



Summary Report of Benefit-Risk Assessment

ADYNOVATE POWDER AND SOLVENT FOR SOLUTION FOR INJECTION 250IU/ 500IU/ 1000IU/ 1500IU/ 2000IU/ 3000IU

NEW DRUG APPLICATION

Active Ingredient(s)	Ruriotocog alfa pegol [Antihemophilic Factor (Recombinant), PEGylated]
Product Registrant	Takeda Pharmaceuticals (Asia Pacific) Pte. Ltd.
Product Registration Number	SIN16048P, SIN16049P, SIN16050P, SIN16051P, SIN16052P, SIN16053P
Application Route	Abridged evaluation
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A INTRODUCTION

Adynovate is indicated in children and adults with hemophilia A [congenital factor VIII (FVIII) deficiency] for on-demand treatment and control of bleeding episodes (BEs); perioperative management and routine prophylaxis to reduce the frequency of BE.

The active substance, rurioctocog alfa pegol is a pegylated recombinant human FVIII with an extended half-life. Rurioctocog alfa pegol is a covalent conjugate of octocog alfa consisting of 2,332 amino acids with polyethylene glycol (PEG) reagent (MW 20 kDa). Rurioctocog alfa pegol temporarily replaces the missing coagulation FVIII needed for effective hemostasis in congenital hemophilia A patients.

Adynovate is available as powder and solvent (sterile water for injection) for solution for injection containing 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU or 3000 IU of rurioctocog alfa pegol. Other ingredients contained in the drug product are calcium chloride dihydrate, glutathione, histidine, mannitol, polysorbate 80, sodium chloride, trehalose dihydrate and tromethamine/ trometamol [tris(hydroxymethyl)- aminomethane].

B ASSESSMENT OF PRODUCT QUALITY

Adynovate Powder and Solvent for Solution for Injection is supplied in a package containing a powder vial, a diluent vial and a device for reconstitution (BAXJECT II Hi-Flow or BAXJECT III). The powder vial contains sterile, non-pyrogenic and white to off-white lyophilized powder with a nominal potency of 250, 500, 1000, 1500, 2000 and 3000 international units (IU) per vial of Rurioctocog alfa pegol, PEGylated recombinant human FVIII. The excipients in the powder vial are mannitol, trehalose dihydrate, sodium chloride, histidine, tris(hydroxymethyl)-aminomethane, calcium chloride dihydrate, polysorbate 80 and glutathione. The diluent vial contains 2 ml or 5ml of sterile water for injection. The vials and reconstitution device may be preassembled for user convenience and are supplied in a sealed blister.

ASSESSMENT OF PRODUCT QUALITY

The drug substance, rurioctocog alfa pegol [Antihemophilic Factor (Recombinant) PEGylated] is manufactured at Baxalta U.S. Inc. California, USA. The drug product is manufactured at Baxalta Manufacturing Sarl, Neuchâtel, Switzerland. The assembly of the drug product vial with BAXJECT II Hi-Flow Reconstitution System is carried out at Baxalta Belgium Manufacturing S.A., Lessines, Belgium. Baxalta U.S. Inc. California, USA is responsible for the assembly of the drug product vial with BAXJECT III Reconstitution System. The Sterile Water for Injection (sWFI) is manufactured by Siegfried Hameln GmbH, Hameln, Germany.

Drug Substance:

Adequate controls have been presented for the raw materials, reagents, cell substrate and cell banking system for the drug substance intermediate and downstream processing to obtain the drug substance. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance intermediate and drug substance are considered appropriate. The drug substance intermediate and drug substance manufacturers are compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches each for the drug substance intermediate and drug substance.

The characterization of the drug substance intermediate, drug substance and their impurities are in accordance with ICH guidelines. Product-related substances including free PEG and aggregates are adequately controlled.

The drug substance intermediate and drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the approved storage condition and shelf life. The packaging for both the drug substance intermediate and drug substance is USP Class VI fluorinated ethylene perfluoroalkyl vinyl ether copolymer (PFA) bottle 1000 mL fitted with PFA screw cap and polytetrafluoroethylene (PTFE) cap insert. The drug substance intermediate and drug substance are approved for storage at -80°C with a shelf life of 24 and 36 months, respectively.

Drug Product-Powder Vial:

The manufacturing process utilizes aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at $5 \pm 3^{\circ}\text{C}$. The in-use period after reconstitution is 'not more than 3 hours when stored below 30°C ' which is supported with appropriate data. The container closure system is a type I glass vial closed with chlorobutyl rubber stopper and aluminium crimp-cap with a polypropylene flip-off disk.

