

## Report on the Deliberation Results

March 3, 2016

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau  
Ministry of Health, Labour and Welfare

[Brand Name]	Adynovate Intravenous 250, 500, 1000, and 2000
[Non-proprietary Name]	Rurioctocog Alfa Pegol (Genetical Recombination) (JAN*)
[Applicant]	Baxter Limited
[Date of Application]	April 16, 2015

### [Results of Deliberation]

In its meeting held on February 26, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug, and the drug product is classified as a biological product.

### [Condition of Approval]

The applicant is required to develop and appropriately implement a risk management plan.

*\*Japanese Accepted Name (modified INN)*

## Review Report

February 3, 2016

Pharmaceuticals and Medical Devices Agency

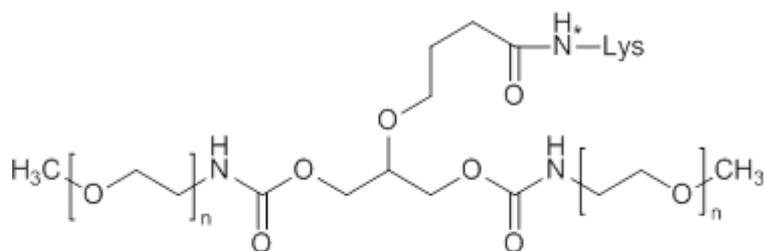
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

[Brand Name]	Adynovate Intravenous 250, 500, 1000, and 2000
[Non-proprietary Name]	Rurioctocog Alfa Pegol (Genetical Recombination)
[Applicant]	Baxter Limited
[Date of Application]	April 16, 2015
[Dosage Form/Strength]	Lyophilized powder in vials to be reconstituted prior to infusion: Each vial contains 250, 500, 1000, or 2000 international units (IUs) of Rurioctocog Alfa Pegol (Genetical Recombination).
[Application Classification]	Prescription drug (1) Drug with a new active ingredient
[Definition]	Rurioctocog Alfa Pegol is a modified glycoprotein (molecular weight: ca. 330,000). Two polyethylene glycol polymers (total average molecular weight: ca. 20,000) are attached via the linker to 2 or 3 Lys of Rurioctocog Alfa (Genetical Recombination).
[Structure]	As shown in the Attachment
[Items Warranting Special Mention]	None
[Reviewing Office]	Office of Vaccines and Blood Products

Main PEGylation sites:

K36, K213, K437, K510, K512, K877, K962, K986, K992, K1002, K1054, K1067, K1098, K1115, K1136, K1147, K1154, K1159, K1164, K1225, K1285, K1329, K1342, K1392, K1424, K1482, K1491, K1543, K1595, K1913, K2065, K2227, K2279

Binding mode of polyethylene glycol:



\*ε-amino group of Lys residue

Molecular formula:  $C_{12257}H_{17863}N_{3220}O_{3552}S_{83}$  (protein moiety)

Molecular weight: ca. 330,000

## Review Results

February 3, 2016

[Brand Name]	Adynovate Intravenous 250, 500, 1000, and 2000
[Non-proprietary Name]	Rurioctocog Alfa Pegol (Genetical Recombination)
[Applicant]	Baxter Limited
[Date of Application]	April 16, 2015

### [Results of Review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in controlling bleeding tendency in patients with blood coagulation factor VIII deficiency has been demonstrated, and that its safety is acceptable in view of its observed benefits. However, PMDA has concluded that its safety in routine clinical use should be investigated further in post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the following indication and dosage and administration, with the following condition.

### [Indication]

Control of bleeding tendency in patients with blood coagulation factor VIII deficiency

### [Dosage and Administration]

The product should be reconstituted with 5 mL of the supplied solvent, and should be slowly infused intravenously. Infusion rate should not exceed 10 mL/min.

The usual adult and adolescent (aged  $\geq 12$  years) dosage for on-demand treatment of bleeding is 10 to 30 IU/kg (body weight) of rurioctocog alfa pegol. The dose may be adjusted according to the patient's clinical condition.

The usual adult and adolescent dosage for routine prophylaxis is 40 to 50 IU/kg (body weight) of rurioctocog alfa pegol twice a week. The dose may be increased to 60 IU/kg (body weight) according to the patient's clinical condition.

### [Condition of Approval]

The applicant is required to develop and appropriately implement a risk management plan.

## Review Report (1)

December 2, 2015

### I. Product Submitted for Approval

[Brand Name]	Adynovate Intravenous 250, 500, 1000, and 2000 (changed from the proposed brand name “Advatepro Intravenous 250, 500, 1000, and 2000”)
[Non-proprietary Name]	Rurioctocog Alfa Pegol (Genetical Recombination)
[Applicant]	Baxter Limited
[Date of Application]	April 16, 2015
[Dosage Form/Strength]	Lyophilized powder in vials to be reconstituted prior to infusion: Each vial contains 250, 500, 1000, or 2000 international units (IUs) of Rurioctocog Alfa Pegol (Genetical Recombination).
[Proposed Indication]	Control of bleeding tendency in patients with blood coagulation factor VIII deficiency
[Proposed Dosage and Administration]	<p>The product should be reconstituted with 5 mL of the supplied solvent, and should be slowly infused intravenously. Infusion rate should not exceed 10 mL/min.</p> <p>The usual dosage for on-demand treatment of bleeding is 10 to 60 IU/kg (body weight) of rurioctocog alfa pegol. The dose may be adjusted according to the patient's clinical condition.</p> <p>The usual dosage for routine prophylaxis is 45 IU/kg (body weight) of rurioctocog alfa pegol twice a week. The dose may be adjusted according to the patient's clinical condition.</p>

### II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

#### 1. Origin or history of discovery, use in foreign countries, and other information

Hemophilia A (congenital blood coagulation factor VIII deficiency) is a bleeding disorder that is caused by a quantitative decrease in or a qualitative abnormality of blood coagulation factor VIII (FVIII) and may lead to serious bleeding episodes. The primary treatment for patients with hemophilia A is to administer an adequate dose of FVIII to ensure normal hemostasis.

FVIII products approved in Japan are as follows: 3 human plasma-derived FVIII products (Cross Eight MC for I.V. and Conco-eight-HT marketed by the Japan Blood Products Organization, and Confact F by Kaketsuken); 3 recombinant FVIII products (Kogenate-FS Bio-Set by Bayer Yakuhin, Ltd., Advate Intravenous by Baxter Limited, and NovoEight by Novo Nordisk Pharma Ltd.); and 1 recombinant FVIII-Fc fusion protein product (Eloctate Intravenous by Biogen Japan Ltd.).

Baxter Healthcare Corporation (U.S.) has developed Rurioctocog Alfa Pegol (Genetical Recombination) (hereinafter referred to as rurioctocog alfa pegol). Rurioctocog alfa pegol is a recombinant FVIII generated by binding polyethylene glycol (PEG) with molecular weight of ca. 20 kDa to Rurioctocog Alfa (Genetical Recombination) (hereinafter referred to as rurioctocog alfa), the active ingredient of Advate Intravenous. The development goal of rurioctocog alfa pegol has been to generate a PEGylated drug that has a longer plasma elimination half-life than that of Advate Intravenous.

For the development of rurioctocog alfa pegol, a global phase I study (Study 261101) in patients with hemophilia A aged  $\geq 18$  and  $< 65$  years was initiated in September 2011 in a total of 4 countries including Japan, and a global phase II/III study (Study 261201) in patients with hemophilia A aged  $\geq 12$  and  $< 65$  years was initiated in January 2013 in a total of 20 countries including Japan. Based on the results from these 2 clinical studies, the marketing application for rurioctocog alfa pegol has been submitted. As of November 2015, rurioctocog alfa pegol is approved only in the U.S. (applied in November 2014; approved in November 2015).

## **2. Data relating to quality**

### **2.A Summary of the submitted data**

#### **2.A.(1) Drug substance**

Rurioctocog alfa pegol, the active ingredient, is a modified protein generated by amide linkage of 2-arm branched polyethylene glycol (PEG) with average molecular weight of ca. 20 kDa mainly to lysine residues of rurioctocog alfa, a recombinant blood coagulation factor VIII (rFVIII). Rurioctocog alfa, the drug substance of Advate Intravenous 250, 500, 1000, 1500, and 2000 (Advate) currently available in Japan, is used as the starting material for the drug substance.

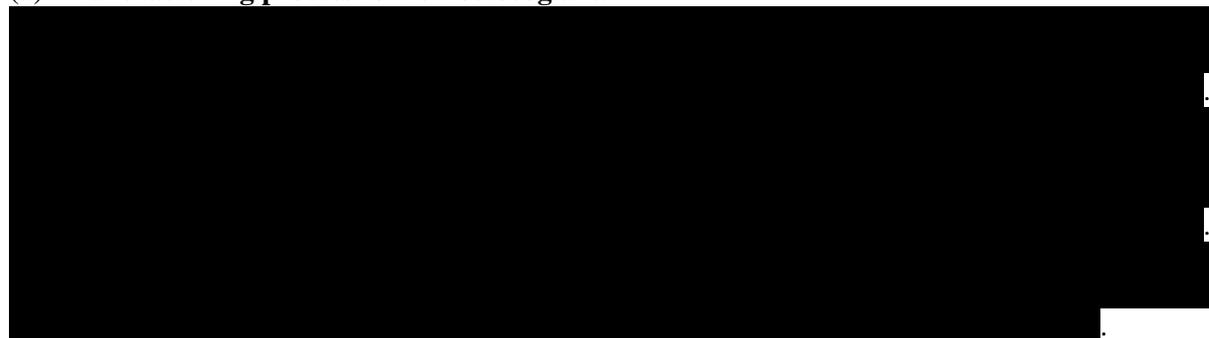
#### **2.A.(1.1) Preparation and control of cell substrate**

The cell species and cell banking system (master cell bank and working cell bank) that are the same as those used for Advate are used.

#### **2.A.(1.2) Manufacturing process**

The manufacturing process for the drug substance is as shown below.

##### **(a) Manufacturing process for rurioctocog alfa**

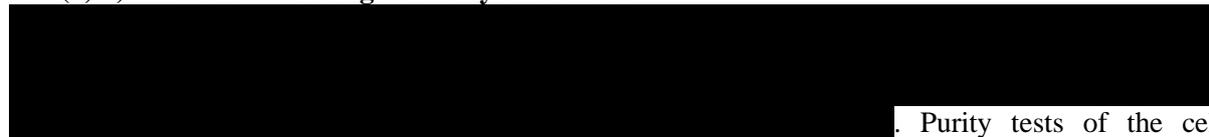


##### **(b) Manufacturing process for the drug substance**



The above manufacturing process for the drug substance was subjected to a process validation on a commercial scale.

#### **2.A.(1.3) Adventitious agent safety evaluation**



Purity tests of the cell banks and virus tests of the unprocessed bulk were appropriately conducted, and already subjected to a regulatory review for Advate.

In addition, the viral clearance robustness of the manufacturing process of rurioctocog alfa was confirmed with viral clearance studies (Table 2-1).

**Table 2-1. Results of viral clearance studies**

Manufacturing process	Virus reduction factor (log <sub>10</sub> )				
	X-MuLV	REO-3	MMV	BVDV	PRV
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	> [REDACTED]	> [REDACTED]
[REDACTED]	> [REDACTED]	[REDACTED]	[REDACTED]	ND	ND
[REDACTED]	> [REDACTED]	ND	ND	> [REDACTED]	> [REDACTED]
[REDACTED]	ND	ND	[REDACTED]*	ND	ND
Overall virus reduction factor	>14.5	7.3	4.1	>12.3	>10.1

X-MuLV, xenotropic murine leukemia virus; Reo-3, Reovirus 3; MMV, minute virus of mice; BVDV, bovine viral diarrhea virus;

PRV, pseudorabies virus

ND: Not determined

\*: Not included in the total

**2.A.(1).4 Manufacturing process development (comparability)**

The following changes have been incorporated in the manufacturing process during the development of the drug substance.

**(a) Manufacturing process for ruriocog alfa**

The major changes are described below (the 3 different manufacturing processes are referred to as Manufacturing Processes 1, 2, and 3 [the proposed manufacturing process]).

- [REDACTED]
- [REDACTED]

**(b) Manufacturing process for the drug substance**

- [REDACTED]
- [REDACTED]
  - [REDACTED]

The quality attributes of the drug substance have been confirmed to be comparable before and after the above-mentioned manufacturing process changes.

