm increased their frequency, with 8 of them moving to the every 5 days arm and remaining 5 patients moving to the 2x per week arm. 7/46 (15.2%) patients in the every 5 days arm at the start of the extension study increased frequency to 2x weekly by the end. The median dose for prophylaxis was 47.8 IU/kg.
The overall median (Q1; Q3) total ABR was 1.49 (0.4; 4.8) and 0.75 (0.0: 2.9) for spontaneous bleeds in the combined prophylaxis groups and total ABR was 34.1 in the on-demand group.
Of note, ABR is not comparable between different factor concentrates and between different clinical studies.
Treatment of bleeding
Of the 702 bleeding events treated with Jivi during the main study, 636 (90.6%) were treated with 1 or 2 injections, thereof 81.1% with 1 injection. The median (range) dose per injection was 31.7 IU/kg (14; 62). During the extension 1902 bleeds were treated with Jivi and 94.0% were controlled with 1 or 2 injections, thereof 84.9% with 1 injection. The median (range) dose was 37.9 (15; 64) IU/kg/injection.
Perioperative Management
A total of 20 major surgical procedures were performed and assessed in 17 patients. The median total dose for major surgeries was 219 IU/kg (range: 50-1500 IU/kg, including postoperative period up to 3 weeks). Perioperative haemostatic efficacy was rated as good or excellent during all major surgeries. Additional 34 minor surgeries were performed in 19 patients. Hemostasis was assessed as good or excellent in all available cases.

Phase III (Paediatric): Pharmacokinetics, safety, and efficacy of Jivi for three prophylaxis regimens (twice weekly, every 5 and every 7 days) and treatment of breakthrough bleeds were evaluated in a multi-national, uncontrolled, open-label trial in 73 paediatric patients (< 12 years of age) during a period of 50 EDs and at least 6 months. 61 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).

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 pediatric patients (n = 44 aged < 6 years and n = 29 aged 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) annualized 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.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of Jivi was compared to that of factor VIII in a crossover Phase I study. PK was also evaluated in 22 subjects (≥12 yrs) and in 16 of these subjects after 6 months of prophylaxis treatment in the Phase II/III study.
The PK data (based on chromogenic assay) indicated that Jivi has a reduced clearance (CL), resulting in a terminal half-life that is 1.4-fold longer and a dose normalized AUC which is 1.4-fold higher, as compared to the comparative factor VIII product. Dose proportional increases were observed between the doses of 25 and 60 IU/kg indicating dose linearity between 25 IU/kg and 60 IU/kg. Table 3 summarizes the PK parameters after single dose of 60 IU/kg from the Phase II/III study where PK was evaluated in 22 subjects. Repeated PK measurements did not indicate any relevant changes in PK characteristics after long-term treatment.

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

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

AUC: area under the curve; AUC, norm: dose normalized AUC Cmax: maximum drug concentration; , t½: terminal half-life; MRT_{IV} : mean residence time after an intravenous administration; VSS: 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**	**≥ 18 years**	**Total (≥ 12 years)**

	N=12	N=133	N=145
AUC (IU.h/dL)*	3341 (34.2)	4052 (31.1)	3997 (31.6)
AUCnorm (kg.h/dL)	57.4 (32.6)	67.5 (30.6)	66.6 (31.0)
$t_{1/2}$ (h)	16.8 (25.2)	17.4 (28.8)	17.4 (28.4)
Vss (dL/kg)	0.423 (15.5)	0.373 (15.6)	0.376 (15.9)
CL (dL/h/kg)	0.0174 (34.2)	0.0148 (31.1)	0.0150 (31.6)

*AUC calculated for a dose of 60 IU/kg

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No dedicated genotoxicity studies have been performed with damoctocog alfa pegol.The PEG-linker moiety was tested *in vivo* (micronucleus rat study_and *in vitro* (Ames test and mouse lymphoma assay) genotoxicity studies and they did not indicate a potential for genotoxicity.

Carcinogenicity

No studies in animals to evaluate the carcinogenic potential of damoctocog alfa pegol have been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

Solvent
Water for injections

6.2 INCOMPATIBILITIES

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

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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.

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. The product is for single use in one patient only. Discard any residue.

6.5 NATURE AND CONTENTS OF CONTAINER

Each package of Jivi contains:

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

Pack sizes

- 1 single pack.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Jivi is a B-domain deleted (BDD) recombinant human coagulation FVIII variant which is site-specifically conjugated at the A3 domain with a 60 kDa branched (two 30 kDa PEG) polyethylene glycol. The molecular weight of the protein is approximately 234 kDa based on the calculated average molecular weight of the BDD-rFVIII variant of 165 kDa, plus glycosylation (~4 kDa), and the average molecular weight of the single maleimide-derivatized 60 kDa branched PEG moiety.
The active protein (or starting molecule), prior to conjugation, is a recombinant B-domain deleted human coagulation factor VIII (BDD rFVIII) variant with K1804C mutation produced by recombinant DNA technology in Baby Hamster Kidney (BHK) cells and the conjugated protein is prepared without the addition of any human or animal derived protein in the cell culture process, purification, pegylation or final formulation.

Amino acid 910 for Jivi corresponds to amino acid 1804 in the full length Factor VIII amino acid sequence.

CAS number

1363853-26-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

Bayer Australia Limited
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875 Pacific Highway
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9 DATE OF FIRST APPROVAL

27 March 2023

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

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