Drug Product-Diluent Vial:

The Sterile Water for Injection (sWFI) is manufactured using terminal sterilization. Proper validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place. The specifications for sWFI are established in accordance with USP, Ph. Eur., and JP monographs. The primary container closure system for the sWFI is a type I vial with a chlorobutyl rubber stopper and aluminium crimp cap with plastic flip-off cap. The stability data submitted was adequate to support the approved shelf-life of 60 months when stored at $+5\pm 3^{\circ}\text{C}$.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of rurioctocog alfa pegol in the treatment and prophylaxis of bleeding in patients with hemophilia A was based on four studies – pivotal study 261201, pediatric study 261202, surgery study 261204 and continuation study 261302.

Study 261201 was a Phase II/III, multi-center, open label study in adolescent and adult male previously treated patients (PTPs) with severe hemophilia A (N=138). Subjects were enrolled to receive either prophylactic treatment with rurioctocog alfa pegol at a dose of 45 ± 5 IU/kg twice weekly for at least 50 exposure days (EDs) or 6 months \pm 2 weeks, whichever occurred last (Arm A) or on-demand therapy with rurioctocog alfa pegol at a dose of 10 to 60 IU/kg dose for approximately 6 months (Arm B). A total of 121 subjects were assigned to Arm A and 17 subjects to Arm B, hence the Full Analysis Set comprised 138 subjects. All subjects in Arm B had previously received on-demand FVIII therapy.

The primary efficacy endpoint was the annualized bleeding rate (ABR). Prophylactic treatment was considered successful if the upper limit of the 95% confidence interval (CI) for the ABR ratio between the treatment regimen did not exceed 0.5 (corresponding to a 50% reduction of the mean ABR compared to the on-demand treatment). The key secondary efficacy endpoint was the rate of success in the treatment of BEs, defined as a rating of 'excellent' or 'good' in the Efficacy Rating Scale for Treatment of BEs measured 24 hours after initiating treatment for the BE.

The demographics and baseline characteristics were generally balanced between both study arms. The majority of subjects were Caucasian (Arm A: 77%; Arm B: 65%). The median age at baseline was 29.0 years (range 12 to 58 years) and was similar in the prophylaxis (median 28.0 years; range 12 to 58 years) and on-demand arms (median 32.0 years; range 13 to 56 years). A total of 25 of 138 subjects (18.1%) were adolescents aged 12 to <18 years (Arm A: 23 of 121 (19.0%); Arm B: 2 of 17 (11.8%).

Study 261201 met its primary efficacy endpoint, as the prophylaxis/on-demand ratio of the mean ABRs was 0.10 (95% CI 0.06, 0.19; $p < 0.0001$). The estimated mean ABRs were 4.3 (95% CI 3.4; 5.5) for prophylaxis and 43.4 (95% CI 25.2; 74.8) for on-demand treatment with rurioctocog alfa pegol. The primary efficacy outcome was also met in adult subjects – the prophylaxis/on-demand ratio of the mean ABRs was 0.10 (95% CI 0.05, 0.19; $p < 0.0001$). However, the result was inconclusive for adolescent subjects given the small number of subjects in the on-demand group ($n=2$) – the prophylaxis/on-demand ratio of the mean ABRs was 0.17 (95% CI 0.04, 0.68; $p=0.0630$).

The results of key secondary endpoints provided supportive evidence on the efficacy. The estimated rate of success for the control of bleeding was 0.97 (95% CI 0.94, 0.98; $p < 0.0001$), which was significantly higher than the predefined lowest clinically acceptable success rate of 70%. There were 591 BEs reported during the observation period of efficacy (OPE) in the Full Analysis Set (prophylaxis arm: 230; on-demand arm: 361). Of the 120 subjects in the prophylactic arm (Per Protocol Analysis Set), 45 (37.5%) reported no BEs during their treatment period, whereas all of the 17 subjects (100%) in the on-demand arm reported BEs during their treatment period. The intervals between BEs were longer for those on prophylaxis compared with those treated on-demand – 15.8% subjects on prophylaxis had ≤ 1 month between BEs (and 39.6% had no BEs) compared with 100% for those treated on-demand. The majority of BEs were treated with 1 or 2 infusions (497/518; 95.9% for all sites/causes), with 443/518 (85.5%) treated with 1 infusion. In addition, out of the 98 subjects who had received pre-study prophylaxis treatment regimen with another FVIII concentrate, 91 (92.9%)