**2.A.(1).5 Characterization**

**(a) Structure**

- Amino acid sequence was determined by peptide mapping and amino-terminal (*N*-terminal) and carboxyl-terminal (*C*-terminal) amino acid sequencing.
- Monosaccharide composition and sialic acid content were determined by monosaccharide analysis.
- Carbohydrate structure of *N*-linked oligosaccharide was determined by liquid chromatography, mass spectrometry, and Western blot using anti- $\alpha$ -galactose antibody.
- Carbohydrate structure of *O*-linked oligosaccharide was determined by liquid chromatography.
- Glycosylation site and sulfation and phosphorylation sites were determined by peptide mapping and mass spectrometry.
- [REDACTED]

- The disulfide bridges were located by peptide mapping under non-reducing and reducing conditions and mass spectrometry.

**(b) Physicochemical properties**

- The heavy and light chains known to be present in ruriotocog alfa molecule, their truncated/extended forms, and their PEGylated forms were confirmed by *N*-terminal amino acid sequencing of each band separated by SDS-PAGE.

- [REDACTED]

- Batch-to-batch consistency of the electrophoretic pattern was confirmed by 2-dimension difference gel electrophoresis.

- In addition, infrared spectrum, particle size, circular dichroism spectrum, and melting point were confirmed.

**(c) Biological properties**

- In the presence of thrombin and blood coagulation factor IX (FIX), cofactor activity for activated FIX (FIXa) in tenase complex (FIXa cofactor activity) and rates of thrombin-induced activation and inactivation were determined by quantitation of generated activated blood coagulation factor X.

- Thrombin generation potential was determined by thrombin generation assay (TGA).

- Loss of the FIXa cofactor activity in the presence of activated protein C (APC) was confirmed.

- [REDACTED]

- [REDACTED]

**(d) Product-related substances/impurities**

[REDACTED]

[REDACTED]. Aggregates and free PEG molecules are controlled by specifications of the drug substance and drug product.

No molecular species were identified as product-related substances.

**(e) Process-related impurities**

[REDACTED]

[REDACTED]. It has been confirmed that all of the process-related impurities are adequately removed through the manufacturing process. Free PEG molecules are controlled by specifications of the drug substance and drug product.

**2.A.(1).6 Control of drug substance**

[REDACTED]

## 2.A.(1).7 Stability of drug substance

Table 2-2 outlines the major stability studies of the drug substance.

**Table 2-2. Outline of major stability studies of the drug substance**

	Manufacturing process for ruriotocog alfa (genetical recombination)	Manufacturing process for the drug substance	Number of batches tested	Storage conditions	Study period	Storage form
Long-term testing	Manufacturing Process 3	Manufacturing Process c	3	-80 ± 10°C	18 months <sup>1</sup>	[REDACTED]
Accelerated testing A	Manufacturing Process 1	Manufacturing Process b	4	-25 ± 5°C	6 or 12 months	
	Manufacturing Process 2	Manufacturing Process b	1		6 months	
Accelerated testing B	Manufacturing Process 3	Manufacturing Process c	3	-40 ± 5°C	12 months	

1. The stability study is ongoing.

2. [REDACTED]

The long-term testing conducted at -80°C showed no changes over time during the study period.

[REDACTED]. Accelerated testing B conducted at -40°C showed no changes over time during the study period.

[REDACTED]. Long-term testing will be continued for 36 months.

## 2.A.(2) Drug product

### 2.A.(2).1 Description and composition of the drug product and formulation development

The drug product is a lyophilized powder to be reconstituted prior to infusion and contains 250, 500, 1000, or 2000 International Units (IUs) of the active ingredient per vial. [REDACTED]

A prefilled glass vial of 5 mL of water for injection (JP) as the solvent for reconstitution is supplied with the drug product.

### 2.A.(2).2 Manufacturing process

The manufacturing process for the drug product consists of the solution preparation, sterile filtration, sterile filling, freeze-drying, labelling and packaging, and storage steps. Solution preparation, sterile filtration, sterile filling, and freeze-drying steps are defined as critical steps.

Process validation has been conducted for the manufacturing process on a commercial scale.

### 2.A.(2).3 Manufacturing process development

The major changes in the manufacturing process during the pharmaceutical development are described below (the 4 different manufacturing processes are referred to as Manufacturing Processes A, B, C, and D [the proposed manufacturing process]).

- Change from Manufacturing Process A to B: Change in manufacturing scale, target activity of bulk, fill volume, and change in lyophilization conditions.
- Change from Manufacturing Process B to C: Change in manufacturing scale, target activity of bulk, fill volume, and change in lyophilization conditions.
- Change from Manufacturing Process C to D: Change in manufacturing scale, target activity of bulk, and vial size.

The quality attributes of the drug product have been confirmed to be comparable between before and after the above-mentioned changes in manufacturing process.

#### 2.A.(2).4 Control of drug product

[REDACTED]

#### 2.A.(2).5 Stability of drug product

The stability studies were conducted according to a bracketing design with 250 IU and 2000 IU formulations as the extremes on a commercial scale to evaluate the stability of the drug product. Table 2-3 outlines the major stability studies of the drug product.

**Table 2-3. Outline of major stability studies of the drug product<sup>1</sup>**

	Manufacturing process for ruriotocog alfa (genetical recombination)	Manufacturing process for the drug substance	Storage conditions	Number of batches tested	Storage form	Study period
Long-term testing	Manufacturing Process 3	Manufacturing Process c	5 ± 3°C	250 IU: 3 batches 500 IU: 1 batch 1000 IU: 1 batch 2000 IU: 3 batches	Glass vial with a rubber stopper	18 months <sup>2</sup>
Accelerated testing A	Manufacturing Process 3	Manufacturing Process c	30 ± 2°C, 65 ± 5%RH			6 months
Accelerated testing B	Manufacturing Process 3	Manufacturing Process c	40 ± 2°C, 75 ± 5%RH			6 months
Stability testing of reconstituted solution	Manufacturing Process 3	Manufacturing Process c	25 ± 2°C			24 hours after reconstitution
Photostability testing	Manufacturing Process 2	Manufacturing Process b	Overall illumination: ≥1.2 million lux·hr Integrated near ultraviolet energy: ≥200 W hr/m <sup>2</sup>	1000 IU: 1 lot		-

1, Only the proposed manufacturing process (Manufacturing Process D) was used for manufacturing of the drug product.

2, The stability study is ongoing.

The long-term testing conducted at 5°C showed no changes over time during the study period. [REDACTED]

[REDACTED]. However, no substantial changes were observed during the study period for the other test attributes. The stability testing of the solution reconstituted with the supplied solvent showed that the solution is stable for 24 hours. The photostability testing showed no changes in the drug product in the vials tested.

Consequently, a shelf-life of 18 months has been proposed for the drug product when stored in a glass vial without freezing at 2°C to 8°C. Long-term testing will be continued for 36 months.

#### 2.A.(3) Reference materials

[REDACTED]

[REDACTED]. The in-house working reference material (for Western blotting) is prepared from the drug substance and stored at ≤ [REDACTED]°C. Specifications have been established for these reference standard and reference material to periodically confirm their qualifications.

#### 2.B Outline of the review by PMDA

On the basis of the submitted data, PMDA has concluded that the qualities of the drug substance and the drug product are controlled appropriately.

### 3. Non-clinical data

#### 3.(i) Summary of pharmacology studies

##### 3.(i).A Summary of the submitted data

The results from the following studies of rurioctocog alfa pegol were submitted as pharmacology data: primary pharmacodynamic studies (an *in vitro* study which evaluated blood clotting time and an *in vivo* study in mice in which blood coagulation factor VIII [FVIII] was knocked out by gene targeting [FVIII ko mice]); a secondary pharmacodynamic study in rabbits; and safety pharmacology studies in cynomolgus monkeys. Rurioctocog alfa pegol was compared with Advate, a recombinant FVIII product, and Feiba NF Intravenous (Feiba), an anti-inhibitor coagulant complex, both of which are manufactured and distributed by Baxter Limited. The administration route was intravenous in all *in vivo* studies.

##### 3.(i).A.(1) Primary pharmacodynamics

###### 3.(i).A.(1.1) *In vitro* study (effects on aPTT) (4.2.1.1-1, Study RD\_VB\_051203)

Activated partial thromboplastin time (aPTT) was determined in rat, cynomolgus monkey, and human plasma diluted with citrate buffer after addition of rurioctocog alfa pegol. The concentrations of added rurioctocog alfa pegol were to be 0 to 10 IUs per mL. The results revealed that aPTT tended to decrease with increasing amount of rurioctocog alfa pegol added (Table 3-1). The applicant explained that the finding indicated the presence of interaction between rurioctocog alfa pegol and the blood coagulation system in rats, cynomolgus monkeys, and humans.

**Table 3-1. Mean aPTT in rat, cynomolgus monkey, and human plasma**

Amount of rurioctocog alfa pegol added (IU/mL)	aPTT (second)		
	Rat plasma	Cynomolgus monkey plasma	Human plasma
0	44.3	46.4	54.0
1	31.6	36.4	40.2
5	24.2	29.5	29.4
10	21.1	25.3	24.9

Each measured in duplicate

###### 3.(i).A.(1.2) *In vivo* studies

The following 2 studies were conducted in FVIII ko mice, in which FVIII activity has been reported to be <1% of normal mice (*Nat Genet.* 1995;10:119-121).

###### (a) Tail-tip bleeding model (4.2.1.1-2, Study WH0210)

Rurioctocog alfa pegol or Advate at a dose of 200 IU/kg (3.3-fold the proposed maximum clinical dose) was administered to FVIII ko mice (n = 8/sex/group), and the animals had the tail-tip removed at 18 to 48 hours post-dose. FVIII ko mice in the negative control group received the vehicle for Advate and had the tail-tip removed at 5 minutes post-dose. Then, the blood loss within the first 60 minutes after tail-tip removal was measured. The results showed that the median total blood loss (range) was 950.5 mg (735.0-1062.0 mg) in the negative control group and 73.0 mg (0.0-975.0 mg) in the rurioctocog alfa pegol group with tail-tip removed at 30 hours post-dose. The applicant explained that rurioctocog alfa pegol clearly decreased total blood loss as evidenced by the above data and that the effect of rurioctocog alfa pegol lasted  $\geq 1.5$  times longer than that of Advate because the median total blood loss (range) in the Advate group was 121.0 mg (4.0-1053.0 mg) in the animals with tail-tip removed at 18 hours post-dose and 775.0 mg (70.0-1033.0 mg) at 30 hours post-dose.

###### (b) FeCl<sub>3</sub>-induced carotid artery occlusion model (4.2.1.1-3, Study WH0110)

Rurioctocog alfa pegol or Advate at a dose of 200 IU/kg was administered to FVIII ko mice (n = 6/sex/group). The carotid artery was exposed at 12 to 64 hours post-dose and vascular endothelial dysfunction was induced by placing a filter paper soaked with 1% FeCl<sub>3</sub> for 3 minutes. FVIII ko mice in the negative control group received the vehicle for Advate and underwent the same surgical treatment as above at 15 minutes post-dose. The time to thrombotic carotid artery occlusion was determined by monitoring average blood flow during the first 30 minutes after the treatment. As a result, while blood vessel occlusion was observed in 0 of 12 animals in the negative control group, it was observed at 24 hours post-dose in 10 of 12 animals in the rurioctocog alfa pegol group, and in 3 of 12 animals in the Advate group. The applicant explained that the above data demonstrated the contribution of rurioctocog alfa pegol to thrombus formation and a trend towards a persistent efficacy of rurioctocog alfa pegol as evidenced by its longer effect than that of Advate.

### **3.(i).A.(2) Secondary pharmacodynamics (evaluation of thrombogenic potential) (4.2.1.2-1, Study PV2450905)**

Rurioctocog alfa pegol or Advate at a dose of 900 IU/kg was administered to rabbits (n = 3/sex/group), or 20 U/kg of Feiba was administered to rabbits (positive control, n = 1/sex). The thrombogenic potential was evaluated using a Wessler venous stasis model in rabbits (*J Appl Physiol.* 1959;14:943-946). As a result, the thrombogenic potential was detected in the positive control rabbit, while not in rabbits receiving rurioctocog alfa pegol or Advate.

### **3.(i).A.(3) Safety pharmacology**

The results of a study in cynomolgus monkeys (Study 1933-019) were submitted as part of the cardiovascular and respiratory safety pharmacology data. In addition, central nervous system safety pharmacology of rurioctocog alfa pegol was evaluated in Study 1933-019, repeat-dose toxicity studies in rats and cynomolgus monkeys (Studies 8202366 and 1933-018), and a repeat-dose toxicity study in cynomolgus monkeys (Study 1933-017) conducted for a preliminary evaluation for Study 1933-018 [see “3.(iii).A.(2) Repeat-dose toxicity”]. The applicant explained that rurioctocog alfa pegol had no effects on the central nervous, cardiovascular, or respiratory system on the basis of the findings described below.

#### **3.(i).A.(3).1 Effects on the central nervous system**

No effects were observed on the central nervous system, on the basis of the results of clinical observations and body temperature measurements in Study 1933-019 in cynomolgus monkeys (the maximum dose, 600 IU/kg [10-fold the proposed maximum clinical dose]); clinical observations in Study 1933-017 in cynomolgus monkeys (the maximum dose, 1500 IU/kg [25-fold the proposed maximum clinical dose]); and clinical observations and histopathological findings in Study 8202366 in rats (the highest dose group, 700 IU/kg [11.7-fold the proposed maximum clinical dose]) and Study 1933-018 in cynomolgus monkeys (the highest dose group, 700 IU/kg [11.7-fold the proposed maximum clinical dose]).

#### **3.(i).A.(3).2 Effects on the cardiovascular and respiratory systems (4.2.1.3-1, Study 1933-019)**

Cynomolgus monkeys (n = 8) received (1) the vehicle for Advate (negative control), (2) 150 or 600 IU/kg of rurioctocog alfa pegol (2.5- or 10-fold the proposed maximum clinical dose), and (3) 600 or 150 IU/kg of rurioctocog alfa pegol in this sequence. These doses were administered at 3 to 5 day intervals. Rurioctocog alfa pegol at 150 and 600 IU/kg had no effects on heart rate, blood pressure, electrocardiogram, respiration rate, or intrathoracic pressure.

### **3.(i).B Outline of the review by PMDA**

Based on the submitted primary pharmacodynamic study data, PMDA has concluded that rurioctocog alfa pegol has FVIII activity and tends to have a persistent clotting activity as compared with Advate, a conventional FVIII product.

PMDA has also concluded that there are no particular safety concerns with rurioctocog alfa pegol based on the review of the submitted safety pharmacology data.

### **3.(ii) Summary of pharmacokinetic studies**

#### **3.(ii).A Summary of the submitted data**

The applicant submitted the results from studies in FVIII ko mice, rats, and cynomolgus monkeys. The FVIII activity in plasma samples was determined by chromogenic assay. FVIII concentrations in plasma samples were determined by ELISA. The tissue radioactivity levels following administration of rurioctocog alfa pegol manufactured with <sup>3</sup>H-labeled polyethylene glycol (PEG) (<sup>3</sup>H-labeled rurioctocog alfa pegol) were determined by liquid scintillation counting.

#### **3.(ii).A.(1) Absorption**

The applicant submitted the results of the following studies in FVIII ko mice, rats, and cynomolgus monkeys and discussed that these study data demonstrated a longer circulation time of rurioctocog alfa pegol in plasma than that of Advate.

### 3.(ii).A.(1).1 Single-dose study in FVIII ko mice (4.2.2.2-1, Study PV2460907)

A single intravenous dose of rurioctocog alfa pegol or Advate at 200 IU/kg was administered to FVIII ko mice (n = 4/sex/group/time point). Two groups of animals received 200 IU/kg of rurioctocog alfa pegol: one group received rurioctocog alfa pegol from a batch; and the other group from another batch. The plasma FVIII activity levels were determined in samples obtained at baseline and at 10 time points (5 minutes to 48 hours after study drug administration). The PK parameters are shown in Table 3-2. The dose-adjusted AUC from time 0 to the last time point (dose-adjusted AUC<sub>0-tlast</sub>), mean residence time (MRT), and terminal half-life (t<sub>1/2terminal</sub>) of rurioctocog alfa pegol (based on the combined data from the 2 rurioctocog alfa pegol groups) were 1.9, 1.6, and 1.4-fold, respectively, those of Advate.

**Table 3-2. PK parameters based on FVIII activity in FVIII ko mice (point estimate [95% confidence interval (CI)])**

Study drug		No. of animals/ time point	Dose-adjusted AUC <sub>0-tlast</sub> (h·IU/mL/IU/kg)	MRT (h)	t <sub>1/2terminal</sub> (h)
Rurioctocog alfa pegol 200 IU/kg	Batch 1	8	0.084 [0.079, 0.089]	8.0 [7.4, 8.7]	5.6 [4.9, 6.6]
	Batch 2	8	0.075 [0.071, 0.080]	7.7 [7.1, 8.5]	6.1 [5.2, 7.5]
	Combined	16	0.080 [0.076, 0.083]	7.9 [7.4, 8.4]	5.9 [5.2, 6.3]
Advate 200 IU/kg		8	0.042 [0.039, 0.046]	4.9 [4.4, 5.6]	4.3 [3.8, 5.0]

### 3.(ii).A.(1).2 Single-dose study in rats (4.2.2.2-2, Study PV2440905)

A single intravenous dose of 200, 350, or 700 IU/kg of rurioctocog alfa pegol or 200 IU/kg of Advate was administered to rats (n = 4/sex/group). There were 2 rurioctocog alfa pegol 200 IU/kg groups: one group received rurioctocog alfa pegol from a batch; and the other group from another batch. Plasma FVIII concentrations were determined in samples obtained at baseline and at 8 time points (5 minutes to 48 hours after study drug administration). The PK parameters are shown in Table 3-3. The dose-adjusted AUC<sub>0-tlast</sub>, MRT, and t<sub>1/2terminal</sub> of rurioctocog alfa pegol (based on the combined data from the 2 rurioctocog alfa pegol groups) at a dose of 200 IU/kg, or the same dose as that of Advate, were 1.4-, 1.2-, and 1.1-fold, respectively, those of Advate.

**Table 3-3. PK parameters based on FVIII concentrations in rats (geometric mean [95% CI])**

Study drug		No. of animals	Dose-adjusted AUC <sub>0-tlast</sub> (h·IU/mL/IU/kg)	MRT (h)	t <sub>1/2terminal</sub> (h)
Rurioctocog alfa pegol 200 IU/kg	Batch 1	8	0.072 [0.054, 0.096]	8.4 [6.0, 11.7]	6.7 [5.0, 8.9]
	Batch 2	8	0.071 [0.052, 0.097]	6.8 [4.2, 11.0]	5.6 [3.7, 8.6]
	Combined	16	0.071 [0.064, 0.079]	7.5 [6.5, 8.7]	6.1 [5.3, 7.1]
Rurioctocog alfa pegol 350 IU/kg		8	0.084 [0.072, 0.097]	7.9 [6.4, 9.7]	7.5 [6.2, 9.2]
Rurioctocog alfa pegol 700 IU/kg		8	0.060 [0.052, 0.070]	6.7 [5.4, 8.2]	6.9 [5.6, 8.4]
Advate 200 IU/kg		8	0.050 [0.043, 0.058]	6.2 [5.0, 7.6]	5.5 [4.5, 6.7]

### 3.(ii).A.(1).3 Study in cynomolgus monkeys (4.2.3.1-1, Study 1933-017)

PK of rurioctocog alfa pegol and Advate was evaluated in cynomolgus monkeys (n = 2/sex/group). Animals in Groups 1 and 2 received rurioctocog alfa pegol at 700 IU/kg on Day 1, and at 1500 IU/kg on Day 8 intravenously. These 2 groups were given rurioctocog alfa pegol from different batches each time. Animals in Group 3 intravenously received 350 IU/kg of rurioctocog alfa pegol on Day 1 and Day 8 from different batches. Animals in Group 4 received a single intravenous dose of 350 IU/kg of Advate. The plasma FVIII activity levels were determined in samples obtained at baseline and at 12 time points (from 5 minutes to 120 hours after study drug administration). For calculation of PK parameters, the baseline FVIII activity level (1.021-2.977 IU/mL) was subtracted from the post-dose FVIII activity level in each animal in order to eliminate the impact of endogenous FVIII activity in plasma (Table 3-4). AUC<sub>0-tlast</sub>, MRT, and t<sub>1/2terminal</sub> of rurioctocog alfa pegol at a dose of 350 IU/kg, the same dose as that of Advate, were 1.3- to 1.6-, 1.4- to 1.6-, and 1.6- to 1.7-fold, respectively, those of Advate.

**Table 3-4. PK parameters based on FVIII activity in cynomolgus monkeys  
(geometric mean [95% CI])**

Group	Study drug	Dose (IU/kg)	Day	No. of animals	AUC <sub>0-tlast</sub> (h-IU/mL)	MRT (h)	t <sub>1/2terminal</sub> (h)
1	Rurioctocog alfa pegol (batch 1)	700	1	4	105 [57, 194]	10.1 [6.1, 16.6]	8.0 [5.1, 12.7]
		1500	8		158 [99, 250]	9.6 [8.2, 11.3]	8.0 [5.5, 11.7]
2	Rurioctocog alfa pegol (batch 2)	700	1	4	165 [85, 321]	14.0 [7.0, 28.0]	12.6 [4.1, 38.7]
		1500	8		298 [174, 509]	12.2 [9.0, 16.6]	10.4 [7.6, 14.2]
3	Rurioctocog alfa pegol (batch 1)	350	1	4	61 [45, 83]	10.7 [9.3, 12.3]	9.0 [6.7, 12.2]
	Rurioctocog alfa pegol (batch 2)		8		77 [38, 156]	12.3 [5.8, 26.0]	9.8 [3.9, 24.5]
4	Advate	350	1	4	47 [20, 109]	7.5 [1.8, 31.8]	5.7 [1.1, 29.1]

### 3.(ii).A.(2) Distribution (4.2.2.2-4, Study 8201148)

A single intravenous dose of 1 mg/kg (equivalent to 2088 IU/kg) of <sup>3</sup>H-labeled rurioctocog alfa pegol was administered to rats (n = 2/sex/time point), and tissue radioactivity was determined at 1, 8, 24, 168, and 672 hours post-dose. The results showed that radioactivity was highest at 1 hour post-dose in plasma, blood, and the kidneys (both sexes), 1 hour (females) or 24 hours (males) post-dose in the adrenal gland, 24 hours post-dose in the spleen and liver (both sexes), and 24 hours (males) or 168 hours (females) post-dose in the mesenteric lymph nodes. The applicant discussed that a high blood flow in the liver, adrenal gland, and kidneys and a high abundance of macrophages with phagocytic activity against rurioctocog alfa pegol or free PEG molecules in the spleen and mesenteric lymph nodes led to the high radioactivity levels detected in these tissues.

### 3.(ii).A.(3) Metabolism (4.2.2.2-4, Study 8201148)

A single intravenous dose of 1 mg/kg (equivalent to 2088 IU/kg) of <sup>3</sup>H-labeled rurioctocog alfa pegol was administered to rats, and metabolites in plasma, urine, feces, the kidneys, liver, and lungs were evaluated by high performance liquid chromatography (n = 2/sex/time point for plasma, n = 3/sex for urine and feces, n = 1/sex/time point for the kidneys, liver, and lungs). At 1 hour post-dose, unchanged rurioctocog alfa pegol detected in plasma, the kidneys, liver, and lungs accounted for 37.1%, 14.9%, 7.0%, and 14.2%, respectively, of the administered dose in males and 36.3%, 17.5%, 1.7%, and 12.3%, respectively, in females. No unchanged drug was detected in urine and feces. Metabolites with low molecular weight compared with unchanged rurioctocog alfa pegol were detected in all samples, and metabolites with high molecular weight compared with unchanged rurioctocog alfa pegol were also detected in plasma. The applicant explained that the metabolites with high molecular weight detected in plasma appeared to be due to binding of plasma proteins such as von Willebrand factor to rurioctocog alfa pegol, and the metabolites with low molecular weight detected in all samples appeared to be rurioctocog alfa pegol with partially truncated FVIII moiety, free PEG molecules, or hydrolysates of free PEG molecules.

### 3.(ii).A.(4) Excretion (4.2.2.2-4, Study 8201148)

A single intravenous dose of 1 mg/kg (equivalent to 2088 IU/kg) of <sup>3</sup>H-labeled rurioctocog alfa pegol was administered to rats (n = 3/sex), and radioactivity levels in urine and feces collected up to 6 weeks post-dose were determined. The radioactivity excreted in urine and feces during the study period accounted for 51.9% and 38.4%, respectively, of the administered dose in males and 55.7% and 44.9%, respectively, in females. The applicant explained that most of the radioactivity from <sup>3</sup>H-labeled rurioctocog alfa pegol was shown to be excreted within 6 weeks post-dose.

### 3.(ii).B Outline of the review by PMDA

Based on the submitted PK study data of 3 animal species, PMDA has concluded that rurioctocog alfa pegol tends to have a longer half-life than that of Advate, a recombinant FVIII product approved in Japan, in all species tested.

### 3.(iii) Summary of toxicology studies

#### 3.(iii).A Summary of the submitted data

The applicant submitted the results from repeat-dose toxicity studies and local tolerance studies as the evaluation data. As the reference data, the applicant also submitted the results from repeat-dose toxicity

and genotoxicity studies of PEG (a molecular species formed through hydrolysis induced by hydroxide ion), which could be released from ruriotocog alfa pegol.