experienced a median (Q1; Q3) reduction in prophylactic dosing frequency of 33.70% (8.10; 37.09) (mean [SD]: 27.46% [26.560]) during prophylactic rurioctocog alfa pegol treatment compared to the pre-study prophylactic regimen. This translated into approximately at least one less prophylactic infusion per week when using rurioctocog alfa pegol for prophylaxis. For subjects whose pre-study prophylactic dosing frequency was twice weekly, the mean [SD] treatment dose decreased from 55.25 (138.38) IU/kg to 43.49 (3.49) IU/kg during the observation period of efficacy.

Summary of Key Efficacy Results (Study 261201)

	Prophylactic treatment (Arm A, N=120)	On-demand therapy (Arm B, N=17)
Mean ABR (95% CI) - FAS	4.3 (3.4; 5.5)	43.4 (25.2; 74.8)
Ratio (95% CI), one-sided p-value	0.10 (0.06 to 0.19), p <0.0001	
Proportion of subjects with BEs - PPAS	37.5%	100%
Proportion of subjects who had ≤1 month between BEs - PPAS	15.8%	100%

FAS: Full Analysis Set; PPAS: Per Protocol Analysis Set

Study 261202 was a Phase III, prospective, uncontrolled, open label, multicenter study in previously treated pediatric patients with severe hemophilia A. There were 2 age cohorts of 30 subjects each (25 evaluable), namely <6 years and 6 to <12 years. Subjects were enrolled to receive twice weekly prophylactic treatment with 50 ±10 IU/kg of rurioctocog alfa pegol over a period of 6 months or at least 50 EDs, whichever occurred last. The hemostatic efficacy of rurioctocog alfa pegol was evaluated as the secondary objective of the study and the key secondary efficacy endpoint was ABR, which was only calculated for subjects who had adequate treatment time (6 months).

A total of 73 subjects were enrolled in the study and 66 were dosed with prophylactic treatment (<6 years: 32 subjects; 6 to <12 years: 34 subjects). The majority of subjects were male (98.5%) and Caucasian (65.2%). The median age was 4.0 years (range: 1 to 5 years) and 8.0 years (range: 6 to 11 years) in the younger and older age cohorts, respectively, with an overall median age of 6.0 years.

The overall mean ABR was 3.04 (95% CI 2.208, 4.186) with a median of 2.00 (Q1; Q3: 0.00; 3.90). The mean ABR was 2.37 (95% CI 1.486, 3.778; median: 1.95 [Q1; Q3: 0.00; 3.85]) in the <6 years cohort and 3.75 (95% CI 2.429, 5.781; median: 2.00 [Q1; Q3: 0.00; 5.90]) in the 6 to <12 years cohort. A total of 25/66 subjects (37.9%) (comprising 13/32 (40.6%) in the younger and 12/34 (35.3%) in the older age cohort) did not experience any BE during prophylaxis with rurioctocog alfa pegol. There were 70 BEs occurred in 34 subjects in this study (<6 years: 25 BEs in 15 subjects; 6 to <12 years: 45 BEs in 19 subjects). Hemostatic efficacy at resolution of bleeding was rated as “excellent” or “good” for 63 BEs corresponding to an overall estimated success rate of 0.900 (95% CI 0.805, 0.959), which is larger than the predefined success rate of 70%.

Summary of Key Efficacy Results (Study 261202) – Full Analysis Set

	Age <6 (N=32)	Age 6 to <12 (N=34)	Total (N=66)
Mean ABR (95% CI)	2.37 (1.486; 3.778)	3.75 (2.429; 5.781)	3.04 (2.208; 4.186)
Median ABR (Q1, Q3)	1.95 (0.00; 3.85)	2.00 (0.00; 5.90)	2.00 (0.00; 3.90)
Proportion without BEs	40.6%	35.3%	37.9%

Q1: first quartile; Q3: third quartile

Study 261204 was a Phase III, prospective, uncontrolled, open-label, multicenter study in previously treated patients with severe hemophilia A subjects (2-75 years of age) undergoing major or minor elective or minor emergency surgical, dental or other invasive procedures. The dose and frequency of rurioctocog alfa pegol administered was individualized based on the subject's pharmacokinetic parameters for major surgeries and incremental recovery (IR) for minor surgeries and the FVIII target levels required for the planned procedure. The duration of treatment also depended on the nature of each subject's procedure. In general, the dose was to be tailored to raise the plasma level of FVIII to 80-100% of normal for major procedures and to 30-60% of normal for minor procedures.