### **3.(iii).A.(1) Single-dose toxicity**

Single-dose toxicity was evaluated in the 4-week intravenous study in cynomolgus monkey (Study 1933-017).

An intravenous dose of 350, 700, or 1500 IU/kg (5.8- to 25-fold the proposed maximum clinical dose) of ruriotocog alfa pegol, or 350 IU/kg of Advate was administered to cynomolgus monkeys (n = 2/sex/group). In all dose levels of ruriotocog alfa pegol, there were 2 groups: one group received ruriotocog alfa pegol from a batch; and the other group from another batch. The results revealed no deaths in any group. In addition, no treatment-related effects were observed other than a reduction in aPTT (attributed to the pharmacological effect of the test article) and increases in thrombin-antithrombin complex (TAT) and D-dimer. The approximate lethal dose of ruriotocog alfa pegol in this study was determined to be  $\geq 1500$  IU/kg.

### **3.(iii).A.(2) Repeat-dose toxicity**

#### **3.(iii).A.(2).1 Four-week intravenous study in rats (4.2.3.2-1, Study 8202366)**

Repeated intravenous doses of 350 or 700 IU/kg (5.8- to 11.7-fold the proposed maximum clinical dose) of ruriotocog alfa pegol or vehicle were administered to rats (n = 10/sex for the vehicle group, n = 15/sex/group for the ruriotocog alfa pegol groups) every other day for 4 weeks. In all dose levels of ruriotocog alfa pegol, there were 2 groups: one group received ruriotocog alfa pegol from a batch and the other group from another batch. One animal in the 350 IU/kg group died immediately post-dose on Day 27 and necropsy showed increases in liver and kidney weights and discoloration of the lung, but none of these findings were observed at necropsy in animals in the other groups. Therefore, these changes and the death of the above animal were considered unrelated to ruriotocog alfa pegol. In the 700 IU/kg group, foamy macrophages in the lung tended to be increased compared with the vehicle group, but these findings were not associated with inflammation or tissue damage and were reversible within 2 weeks after treatment completion. The finding of foamy macrophages in the lung was considered unrelated to ruriotocog alfa pegol because no difference was observed in the degree of foaming between the vehicle and 350 IU/kg groups.

#### **3.(iii).A.(2).2 Four-week intravenous studies in cynomolgus monkeys (4.2.3.1-1, Study 1933-017; 4.2.3.2-3, Study 1933-018)**

In Study 1933-017, repeated intravenous doses of 700 IU/kg (11.7-fold the proposed maximum clinical dose) of ruriotocog alfa pegol or vehicle were administered to cynomolgus monkeys (n = 1/sex/group for the vehicle group, n = 2/sex/group for the ruriotocog alfa pegol group) every 5 days for 4 weeks. In Study 1933-018, repeated intravenous doses of 150, 350, or 700 IU/kg (2.5- to 11.7-fold the proposed maximum clinical dose) of ruriotocog alfa pegol or vehicle were administered to cynomolgus monkeys (n = 5/sex/group) every 5 days for 4 weeks. As a result, no deaths were observed in either study. In Study 1933-017, a reduction in aPTT was observed after the first dose of ruriotocog alfa pegol and an increase in TAT was observed after repeated doses of ruriotocog alfa pegol, and both were attributed to the pharmacological effect of ruriotocog alfa pegol.

### **3.(iii).A.(3) Genotoxicity**

Since ruriotocog alfa pegol is a PEGylated recombinant protein product, no genotoxicity studies were conducted in light of the guidance “Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals” (PFSB/ELD Notification No. 0323-1 dated March 23, 2012) (ICH-S6 [R1]).

### **3.(iii).A.(4) Carcinogenicity**

The drug substance of Advate, a recombinant FVIII product, is used as the starting material for ruriotocog alfa pegol. Based on clinical experience with Advate, ruriotocog alfa pegol is considered to have no carcinogenic potential. There were no literature data suggesting carcinogenic potential of PEG, and based on the results of the 28-day repeat-dose toxicity study in rats and genotoxicity studies of PEG (a molecular species formed through hydrolysis induced by hydroxide ion), which could be released through metabolism of ruriotocog alfa pegol, ruriotocog alfa pegol is unlikely to have

carcinogenic potential. Taking account of the above discussion and also of ICH-S6 (R1), no carcinogenicity studies of rurioctocog alfa pegol were conducted.

### **3.(iii).A.(5) Reproductive and developmental toxicity**

Since hypercoagulation is a risk factor for recurrent miscarriage (*Obstet Gynecol.* 2007;109:1146-1155.), it is predictable that hypercoagulation due to overdose of rurioctocog alfa pegol causes toxicity during ontogeny and that some animals cannot maintain adequate drug exposure for evaluation due to development of neutralizing antibodies against rurioctocog alfa pegol. Thus, no reproductive and developmental toxicity studies were conducted. In the repeat-dose toxicity study in male and female rats (Study 8202366) and the repeat-dose toxicity study in male and female cynomolgus monkeys (Study 1933-018), no changes related to rurioctocog alfa pegol were observed in reproductive organs of males (testis, epididymis, prostate gland, and seminal vesicle) or females (ovary, uterine, and vagina). The applicant explained that, although no reproductive and developmental toxicity studies of rurioctocog alfa pegol were conducted, considering the anticipated risks associated with blood coagulation, a caution will be provided to ensure that rurioctocog alfa pegol should be given to pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

### **3.(iii).A.(6) Local tolerance**

Local tolerance of rurioctocog alfa pegol was evaluated in the repeat-dose toxicity study in rats (Study 8202366) and repeat-dose toxicity study in cynomolgus monkeys (Study 1933-018). No impact of rurioctocog alfa pegol was found about findings from gross observation or histopathological examination of injection sites. Additionally, a local tolerance study in rabbits (4.2.3.6-2, Study PV2651201) was conducted.

Rabbits (n = 2/sex) received vehicle, rurioctocog alfa pegol (2000 IU/5 mL), or Advate (2000 IU/5 mL) intravenously (5 mL), intra-arterially (5 mL), or paravenously (0.5 mL). Each animal received, as negative control, saline of the same volume by the same administration route as those of the test article. The findings from gross observation or histopathological examination were similar between rurioctocog alfa pegol, vehicle, and Advate (control) for all administration routes tested, and no new effects of rurioctocog alfa pegol were identified.

Based on the above, there was no particular concern about local tolerance of rurioctocog alfa pegol.

### **3.(iii).B Outline of the review by PMDA**

On the basis of the findings from the toxicity studies of rurioctocog alfa pegol, PMDA has concluded that there are no specific problems with systemic toxicity and local tolerance. PMDA has concluded that the applicant's explanation is acceptable regarding the omission of reproductive and developmental toxicity, genotoxicity, and carcinogenicity studies.

#### **3.(iii).B.1 Dosing duration used in repeat dose toxicity studies**

Rurioctocog alfa pegol is expected to be administered to patients with FVIII-deficiency on long-term treatment in routine clinical use. ICH-S6 (R1) recommends a 6 month duration generally for a repeat-dose toxicity study of biotechnology products. However, the applicant employed 4-week duration in the repeat-dose toxicity studies in rats and cynomolgus monkeys.

The applicant's explanation of the appropriateness of the duration:

In the 4-week intravenous study in rats (Study 8202366),  $C_{max}$  and AUC in rats receiving 700 IU/kg of rurioctocog alfa pegol decreased from 338 ng/mL and 1505 h·ng/mL, respectively, on Day 1 to 55 ng/mL and 114 h·ng/mL, respectively, on Day 29 and a similar trend was observed with the drug from the other batch. In addition, the plasma FVIII activity increased at 5 or 30 minutes post-dose on Day 1, while such increases were not observed on Day 29. The decrease in the exposure to rurioctocog alfa pegol appears to correlate with the development of neutralizing antibodies against rurioctocog alfa pegol identified during the dosing period. In the 4-week intravenous study in cynomolgus monkeys (Study 1933-018), the plasma FVIII activity at the end of the study was below the limit of quantitation in 29 of 30 animals receiving rurioctocog alfa pegol, showing a notable decrease in plasma concentrations of PEGylated FVIII at all dose groups tested. The decrease in the exposure to rurioctocog alfa pegol appears related

to the development of neutralizing antibodies against rurioctocog alfa pegol identified during the dosing period. On the basis of above findings, both in rats and cynomolgus monkeys, drug-related toxicity is still unlikely to be identified through a repeat-dose toxicity study lasting for >4 weeks due to decrease in the exposure to rurioctocog alfa pegol caused by neutralizing antibodies.

PMDA's view:

Taking account of the observed decrease in the exposure to rurioctocog alfa pegol caused by its neutralizing antibodies that arose in animal species tested, PMDA has concluded that the applicant's claim is acceptable in that conducting a >4 week repeat-dose toxicity study is impractical.

#### **4. Clinical data**

##### **4.(i) Summary of biopharmaceutic studies and associated analytical methods**

###### **4.(i).A Summary of the submitted data**

The blood coagulation factor VIII (FVIII) activity was determined by one-stage clotting assay.

##### **4.(ii) Summary of clinical pharmacology studies**

###### **4.(ii).A Summary of the submitted data**

The applicant submitted the following study results as the evaluation data for clinical pharmacology of rurioctocog alfa pegol: a global phase I study (5.3.3.2-1, Study 261101) and a global phase II/III study (5.3.5.1-1, Study 261201) in patients with hemophilia A.

###### **4.(ii).A.(1) Studies using human biomaterials**

No studies were conducted in human biomaterials.

###### **4.(ii).A.(2) Studies in healthy adult subjects**

No studies were conducted in healthy adult subjects.

###### **4.(ii).A.(3) Studies in patients**

###### **4.(ii).A.(3).1 Global phase I study (5.3.3.2-1, Study 261101 [September 2011 to July 2012])**

A total of 19 patients with severe hemophilia A (FVIII activity <1%) aged  $\geq 18$  and  $\leq 65$  years with no inhibitors who previously received treatment ( $\geq 150$  exposure days) with other FVIII products first received a single intravenous dose of Advate at 30 IU/kg (9 patients) or 60 IU/kg (10 patients including 2 patients who participated at a Japanese study site [Japanese patients]); then underwent a washout period of 96 hours to 4 weeks; and finally received a single intravenous dose of Adynovate at the same dose as that of Advate. The plasma FVIII activities were determined in samples obtained at baseline and at a total of 7 time points after administration of Advate (0.5-48 hours post-dose), and in samples obtained at baseline and at a total of 14 time points after administration of rurioctocog alfa pegol (0.5-168 hours post-dose).

Evaluable PK data were obtained from 18 patients. Excluded was 1 patient who experienced bleeding within 4 days after dosing of rurioctocog alfa pegol. The PK parameters obtained from 16 out of these 18 patients excluding 2 Japanese patients were as shown in Table 4-1. The half-life ( $t_{1/2}$ ) of rurioctocog alfa pegol was 1.4- to 1.5-fold that of Advate.

**Table 4-1. PK parameters of rurioctocog alfa pegol and Advate based on FVIII activity (mean ± standard deviation)**

	30 IU/kg (n = 8)		60 IU/kg (n = 8)	
	Advate	Rurioctocog alfa pegol	Advate	Rurioctocog alfa pegol
t <sub>1/2</sub> (h)	9.90 ± 1.70	13.60 ± 2.79	11.11 ± 1.84	16.64 ± 3.60
MRT (h)	12.88 ± 2.89	18.41 ± 3.88	15.14 ± 2.88	21.86 ± 3.79
CL (dL/h/kg)	0.0377 ± 0.0154	0.0215 ± 0.0072	0.0315 ± 0.0092	0.0198 ± 0.0041
IR [(IU/dL)/(IU/kg)]	2.58 ± 0.66	2.73 ± 0.59	2.34 ± 0.54	2.49 ± 0.38
AUC <sub>0-∞</sub> (h·IU/dL)	913.0 ± 314.3	1540.6 ± 432.4	2055.6 ± 597.9	3096.1 ± 736.3
V <sub>ss</sub> (dL/kg)	0.4533 ± 0.0994	0.3760 ± 0.0685	0.4609 ± 0.0954	0.4223 ± 0.0475
C <sub>max</sub> (IU/dL)	78.38 ± 20.33	82.88 ± 16.48	141.00 ± 32.52	146.75 ± 23.06
t <sub>max</sub> (h)	0.58 ± 0.17	0.60 ± 0.26	0.75 ± 0.26	1.11 ± 1.22

t<sub>1/2</sub>, half-life; MRT, mean residence time; CL, clearance; IR, incremental recovery; AUC<sub>0-∞</sub>, AUC from time 0 to infinity; V<sub>ss</sub>, distribution volume at steady state; C<sub>max</sub>, maximum plasma activity; t<sub>max</sub>, time to maximum plasma activity

The data from 2 Japanese patients in the 60 IU/kg group were separately analyzed. The results are shown in Table 4-2. The applicant explained that t<sub>1/2</sub> of rurioctocog alfa pegol tended to be longer than that of Advate in the 2 Japanese patients, as with the other 16 non-Japanese patients.

**Table 4-2. PK parameters of rurioctocog alfa pegol and Advate in Japanese patients based on FVIII activity**

	60 IU/kg (Patient 1)		60 IU/kg (Patient 2)	
	Advate	Rurioctocog alfa pegol	Advate	Rurioctocog alfa pegol
t <sub>1/2</sub> (h)	7.4	11.5	7.5	24.2
MRT (h)	10.5	15.1	13.3	32.7
CL (dL/h/kg)	0.056	0.027	0.025	0.012
IR [(IU/dL)/(IU/kg)]	1.8	2.3	2.4	2.5
AUC <sub>0-∞</sub> (h·IU/dL)	1062.9	2219.7	2260.1	4785.4
V <sub>ss</sub> (dL/kg)	0.588	0.407	0.331	0.387
C <sub>max</sub> (IU/dL)	109.0	137.0	135.0	144.0
t <sub>max</sub> (h)	0.6	0.6	0.6	0.6

t<sub>1/2</sub>, half-life; MRT, mean residence time; CL, clearance; IR, incremental recovery; AUC<sub>0-∞</sub>, AUC from time 0 to infinity; V<sub>ss</sub>, distribution volume at steady state; C<sub>max</sub>, maximum plasma activity; t<sub>max</sub>, time to maximum plasma activity

#### 4.(ii).A.(3).2 Global phase II/III study (5.3.5.1-1, Study 261201 [January 2013 to July 2014])

PK of rurioctocog alfa pegol was evaluated in the phase II part in this study. A total of 26 patients (including 2 Japanese patients) with severe hemophilia A (FVIII activity <1%) aged ≥12 and ≤65 years with no inhibitors who previously received treatment (≥150 exposure days) with other FVIII products first received a single intravenous dose of Advate at 45 IU/kg; then underwent a washout period of ≥72 hours; and finally received a single intravenous dose of rurioctocog alfa pegol at 45 IU/kg. The plasma FVIII activities were determined in samples obtained at baseline and at a total of 10 time points after administration of Advate (10 minutes to 56 hours post-dose), and in samples obtained at baseline and at a total of 12 time points after administration of rurioctocog alfa pegol (10 minutes to 96 hours post-dose).

The PK parameters of Advate and rurioctocog alfa pegol are shown in Table 4-3. The t<sub>1/2</sub> of rurioctocog alfa pegol was 1.4-fold that of Advate.

**Table 4-3. PK parameters of rurioctocog alfa pegol and Advate based on FVIII activity (mean ± standard deviation)**

	Advate (n = 26)	Rurioctocog alfa pegol (n = 26)	Ratio (rurioctocog alfa pegol/Advate)
t <sub>1/2</sub> (h)	10.40 ± 2.24	14.30 ± 3.84	1.382 ± 0.254
MRT (h)	12.86 ± 3.04	19.56 ± 5.32	1.515 ± 0.179
CL (dL/h/kg)	0.0455 ± 0.0217	0.0276 ± 0.0203	0.613 ± 0.275
IR [(IU/dL)/(IU/kg)]	2.37 ± 0.54	2.49 ± 0.69	1.093 ± 0.362
AUC <sub>0-∞</sub> (h·IU/dL)	1168.0 ± 425.4	2073.3 ± 778.4	1.897 ± 0.913
V <sub>ss</sub> (dL/kg)	0.5487 ± 0.2021	0.4715 ± 0.1460	0.902 ± 0.293
C <sub>max</sub> (IU/dL)	108.45 ± 26.25	113.68 ± 30.26	1.117 ± 0.471
t <sub>max</sub> (h)	0.30 ± 0.17	0.40 ± 0.26	1.597 ± 1.069

t<sub>1/2</sub>, half-life; MRT, mean residence time; CL, clearance; IR, incremental recovery; AUC<sub>0-∞</sub>, AUC from time 0 to infinity; V<sub>ss</sub>, distribution volume at steady state; C<sub>max</sub>, maximum plasma activity; t<sub>max</sub>, time to maximum plasma activity

In the 2 Japanese patients who underwent PK evaluation in this study, the  $t_{1/2}$  of rurioctocog alfa pegol tended to be longer than that of Advate (Table 4-4), as in the whole study population (n = 26).

**Table 4-4. PK parameters of rurioctocog alfa pegol and Advate in Japanese patients based on FVIII activity (mean)**

	Advate (n = 2)	Rurioctocog alfa pegol (n = 2)	Ratio (rurioctocog alfa pegol/Advate)
$t_{1/2}$ (h)	12.22	20.59	1.739
MRT (h)	16.93	27.94	1.668
CL (dL/h/kg)	0.0297	0.0156	0.532
IR [(IU/dL)/(IU/kg)]	2.60	2.58	0.992
AUC <sub>0-∞</sub> (h·IU/dL)	1602.8	2885.3	1.862
V <sub>ss</sub> (dL/kg)	0.4850	0.4295	0.884
C <sub>max</sub> (IU/dL)	119.80	116.15	0.978
t <sub>max</sub> (h)	0.18	0.38	1.975

$t_{1/2}$ , half-life; MRT, mean residence time; CL, clearance; IR, incremental recovery; AUC<sub>0-∞</sub>, AUC from time 0 to infinity; V<sub>ss</sub>, distribution volume at steady state; C<sub>max</sub>, maximum plasma activity; t<sub>max</sub>, time to maximum plasma activity

The PK parameters were evaluated after multiple doses of 45 IU/kg of rurioctocog alfa pegol, the same dose as that for the PK evaluation of the initial dose, in 22 patients (including 1 Japanese patient) who had received routine prophylactic treatment of  $\geq 50$  exposure days or 6 months duration, whichever came later. The PK parameter values of rurioctocog alfa pegol after multiple doses were similar to those after the initial dose, and no impact was observed on the PK such as accumulation of the drug or decreased exposure after multiple administration.

#### 4.(ii).A.(4) Drug interactions

No studies were conducted to evaluate drug interactions.

#### 4.(ii).B Outline of the review by PMDA

On the basis of the submitted data, PMDA has concluded that the half-life of rurioctocog alfa pegol tends to be longer than that of Advate.

#### 4.(iii) Summary of clinical efficacy and safety

##### 4.(iii).A Summary of the submitted data

The applicant submitted the following study results as the efficacy and safety evaluation data: a global phase I study and a global phase II/III study. A list of the clinical studies is shown in Table 4-5.

**Table 4-5. List of clinical studies on the efficacy and safety of rurioctocog alfa pegol**

Site	Phase	Study number	Participants	No. of patients receiving the drug	Outline of dosage regimens
Global	I	261101	Patients with severe hemophilia A (18-65 years of age)	19 patients 9 in the 30 IU/kg group 10 in the 60 IU/kg group	Single doses of rurioctocog alfa pegol and Advate at 30 or 60 IU/kg were given.
Global	II/III	261201	Patients with severe hemophilia A (12-65 years of age)	138 patients 121 in Group A 17 in Group B	Group A (prophylaxis group): Rurioctocog alfa pegol at 45 IU/kg was given twice a week (the dose was allowed to be increased up to 60 IU/kg according to the patient's clinical condition). Group B (on-demand group): Rurioctocog alfa pegol at 10 to 60 IU/kg was given at the time of bleeding according to the severity.

An overview of clinical studies is described below.

##### 4.(iii).A.(1) Global phase I study (5.3.3.2-1, Study 261101 [September 2011 to July 2012])

An open-label, crossover, dose escalation study was conducted at 5 institutions in 4 countries including Japan in order to evaluate the safety and PK of rurioctocog alfa pegol in patients with severe hemophilia A (FVIII activity <1%) aged  $\geq 18$  and  $\leq 65$  years with no inhibitors who previously received treatment

( $\geq 150$  exposure days) with other FVIII products. The target sample size was 16 patients, but was changed to 18 patients during the course of the study in order to collect data from 2 Japanese patients.

Patients received a single intravenous dose of Advate at 30 or 60 IU/kg followed by a washout period of 96 hours to 4 weeks, and then received a single intravenous dose of rurioctocog alfa pegol at the same dose as that of Advate.

All 19 patients enrolled and treated with the study drug (9 patients in the 30 IU/kg group, 10 patients in the 60 IU/kg group) were included in the safety analysis set. The results of PK analysis in this study are described in the section “4.(ii) Summary of clinical pharmacology studies.”

Three adverse events (1 event each of laceration and rash maculo-papular in the 30 IU/kg group, 1 event of headache in the 60 IU/kg group) were reported by 3 of 19 patients (15.8%) during the period after administration of Advate and until before administration of rurioctocog alfa pegol, and 8 adverse events (1 event each of vomiting, nasopharyngitis, upper respiratory tract infection, local swelling, and arthralgia in the 30 IU/kg group; 2 events of headache and 1 event of influenza like illness in the 60 IU/kg group) were reported by 6 of 19 patients (31.6%) after administration of rurioctocog alfa pegol. The 2 events of headache were reported by a Japanese patient. A causal relationship to the study drug was ruled out for all these adverse events, and no deaths or serious adverse events were reported during the study.

#### **4.(iii).A.(2) Global phase II/III study (5.3.5.1-1, Study 261201 [January 2013 to July 2014])**

A non-randomized, open-label, parallel group study was conducted at 72 institutions in 20 countries including Japan in order to evaluate the efficacy, safety, and PK of rurioctocog alfa pegol in patients with severe hemophilia A (FVIII activity  $< 1\%$ ) aged  $\geq 12$  and  $\leq 65$  years with no inhibitors who previously received treatment ( $\geq 150$  exposure days) with other FVIII products. The target sample size was 132 patients (115 in Group A, 17 in Group B).

The study population consisted of 2 groups (Groups A and B), in which different dosage regimens, shown below, were employed.

**Group A:** In order to prevent bleeding episodes, patients were to regularly receive 45 IU/kg of rurioctocog alfa pegol twice a week (once every 3-4 days) for  $\geq 50$  exposure days (this requirement was changed to “ $\geq 50$  exposure days or 6 months duration, whichever came later” during the course of the study). The dose was allowed to be increased to 60 IU/kg in any of the following patients: (a) who had  $\geq 2$  episodes of spontaneous bleeding (not associated with trauma) at a single target joint within 2 months; (b) who had  $\geq 1$  episode(s) of spontaneous bleeding (not associated with trauma) at a non-target joint within 2 months; or (c) who had a trough level of FVIII activity of  $< 1\%$  and were judged to be at increased bleeding risk by the investigator. Before the routine prophylactic treatment with rurioctocog alfa pegol, PK evaluation was performed in 25 patients. These patients first received 45 IU/kg of Advate, then underwent a washout period of  $\geq 72$  hours, and finally received 45 IU/kg of rurioctocog alfa pegol. After completing the routine prophylactic treatment, the 25 patients underwent a washout period of 84 to 96 hours again, and then received 45 IU/kg of rurioctocog alfa pegol, and underwent another PK evaluation.

**Group B:** In order to obtain hemostasis of bleeding, patients received 10 to 60 IU/kg of rurioctocog alfa pegol according to the severity of the bleeding episode for a treatment duration of 6 months.

Patients who had been receiving a routine prophylactic treatment with an FVIII product before participating in the study were included in Group A. Patients who had received an FVIII product only for the purpose of on-demand treatment of bleeding before participating in the study were included in Group B. However, once the number of patients in Group B reached 17, all subsequent patients were included in Group A irrespective of the treatment they had received before participating in the study.

The results of PK analysis in this study are described in the section “4.(ii) Summary of clinical pharmacology studies.” All 138 patients (121 in Group A, 17 in Group B) who participated in the study were included in the Full Analysis Set (FAS); of these, 137 patients were included in the safety analysis set. Excluded was 1 patient in Group A who did not receive. The Per Protocol Analysis Set (PPAS) was defined as the population of patients who met the criteria specified in the protocol (e.g., treatment for breakthrough bleeding, and dosing interval and minimum/maximum doses for patients in Group A), and included 101 patients in Group A and 17 patients in Group B. All 11 Japanese patients were included in Group A.

The study drug exposure (days) per patient (mean ± standard deviation [SD]) were 52.1 ± 12.42 days (range, 1-91 days) in Group A and 27.2 ± 10.30 days (range, 12-48 days) in Group B.