The primary efficacy endpoint was the Global Hemostatic Efficacy Assessment (GHEA) score at 24 hours and on Day 14 (or at discharge, whichever is first). The secondary efficacy endpoints included actual intra- and postoperative blood loss and the occurrence of BEs.

A total of 21 subjects who underwent 26 procedures (21 major procedures and 5 minor) were enrolled in the study. All subjects were male and between 16 and 61 years of age (mean [SD]: 34.8 ± 13.47 years) at the time of enrolment and 95.2% of subjects were 18 to 75 years old.

All 24 surgeries (21 major and 3 minor) with available GHEA scores were rated excellent and therefore considered a treatment success (90 % CI 88.3%, 100.0%; 95 % CI 85.8%, 100.0%). The median intraoperative blood loss for major orthopedic surgeries (10.0 mL) was substantially less than the average volume predicted pre-operatively by the investigator/surgeon (150.0 mL), while it was similar to the predicted volumes for non-orthopedic major surgeries and other minor surgeries (10.0 mL). With regard to postoperative blood loss, although the median actual blood loss for major orthopedic surgeries was 50 mL greater than the average volume predicted, it was 100 mL less when compared to the predicted maximum blood loss. Postoperative blood loss for non-orthopedic major surgeries and other minor surgeries was similar to the predicted values. A total of 5 BEs in 5 subjects occurred from the start of surgery until the last intensified treatment after hospital discharge (or until hospital discharge if there was no intensified treatment); 1 occurred following minor surgery and 4 BEs occurred following orthopedic (n=2) or non-orthopedic (n=2) major surgeries. In terms of severity, 3 BEs were mild, 1 was moderate and 1 was severe. Three required no treatment with FVIII products and the remainder was treated with rurioctocog alfa pegol. All BEs were categorized as injury-related.

Summary of Key Efficacy Results (Study 261204)

		Major Surgeries		Minor Surgeries	All Surgeries
		Orthopedic	Non-Orthopedic		
GHEA scores rated as excellent					
n/N (%)		14/14 (100%)	7/7 (100%)	3/3 (100%)	24/24 (100%)
90% CI		80.7, 100.0	65.2, 100.0	36.8, 100.0	88.3, 100.0
95% CI		76.8, 100.0	59.0, 100.0	29.2, 100.0	85.8, 100.0
Median (Q1; Q3) intraoperative blood loss (ml)	Actual	10.0 (10.0, 30.0) (N=14)	4.5 (3.0, 50.0) (N=6)	5.0 (0.0, 15.0) (N=5)	10.0 (4.0, 30.0) (N=25)
	Predicted	150.0 (10.0, 150.0) (N=14)	10.0 (5.0, 50.0) (N=7)	5.0 (0.0, 15.0) (N=5)	20.0 (5.0, 150.0) (N=26)
	Difference	125.0 (0.0, 140.0)	1.5 (0.0, 6.0)	0.0 (0.0, 0.0)	6.0 (0.0, 135.0)
Median (Q1; Q3) postoperative blood loss (ml)	Actual	750.0 (15.0, 1100.0) (N=9)	1.0 (0.0, 33.5) (N=4)	0.0 (0.0, 4.0) (N=3)	10.0 (0.0, 825.0) (N=16)
	Predicted	213.5 (30.0, 700.0) (N=14)	1.0 (0.0, 25.0) (N=7)	0.0 (0.0, 0.0) (N=5)	27.5 (0.0, 300.0) (N=26)
	Difference	-50.0 (-400.0, -15.0)	4.0 (-7.5, 16.5)	0.0 (0.0, 196.0)	-7.5 (-125.0, 4.0)
BEs		2	2	1	5

Q1: first quartile; Q3: third quartile

Study 261302 was Phase IIIb, prospective, open label, multicenter efficacy and safety uncontrolled continuation study in pediatric and adult PTPs ≤75 years of age with severe hemophilia A. This study included subjects from other studies who had treated with rurioctocog alfa pegol as well those who were naïve to rurioctocog alfa pegol. Subjects were to receive either a fixed-dose prophylaxis with rurioctocog alfa pegol consisting of 45 ± 5 IU/kg for subjects aged ≥12 years or 50 ± 10 IU/kg for subjects aged <12 years twice weekly or a pharmacokinetically-tailored (PK-tailored) prophylactic dose regimen based on the subject's individual PK to maintain FVIII trough levels of ≥3%. The frequency of PK-tailored prophylactic rurioctocog alfa pegol dosing was to be at least twice weekly. The primary efficacy endpoint was the ABR of spontaneous BEs ('spontaneous ABR').