The primary efficacy endpoint was annualized bleeding rate (ABR), which is tabulated for Group A and B in Table 4-6. The ABR was statistically significantly lower in Group A than in Group B.

**Table 4-6. Between-group comparison of ABR (bleeds/patient-year) (FAS)**

	Group A (n = 121 <sup>1</sup> )	Group B (n = 17)
Number of patients with bleeding episode(s)	75	17
Number of bleeding episodes treated	230	361
ABR (mean ± SD)	4.7 ± 8.6	40.8 ± 16.3
Between-group ratio <sup>2</sup> [95% CI] <sup>2</sup>	0.10 [0.06, 0.19]	-
P value <sup>2</sup>	<0.0001	-

1; Of 121 patients in the FAS, 1 patient was excluded from the efficacy analysis because the patient did not receive rurioctocog alfa pegol.

2; A negative binomial regression model with treatment group, presence/absence of target joint at screening, and age at screening as explanatory variables and logarithm of efficacy assessment duration as the offset variable.

The median ABR (range) in the FAS was 1.9 (0.0-59.6) bleeds/patient-year in Group A and 41.5 (12.9-67.9) bleeds/patient-year in Group B. The ABR in Japanese patients (all in Group A) was 4.0 (0.0-10.4) bleeds/patient-year.

As a secondary efficacy endpoint, the efficacy of rurioctocog alfa pegol used for hemostasis for the bleeding episode was evaluated in Groups A and B. This evaluation was completed by patients at 24 hours after the first dose of rurioctocog alfa pegol according to a 4-point scale shown in Table 4-7.

**Table 4-7. Definition of hemostatic response (treatment of bleeding)**

Excellent	Pain was rapidly mitigated, and/or bleeding symptoms were rapidly improved after the first dose. Bleeding was controlled without an additional injection. Additional injections to maintain hemostasis are not taken into account in the evaluation.
Good	Pain was clearly mitigated, and/or bleeding symptoms were clearly improved after the first dose, but ≥1 additional injection may be needed for complete resolution.
Fair	Pain was mitigated, or bleeding symptoms were probably or slightly improved after the first dose, but ≥1 additional injection were needed for complete resolution.
None	No improvement was achieved, or symptoms worsened.

During the study, a total of 518 bleeding episodes were reported in the PPAS. The percentage of bleeding episodes for which hemostatic response was rated as “Excellent” or “Good” at 24 hours after the first dose of rurioctocog alfa pegol was 96.1% (498 of 518 bleeds). The percentage of bleeding episodes for which hemostasis was achieved after the first or second dose was 95.9% (497 of 518 bleeds), and the percentage of bleeding episodes for which hemostasis was achieved after the first dose was 85.5% (443 of 518 bleeds).

Japanese patients experienced 13 bleeding episodes during the study. The percentage of bleeding episodes for which hemostatic response was rated as “Excellent” or “Good” at 24 hours after the first dose of rurioctocog alfa pegol was 92.3% (12 of 13 bleeds), and the rating was not reported for the remaining 1 episode. The percentage of bleeding episodes for which hemostasis was achieved after the first dose was 92.3% (12 of 13 bleeds); hemostasis was achieved also for the remaining 1 episode at the second dose.

During the study, 73 of 137 patients (53.3%) experienced  $\geq 1$  adverse event after administration of rurioctocog alfa pegol. Adverse events reported by  $\geq 2$  patients in either group in the safety analysis set are shown in Table 4-8.

**Table 4-8. Adverse events reported by  $\geq 2$  patients in either group (safety analysis set)**

	Group A (n = 120)		Group B (n = 17)	
	No. of patients with events	Incidence (%)	No. of patients with events	Incidence (%)
Nasopharyngitis	14	11.7	0	-
Upper respiratory tract infection	7	5.8	2	11.8
Headache	7	5.8	0	-
Diarrhoea	5	4.2	0	-
Influenza	4	3.3	0	-
Viral infection	3	2.5	1	5.9
Arthralgia	3	2.5	0	-
Back pain	3	2.5	0	-
Osteoarthritis	3	2.5	0	-
Abdominal pain	2	1.7	0	-
Gastritis	2	1.7	0	-
Nausea	2	1.7	0	-
Toothache	2	1.7	0	-
Pharyngitis	2	1.7	0	-
Rhinitis	2	1.7	0	-
Sinusitis	2	1.7	0	-
Excoriation	2	1.7	0	-
Hyperglycaemia	2	1.7	0	-
Joint swelling	2	1.7	0	-
Pain in extremity	2	1.7	0	-
Insomnia	2	1.7	0	-
Nasal congestion	2	1.7	0	-
Blister	2	1.7	0	-
Hypertension	2	1.7	0	-

During the study, 12 adverse events for which a causal relationship to the study drug could not be ruled out were reported by 10 patients (4 events of headache in 3 patients, 1 event each of diarrhoea, nausea, transaminases increased, arthralgia, and flushing in 1 patient each, and 2 events of injection site pain in 1 patient in Group A; 1 event of hyperbilirubinaemia in 1 patient in Group B).

During the study, 5 serious adverse events were reported by 5 patients after administration of rurioctocog alfa pegol (1 event each of osteoarthritis, humerus fracture, muscle haemorrhage, and neuroendocrine carcinoma in 1 patient each in Group A; 1 event of herpes zoster infection neurological in 1 patient in Group B). A causal relationship to the study drug was ruled out for all of these serious adverse events. The outcome of neuroendocrine carcinoma was reported as death, and the outcomes of the remaining 4 events were reported as recovered/resolved. A total of 4 adverse events leading to study discontinuation (other than death) were reported by 4 patients (1 event each of arthralgia, muscle haemorrhage, humerus fracture, and hepatitis C in 1 patient each in Group A).

During the study, 12 adverse events were reported by 7 of 11 Japanese patients (63.6%) included in the safety analysis set, including 1 serious adverse event of muscle haemorrhage in 1 patient. An adverse event for which a causal relationship to the study drug could not be ruled out was reported by 1 patient (nausea).

During the study, no patients developed FVIII inhibitors of  $\geq 0.6$  BU/mL.

#### **4.(iii).B Outline of the review by PMDA**

##### **4.(iii).B.(1) Data for review**

##### **4.(iii).B.(1).1 Safety and efficacy evaluation**

Since FVIII deficiency is a bleeding disorder caused by a quantitative decrease in or a qualitative abnormality of intrinsic FVIII, replacement therapy to achieve hemostasis for bleeding and routine prophylactic therapy to prevent bleeding episodes have been used in clinical practice (the National Surveillance of Coagulation Disorders, Annual Report for FY 2014. *Japanese Journal of Thrombosis*

*and Hemostasis*. 2013;24:619-639.). Given the paucity of patients with hemophilia A in Japan (4871 patients based on the above-mentioned surveillance report), the applicant's claim is understandable in that conducting a comparative study in Japanese patients alone is difficult. In addition, rurioctocog alfa pegol is activated by thrombin to form activated FVIII in the same manner as the intrinsic FVIII, and there were no marked differences between Japanese and non-Japanese patients with FVIII deficiency including hemophilia A in terms of intrinsic and extrinsic ethnic factors such as epidemiological backgrounds, pathological conditions of bleeding tendency, and therapy concepts for hemostasis and control of bleeding tendency. Consequently, PMDA considered the efficacy of rurioctocog alfa pegol was able to be evaluated in the global clinical studies which compared rurioctocog alfa pegol with conventional FVIII products with proven efficacy in terms of pharmacological activities and PK. PMDA reviewed the hemostatic effect of rurioctocog alfa pegol used in bleeding episodes and the effectiveness of rurioctocog alfa pegol in routine prophylactic treatment to control bleeding tendency (i.e., to reduce ABR). PMDA also reviewed the safety with a focus on the incidence of adverse events and development of inhibitors. Additionally, PMDA reviewed the incidence of adverse events in a study in adolescents (Study 261202), a surgical study (Study 261204), and an extension study (Study 261302) currently being conducted by the applicant, although these study data are not included in the submitted data package (Table 4-5).

#### **4.(iii).B.(2) Efficacy**

##### **4.(iii).B.(2).1 Comparison between rurioctocog alfa pegol and conventional FVIII products**

In Study 261101, the PK parameters of rurioctocog alfa pegol based on FVIII activity were compared with those of Advate, an FVIII product available in Japan [see "4.(ii).A.(3) Studies in patients"]. In view of the results of this comparison, PMDA has concluded that rurioctocog alfa pegol is expected to have a higher hemostatic effect than Advate on the basis of the observed trend towards persistent plasma levels and FVIII activity.

##### **4.(iii).B.(2).2 Efficacy of rurioctocog alfa pegol used to achieve hemostasis for bleeding**

In Study 261201, the hemostatic effect against bleeding episodes was evaluated according to the predefined 4-point scale (Table 4-7). As a result, the percentage of bleeding episodes for which hemostatic response was rated as "Excellent" or "Good" at 24 hours after the first dose of rurioctocog alfa pegol was 96.1% (498 of 518 bleeds) in the PPAS, which exceeded the predefined clinically significant hemostasis success rate of 70%. The percentage of bleeding episodes for which hemostasis was achieved after the first dose was 85.5% (443 of 518 bleeds) in the PPAS. In the FAS, the respective percentages were similar; the percentage of bleeding episodes for which hemostatic response was rated as "Excellent" or "Good" at 24 hours after the first dose of rurioctocog alfa pegol was 95.2% (563 of 591 bleeds) and the percentage of bleeding episodes for which hemostasis was achieved after the first dose was 85.4% (505 of 591 bleeds).

PMDA has concluded that rurioctocog alfa pegol is expected to be effective when used to achieve hemostasis for bleeding given the high success rates demonstrated in Study 261201. The percentage of bleeding episodes for which hemostatic response was rated as "Excellent" or "Good" after the first dose of rurioctocog alfa pegol (96.1%) and the percentage of bleeding episodes for which hemostasis was achieved after the first dose (85.5%) in Study 261201 were similar to those reported from studies of other FVIII products including Advate (70.6%-93.8% and 64.7%-87.3%, respectively) (*Thromb Haemost.* 2000;83:811-816, *Haemophilia*. 2004;10:428-437, *J Thromb Haemost.* 2008;6:1319-1326, *Haemophilia*. 2009;15:869-880, *J Thromb Haemost.* 2012;10:359-367, *Haemophilia*. 2013;19:691-697, *Blood*. 2014;123:317-325). Although there are limitations to a comparative evaluation with published literature data, the hemostatic effect of rurioctocog alfa pegol appears to be comparable to those of conventional FVIII products including Advate. In Study 261201, some patients who had "Excellent" or "Good" response at 24 hours after the first dose received  $\geq 3$  doses or  $\geq 5$  doses in total, respectively. The criteria included the following statements: "additional injections to maintain hemostasis are not taken into account in the evaluation" for Excellent; and "at least one additional injection may be needed for complete resolution" for Good. The patients mentioned above were appropriately evaluated because all of the relevant cases had traumatic bleeding episodes, for which determination of hemostasis achievement is difficult and additional injections are normally given to maintain hemostasis.

**4.(iii).B.(2).3) Efficacy of rurioctocog alfa pegol used for routine prophylactic treatment for bleeding**

In Study 261201, patients in Group A on routine prophylactic treatment with rurioctocog alfa pegol at 45 IU/kg twice a week (once every 3-4 days) against bleeding were compared in terms of ABR with patients in Group B treated with rurioctocog alfa pegol at the time of bleeding. However, Study 261201 was not a randomized study.

The applicant’s rationale of comparison between Groups A and B:

Since routine prophylactic treatment with FVIII products has been used in clinical practice as a standard therapy in many of the countries that participated in Study 261201, some patients enrolled in the study were assumed to have been on routine prophylactic treatment. A study design that exposes those patients to bleeding risks by randomizing them to the on-demand treatment group was considered inappropriate. Therefore, patients who had been receiving routine prophylactic treatment with a conventional FVIII product as previous treatment prior to entry into the study were included in Group A. Patients who had received treatment for bleeds as previous treatment were primarily enrolled in Group B until the number of enrolled patients reached 17, and enrolled in Group A thereafter. Of the patients who were already on routine prophylactic treatment before participating in the study, a small proportion had a “target joint at screening,” that was believed to confound efficacy evaluation. Patient characteristics—distribution of race, age, and blood group, prior history of HCV and HIV, and state of joint damage at screening—were similar between Groups A and B. A subgroup analysis was performed by 2 factors of patient characteristics (“prior therapy” and “presence of target joint”) in which Groups A and B were not similar. The results showed that the median on-study ABR (Table 4-10) in Group A was lower than the median ABR calculated from the number of bleeding episodes within the previous 3- to 6-month period (Table 4-9) irrespective of the prior therapy. In both subgroups of patients with and without a target joint, the ABR was lower in Group A than in Group B, although only a limited number (2 patients) of Group B were included in the subgroup of patients without a target joint (Table 4-10). Based on the above, the difference in these patient characteristics would have no impact on the efficacy conclusions.

**Table 4-9. ABR calculated from the number of bleeding episodes within 3 to 6 months before initiation of Study 261201 (PPAS)**

Prior therapy	Group A (n = 101)		Group B (n = 17)	
	No. of patients	Median (minimum, maximum)	No. of patients	Median (minimum, maximum)
Routine prophylactic treatment	82	7 (0, 52)	0	-
On-demand treatment of bleeding	19	24 (8, 80)	17	24 (10, 80)

**Table 4-10. Results of subgroup analysis on ABR (bleeds/patient-year) in Study 261201 (PPAS)**

		Group A (n = 101)		Group B (n = 17)	
		No. of patients	Median (minimum, maximum)	No. of patients	Median (minimum, maximum)
Prior therapy	Routine prophylactic treatment	82	2.0 (0.0, 18.4)	0	-
	On-demand treatment of bleeding	19	1.8 (0.0, 7.8)	17	41.5 (12.9, 67.9)
Target joint	No	32	3.4 (0.0, 17.1)	2	40.4 (13.0, 67.9)
	Yes	69	1.9 (0.0, 18.4)	15	41.5 (12.9, 62.2)

PMDA’s view:

The applicant's explanation is acceptable in that randomization of patients who were already on routine prophylactic treatment before participating in the study to Group B is inappropriate in light of current practices of routine prophylactic treatment with FVIII products in patients with severe hemophilia A in the countries that participated in Study 261201. The “hemostatic treatment guidelines for hemophilia patients without inhibitors, 2013 revised edition” (the Japanese Society on Thrombosis and Hemostasis. *Japanese Journal of Thrombosis and Hemostasis*. 2013;24:619-639) describing the regular replacement therapy reported that 1381 of 2416 patients (56.3%) with hemophilia A in Japan are on a routine prophylactic treatment (the National Surveillance of Coagulation Disorders, Annual Report for FY 2014, A Project Commissioned by the Ministry of Health, Labour and Welfare). Japanese patients who participated in Study 261201 were enrolled in Group A, all of whom (11 patients) had already been on routine prophylactic treatment before participating in the study.

The overall results of Study 261201 showed a 90% reduction in ABR in Group A as compared with Group B (Table 4-6), although difference was found between the groups in some patient characteristic factors. In addition, the results of the subgroup analysis were consistent with the overall study results, although the evaluation was possible only to a limited extent due to the small sample size. Based on the above, rurioctocog alfa pegol is expected to be effective when used for routine prophylactic treatment for bleeding.

**4.(iii).B.(2).4) Consistency of results between the total study population and Japanese patient population**

PMDA’s view on the consistency of efficacy results between the total study population and Japanese patient population:

The results of efficacy evaluation in the total population and Japanese patient population in Study 261201 are shown in Table 4-11. Study data for Japanese patients in Group B were not obtained because all 11 Japanese patients had been receiving routine prophylactic treatment with an FVIII product prior to participating in the study. The median ABR in Japanese patients in Group A (4.0 bleeds/patient-year) was markedly lower than that in Group B in the overall population (41.5 bleeds/patient-year). The results obtained in the study are thus consistent between the total study population and Japanese patient population. Furthermore, both the percentage of bleeding episodes for which hemostatic response was rated as “Excellent” or “Good” after the first dose and the percentage of bleeding episodes for which hemostasis was achieved after the first dose were similar between the total population and Japanese patient population. Therefore, no substantial difference exists in the hemostatic effect of rurioctocog alfa pegol between the two populations. Consequently, rurioctocog alfa pegol is expected to be also effective in Japanese patients.

**Table 4-11. Results of efficacy evaluation in Study 261201 (PPAS)**

Efficacy endpoint		Japanese patient population		Total study population	
		No. of patients		No. of patients	
Percentage of bleeding episodes for which hemostatic response was rated as “Excellent” or “Good” after the first dose		11	92.3% (12 of 13 bleeds)	118	96.1% (498 of 518 bleeds)
Percentage of bleeding episodes for which hemostasis was achieved after the first dose		11	92.3% (12 of 13 bleeds)	118	85.5% (443 of 518 bleeds)
Median ABR (minimum, maximum)	Group A	11	4.0 bleeds/patient-year (0.0, 10.4)	101	1.9 bleeds/patient-year (0.0, 18.4)
	Group B	0	-	17	41.5 bleeds/patient-year (12.9, 67.9)

**4.(iii).B.(3) Safety**

**4.(iii).B.(3).1) Adverse events reported by patients receiving conventional FVIII products**

In Study 261201, 4 serious adverse events were reported by 4 patients in Group A (osteoarthritis, muscle haemorrhage, humerus fracture, and neuroendocrine carcinoma) and 1 serious adverse event was reported by 1 patient in Group B (herpes zoster infection neurological), and the patient who experienced neuroendocrine carcinoma had a fatal outcome. A causal relationship to the study drug was ruled out for all these events. Otherwise, adverse events of particular clinical significance were not reported.

PMDA considers that the safety profile of rurioctocog alfa pegol is tolerable. However, development of FVIII inhibitors and shock/anaphylaxis have been reported in association with conventional FVIII products

The applicant’s explanation of these risks:

In Study 261201, of 137 patients who received  $\geq 1$  dose of rurioctocog alfa pegol, 101 patients received treatment of  $\geq 50$  exposure days. In this study, no patients developed FVIII inhibitors. During the study, 9 patients developed antibodies binding to FVIII, PEG-FVIII, or PEG before receiving rurioctocog alfa pegol, and 7 patients developed antibodies binding to FVIII or PEG-FVIII after receiving rurioctocog alfa pegol, but these antibodies were only temporarily observed, with no persistent binding antibodies being observed. In addition, as of October 15, 2015, neither development of inhibitors nor shock/anaphylaxis has been reported in the following ongoing studies that are not included in the

currently submitted data package: A study in children (aged <12 years) (Study 261202), a surgical study (Study 261204), and an extension study (Study 261302). Since the risks of such events associated with rurioctocog alfa pegol cannot be ruled out as is the case with conventional FVIII products, appropriate cautionary statements will be included in the package insert etc.

PMDA's view:

It is appropriate to provide cautions regarding development of FVIII inhibitors and shock/anaphylaxis in the package insert etc. Since conventional FVIII products may cause anaphylaxis or allergic reactions also in patients with hemophilia A, albeit at a lower frequency, as in patients with hemophilia B (*Blood Coagul Fibrinolysis*. 2009;20:225-229), and since neutralization by inhibitors may have an impact on the efficacy of rurioctocog alfa pegol, information on FVIII inhibitors is crucial. Therefore, information collected from the ongoing clinical studies and post-marketing surveillance should be provided promptly and appropriately to healthcare professionals in clinical settings.

#### **4.(iii).B.(3).2) Safety in adolescents**

The applicant's explanation on the safety of rurioctocog alfa pegol in adolescents with hemophilia A: In Study 261201, the proportion of patients with  $\geq 1$  adverse event was 48.0% (12 of 25 patients) among patients aged  $\geq 12$  and <18 years and 54.5% (61 of 112 patients) among patients aged  $\geq 18$  years, and the proportion of patients experienced a serious adverse event was 4.0% (1 of 25 patients) among patients aged  $\geq 12$  and <18 years and 3.6% (4 of 112 patients) among patients aged  $\geq 18$  years, showing similar proportions between the 2 age groups. In patients aged  $\geq 12$  and <18 years, 1 patient discontinued the study due to an adverse event (humerus fracture), and 3 patients aged  $\geq 18$  years discontinued the study due to an adverse event (arthralgia, muscle haemorrhage, and hepatitis C). Of these, a causal relationship to the study drug was ruled out for all events except for arthralgia, and the outcome was reported as recovered/resolved for all adverse events except for hepatitis C, for which the outcome was reported as recovering/resolving. Based on the above, the safety profile is similar between adults and adolescents. In addition, as of October 15, 2015, serious adverse events for which a causal relationship to the study drug could not be ruled out have not been reported in ongoing Study 261202 in children (aged <12 years) that is not included in the currently submitted data package.

PMDA has concluded that there is no difference in the safety profile between adolescents and adults based on the submitted clinical study data.

#### **4.(iii).B.(4) Indication**

Based on the data of clinical studies of rurioctocog alfa pegol used to achieve hemostasis for bleeding and used for routine prophylactic treatment for bleeding in patients with severe hemophilia A (FVIII activity <1%), PMDA has concluded that the efficacy of rurioctocog alfa pegol has been demonstrated and that its clinical positioning is similar to that of FVIII products. Accordingly, PMDA has concluded that the proposed indication of "control of bleeding tendency in patients with blood coagulation factor VIII deficiency," the same indication as that established for conventional FVIII products, is acceptable.

#### **4.(iii).B.(5) Dosage and administration**

##### **4.(iii).B.(5).1) For hemostasis of bleeding**

The applicant's explanation on the proposed dosage and administration to achieve hemostasis for bleeding:

In Study 261201, bleeding patients were to receive 10 to 60 IU/kg of rurioctocog alfa pegol according to the severity of the bleeding episode. The median dose per administration in bleeding patients (range) was 29.0 (6.8-61.4) IU/kg and the median total dose per bleeding episode (range) was 30.9 (6.8-400.0) IU/kg. Since the severity of FVIII deficiency and the location and extent of bleeding need to be taken into account for treatment of bleeding, the following statement was proposed: "The usual dosage is 10 to 60 IU of rurioctocog alfa pegol per kg body weight for on-demand treatment of bleeding. The dose may be adjusted according to the patient's clinical condition."

PMDA's view:

Given the median dose per administration in the clinical studies (approximately 30 IU/kg) and the descriptions of the Dosage and Administration section for conventional recombinant FVIII products (Kogenate, Advate, NovoEight, and Eloctate), the usual dosage should be 10 to 30 IU/kg of rurioctocog

alfa pegol per administration. The inclusion of the statement “The dose may be adjusted according to the patient's clinical condition” is acceptable since the actual dose per administration in bleeding patients ranged 6.8-61.4 IU/kg in the clinical studies and the dose was to be adjusted according to the location and extent of bleeding.

#### **4.(iii).B.(5).2 For routine prophylactic treatment**

The applicant's explanation on the proposed dosage and administration for routine prophylactic treatment for bleeding:

In Study 261201, the dose for Group A (prophylaxis group) was planned to be 45 IU/kg, which would provide a consistent FVIII activity of >1% in patients with hemophilia A through routine twice-weekly treatment based on the PK data from Study 261101. As a result, the ABR was decreased by 90% in Group A as compared with Group B (on-demand group). In Group A, the median dose per administration (range) was 44.8 (16.7-53.4) IU/kg and the median dosing frequency per week (range) was 1.96 (0.07-2.10) times. Given the facts (1) the ABR in 2 patients with a high bleeding frequency decreased after a dose increase to 60 IU/kg (59.6 and 35.7 bleeds/patient-year before dose increase to 22.3 and 32.3 bleeds/patient-year after dose increase, respectively) with no safety issues, and (2) the dose needs to be adjusted depending on the severity of joint damage, age, and life style of the patient, the following description of the Dosage and Administration section was proposed: “For routine prophylaxis, the usual dosage is 45 IU/kg of rurioctocog alfa pegol twice a week. The dose may be adjusted according to the patient's clinical condition.” However, taking into consideration the fact that a dose error of  $\pm 5$  IU/kg was allowed and that the dose was allowed to be increased only to 60 IU/kg in Study 261201, the proposed description was changed to “For routine prophylaxis, the usual dosage is 40 to 50 IU/kg of rurioctocog alfa pegol twice a week. The dose should be increased to 60 IU/kg of rurioctocog alfa pegol when bleeding is not effectively prevented.”

PMDA's view:

Since 101 patients safely received routine prophylactic treatment with rurioctocog alfa pegol of  $\geq 50$  exposure days in Study 261201 conducted in patients aged  $\geq 12$  years with hemophilia A [see “4.(iii).B.(3) Safety”], the dosage and administration should be 40 to 50 IU/kg of rurioctocog alfa pegol twice a week as used in the clinical study, and the dose should be allowed to be increased to 60 IU/kg according to the patient's clinical condition. The Dosage and Administration section should state that the intended population is patients aged  $\geq 12$  years, because the ongoing clinical study in patients aged <12 years is not included in the submitted data package.

#### **4.(iii).B.(5).3 Infusion rate**

The applicant's explanation on the proposed infusion rate in the Dosage and Administration section: Advate Intravenous is recommended to be infused slowly at a rate of not exceeding 10 mL/minute because the drug may cause cyanosis or palpitations when infused at a too high infusion rate. Clinical studies of rurioctocog alfa pegol (Studies 261101 and 261201) also required that “rurioctocog alfa pegol be infused at a rate not exceeding 10 mL/minute.” Since clinical studies conducted under such a requirement showed no particular safety issues associated with infusion, the description of Dosage and Administration was proposed as “The product should be slowly infused intravenously. Infusion rate should not exceed 10 mL/min.”

PMDA considers that the applicant's proposal to state in the Dosage and Administration section that “Infusion rate should not exceed 10 mL/min,” in a similar manner as required in the clinical studies, is acceptable.

On the basis of the review described in the above sections 1) to 3), PMDA has concluded that the Dosage and Administration for rurioctocog alfa pegol should be as follows:

[Dosage and Administration]

The product should be reconstituted with 5 mL of the supplied solvent, and the reconstituted solution should be slowly infused intravenously. Infusion rate should not exceed 10 mL/min.

The usual adult and adolescent (aged  $\geq 12$  years) dosage for on-demand treatment of bleeding is 10 to 30 IU/kg (body weight) of rurioctocog alfa pegol. The dose may be adjusted according to the patient's clinical condition.

The usual adult and adolescent dosage for routine prophylaxis is 40 to 50 IU/kg (body weight) of rurioctocog alfa pegol twice a week. The dose may be increased to 60 IU/kg (body weight) according to the patient's clinical condition.

#### **4.(iii).B.(6) Post-marketing investigations**

The applicant's explanation about post-marketing surveillance for rurioctocog alfa pegol:

In order to confirm the safety and efficacy of rurioctocog alfa pegol in routine clinical use, a drug use-results survey will be conducted in patients previously treated (target sample size of 120; observation period of 1 year) and not treated (unspecified sample size; observation period of 2 years) with an FVIII product to investigate development of neutralizing antibodies (FVIII inhibitors) and shock/anaphylaxis as priority items. The target sample size was selected taking account of the number of patients to be treated with the drug estimated by market research in Japan as well as the feasibility. The number of patients aged  $\geq 12$  years who have not been previously treated with an FVIII product is likely to be limited, and information will be collected on as many patients who have received treatment with rurioctocog alfa pegol as possible during the registration period of this survey.

PMDA's view:

Since clinical experience with rurioctocog alfa pegol in Japanese clinical settings is restricted due to the very limited number of Japanese patients who participated in the clinical studies of rurioctocog alfa pegol, the applicant should conduct post-marketing surveillance of rurioctocog alfa pegol in routine clinical settings. It is important to conduct an evaluation of safety information collected via post-marketing surveillance including a comparative evaluation with safety information obtained from the clinical studies, to determine the necessity for further surveillance. In addition, appropriate actions should be taken including modification of dosage and administration taking account of the data of the study in children (aged  $< 12$  years) (Study 261202) and surgical study (Study 261204) currently being conducted by the applicant.

### **III. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA**

The assessment is ongoing. Its results and the conclusion by PMDA are described in the Review Report (2).

### **IV. Overall Evaluation**

Based on the submitted data, PMDA has concluded that the efficacy of rurioctocog alfa pegol in controlling bleeding tendency in patients with blood coagulation factor VIII deficiency is expected, and that its safety is acceptable in view of its observed benefits. PMDA considers that rurioctocog alfa pegol is clinically significant as a treatment option for controlling bleeding tendency in patients with blood coagulation factor VIII deficiency.

This application may be approved when efficacy, safety, post-marketing surveillance, etc., are further reviewed in the Expert Discussion and considered to have no particular problems.

## Review Report (2)

February 2, 2016

### I. Product Submitted for Registration

[Brand Name]	Adynovate Intravenous 250, 500, 1000, and 2000
[Non-proprietary Name]	Rurioctocog Alfa Pegol (Genetical Recombination)
[Name of Applicant]	Baxter Limited
[Date of Application]	April 16, 2015

### II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors present during the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for marketing approval, in accordance with the provisions of the “Rules for Convening Expert Discussions etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

#### (1) Efficacy

##### 1) For hemostasis of bleeding

In Study 261201, the efficacy of rurioctocog alfa pegol used to achieve hemostasis for bleeding was evaluated based on the hemostatic effect measured by a predefined rating scale [Review Report (1), Table 4-7]. The results showed that the percentage of bleeding episodes for which hemostatic response was rated as “Excellent” or “Good” at 24 hours after the first dose of rurioctocog alfa pegol was as high as 96.1% (498 of 518 bleeds), and the percentage of bleeding episodes for which hemostasis was achieved after the first dose was as high as 85.5% (443 of 518 bleeds). Therefore, PMDA has concluded that the efficacy of rurioctocog alfa pegol is expected when used to achieve hemostasis for bleeding.

The above conclusion by PMDA was supported by the expert advisors.

##### 2) For routine prophylactic treatment for bleeding

In Study 261201, patients in Group A received routine prophylactic treatment with rurioctocog alfa pegol at 45 IU/kg twice a week (once every 3-4 days) against bleeding, and were compared with patients in Group B, who received rurioctocog alfa pegol at the time of bleeding, in terms of annualized bleeding rate (ABR). The results showed a 90% reduction in ABR in Group A as compared with Group B [Review Report (1), Table 4-6]. In addition, the results of the subgroup analysis by 2 factors of patient characteristics (“prior therapy” and “presence of target joint”) in which Groups A and B were not similar were consistent with the overall study results, although there are limitations to the evaluation due to the small sample size [Review Report (1), Table 4-10]. Consequently, PMDA has concluded that the efficacy of rurioctocog alfa pegol is expected when used for routine prophylactic treatment for bleeding.

The above conclusion by PMDA was supported by the expert advisors.

The following comments were raised from the expert advisors:

- The regression model used in the primary analysis and the results of the subgroup analysis indicate that patient characteristic factors were taken into account in the efficacy analysis. However, given the non-randomized nature of the study and its patient assignment by prior therapy (routine prophylactic treatment or on-demand treatment of bleeding), an analysis using propensity score for selection of prior therapy would further support the efficacy.

PMDA instructed the applicant to perform a propensity score-based analysis for selection of prior therapy, and confirmed that the analysis results supported the efficacy of routine prophylactic treatment with rurioctocog alfa pegol, as was the case with the primary analysis.

## **(2) Safety**

PMDA has concluded that rurioctocog alfa pegol is tolerable on the basis of the submitted data. A cautionary statement regarding development of inhibitors and shock/anaphylaxis should be included in the package insert, etc., as included in conventional blood coagulation factor VIII (FVIII) products. In particular, information on FVIII inhibitors is crucial and should be provided promptly and appropriately to healthcare professionals in clinical settings, including reports from the clinical studies being currently conducted by the applicant and post-marketing surveillance.

The above conclusion by PMDA was supported by the expert advisors.

## **(3) Indication**

PMDA has concluded that the proposed indication of “control of bleeding tendency in patients with blood coagulation factor VIII deficiency,” the same indication as that established for conventional FVIII products, is acceptable, and that the clinical positioning of rurioctocog alfa pegol is similar to conventional FVIII products.

The above conclusion by PMDA was supported by the expert advisors.

## **(4) Dosage and administration**

### **1) For hemostasis of bleeding**

Given the median dose per administration in Study 261201 (approximately 30 IU/kg) and the descriptions of the Dosage and Administration section for conventional recombinant FVIII products, the usual dosage for bleeding patients should be “10 to 30 IU/kg of rurioctocog alfa pegol per administration.” The inclusion of the statement “The dose may be adjusted according to the patient's clinical condition” is acceptable since the dose was allowed to be adjusted according to the location and extent of bleeding in Study 261201.

The above conclusion by PMDA was supported by the expert advisors.

### **2) For routine prophylactic treatment**

On the basis of the dosage regimen used in Study 261201, PMDA has concluded that the dosage and administration for routine prophylactic treatment with rurioctocog alfa pegol (in patients aged  $\geq 12$  years) should be “40 to 50 IU/kg of rurioctocog alfa pegol twice a week; the dose may be increased to 60 IU/kg of rurioctocog alfa pegol according to the patient's clinical condition.”

The above conclusion by PMDA was supported by the expert advisors.

### **3) Infusion rate**

PMDA has concluded that the applicant's proposal to state in the Dosage and Administration section that “Infusion rate should not exceed 10 mL/min,” in a similar manner as required in the clinical studies of rurioctocog alfa pegol (Studies 261101 and 261201), is acceptable.

The above conclusion by PMDA was supported by the expert advisors.

Taking account of the comments raised in the Expert Discussion as outlined in the above sections 1) to 3), PMDA requested the applicant to change the descriptions of the Dosage and Administration section to the following:

[Dosage and Administration]

The product should be reconstituted with 5 mL of the supplied solvent, and the reconstituted solution should be slowly infused intravenously. Infusion rate should not exceed 10 mL/min.

The usual adult and adolescent (aged  $\geq 12$  years) dosage for on-demand treatment of bleeding is 10 to 30 IU/kg (body weight) of rurioctocog alfa pegol. The dose may be adjusted according to the patient's clinical condition.

The usual adult and adolescent dosage for routine prophylaxis is 40 to 50 IU/kg (body weight) of rurioctocog alfa pegol twice a week. The dose may be increased to 60 IU/ kg (body weight) according to the patient's clinical condition.

**(5) Risk management plan (draft)**

On the basis of the results of review in the section “4.(iii).B.(6) Post-marketing investigations” of the Review Report (1), PMDA has concluded that the applicant should conduct post-marketing surveillance of rurioctocog alfa pegol in routine clinical use. PMDA has also concluded that the applicant should determine whether further collection of safety data and/or provision of cautionary statements are needed on the basis of the assessment of safety information collected via the proposed drug use-results survey, including a comparative evaluation with safety information obtained from the clinical studies.

The above conclusion by PMDA was supported by the expert advisors.

The following comments were raised from the expert advisors:

- Since rurioctocog alfa pegol is a PEGylated protein product unlike conventional FVIII products, (1) occurrence of adverse drug reactions dissimilar to that of the reactions associated with conventional FVIII products cannot be ruled out and (2) persistent adverse drug reactions due to the longer half-life (albeit approximately by 1.4-fold only) may occur. Therefore, it is important to collect post-marketing safety information.

PMDA has concluded that, at present, the draft risk management plan for rurioctocog alfa pegol should include the safety and efficacy specifications listed in Table 1 and additional pharmacovigilance and risk minimization activities listed in Table 2.

**Table 1. Safety and efficacy specifications in draft risk management plan**

Safety specifications		
Important identified risks	Important potential risks	Important missing information
Not applicable	- Development of FVIII inhibitors - Shock/anaphylaxis	Not applicable
Efficacy specifications		
Not applicable		

**Table 2. Outline of additional pharmacovigilance activities and risk minimization activities in draft risk management plan**

Additional pharmacovigilance activities	Additional risk minimization activities
- Early post-marketing phase vigilance - Drug use-results survey (see Table 3)	- Early post-marketing phase vigilance

**Table 3. Outline of draft drug use-results survey plan**

Objective	To investigate the long-term safety and efficacy of rurioctocog alfa pegol in routine clinical use
Method	Central registration
Population	Patients with blood coagulation factor VIII deficiency
Observation period	1 year for previously treated patients, 2 years for previously untreated patients
Target sample size	120 patients who had been previously treated (unspecified for previously untreated patients)
Main investigation items	Patient characteristics, status of treatment with rurioctocog alfa pegol, concomitant drugs and concomitant therapies, clinically significant laboratory changes, adverse events, efficacy

**III. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA**

**1. PMDA’s conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment**

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 2. PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (5.3.5.1-1) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed no noteworthy issues. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## IV. Overall Evaluation

Based on the above review, PMDA has concluded that ruriotocog alfa pegol may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions. The product is a drug with a new active ingredient. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug, and the product is classified as a biological product.

[Indication]	Control of bleeding tendency in patients with blood coagulation factor VIII deficiency
[Dosage and administration]	<p>The product should be reconstituted with 5 mL of the supplied solvent, and the reconstituted solution should be slowly infused intravenously. Infusion rate should not exceed 10 mL/min.</p> <p>The usual adult and adolescent (aged <math>\geq 12</math> years) dosage for on-demand treatment of bleeding is 10 to 30 IU/kg (body weight) of ruriotocog alfa pegol. The dose may be adjusted according to the patient's clinical condition.</p> <p>The usual adult and adolescent dosage for routine prophylaxis is 40 to 50 IU/kg (body weight) of ruriotocog alfa pegol twice a week. The dose may be increased to 60 IU/kg (body weight) according to the patient's clinical condition.</p>
[Condition of Approval]	The applicant is required to develop and appropriately implement a risk management plan.