A total of 216 subjects were treated in the study, the majority of whom were male (99.5%) and Caucasian (70.4%). The median age was 20.0 years (range 1 to 61 years old). The overall mean [SD] historical spontaneous ABR based on the previous 3 to 6 months prior to the continuation study was 4.7 (12.58).

While on the fixed-dose, twice-weekly prophylaxis, the mean spontaneous ABR was 1.197 (95% CI: 0.918 - 1.561), which was similar to that of the PK-tailored regimen (0.964; 95% CI 0.542, 1.714). The mean total ABR analyzed using a generalized linear model was 2.230 (95% CI: 1.852 - 2.686) in the 186 subjects who qualified for the analysis. It was similar for subjects ≥18 years old (2.166 [1.667 - 2.813]) and for subjects ≥6 to <12 years of age (1.997 [1.317 - 3.029]), lower for subjects aged <6 years (1.519 [1.037 - 2.225]), and higher for the ≥12 to <18 years old category (3.151 [2.256 - 4.401]).

Summary of Primary Efficacy Results (Study 261302)

	N	Spontaneous bleeds	Spontaneous ABR (95% CI)	Total ABR (95% CI)
Fixed dose - Twice weekly	186	372	1.197 (0.918 - 1.561)	2.230 (1.852 - 2.686)
PK-tailored regimen	25	35	0.964 (0.542 - 1.714)	2.638 (1.704 - 4.084)

q5d: every 5 days; q7d: every 7 days

Overall, the results of the four studies demonstrated the efficacy of rurioctocog alfa pegol in children and adults with hemophilia A for on-demand treatment and control of BEs, perioperative management and routine prophylaxis to reduce the frequency of BEs.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of rurioctocog alfa pegol was based primarily on safety data derived from subjects aged 0 to 61 years who had participated in one or more of 7 clinical studies of rurioctocog alfa pegol administered to subjects for prophylaxis, treatment of BEs, perioperative management, or who received a single-dose for a PK evaluation. The analysis included 243 subjects who received at least one dose of rurioctocog alfa pegol with the median duration (Q1; Q3) of 401.0 (271.0; 767.0) days per subject. Subjects were exposed to rurioctocog alfa pegol for a median (Q1; Q3) of 111.0 (73.0;196.0) EDs. Pediatric patients had a shorter exposure to rurioctocog alfa pegol (6 to <12 years: mean 87.5 days; <6 years: mean 75.8 days).

Summary of Safety Profile

	Rurioctocog alfa pegol (N=243)
AEs	182 (74.9%)
AEs related* to rurioctocog alfa pegol	10 (4.1%)
SAE	29 (11.9%)
SAE related* to rurioctocog alfa pegol	0
Discontinuations due to AE	9 (3.7%)
Death	1 (0.4%)
Death related* to rurioctocog alfa pegol	0

*as determined by the investigator

AEs considered related by the sponsor as reported in the analysis included diarrhea, nausea, headache, hypersensitivity, rash and flushing. These were consistent with the AEs seen with other FVIII products.

There were 46 serious adverse events (SAEs) in 29/243 subjects (11.9%), none of which were assessed by the sponsor or the investigator as being related to rurioctocog alfa pegol treatment. There was one fatal SAE in study 261302 (neuroendocrine carcinoma) which was considered unrelated to treatment with rurioctocog alfa pegol.

Children aged <12 years old had a similar rate of SAEs per infusion to other age groups. While they tended to have a higher rate of non-serious AEs per infusion, the overall incidence rate was < 5%. In adolescents, the rates of serious and non-serious AEs per infusion were similar to the rates observed in the adult population and overall population.

None of the subjects exposed to rurioctocog alfa pegol in the studies developed inhibitory antibodies to FVIII of ≥ 0.6 Bethesda units/mL. The majority of subjects (238/243) in the integrated analysis did not develop a persistent binding antibody response against FVIII, PEG-FVIII, PEG, or CHO protein during the studies.

Overall, rurioctocog alfa pegol was well tolerated and the AEs were manageable with no major safety concerns. The related AEs reported were consistent with the safety profile of other FVIII products.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current standard treatment for hemophilia A patients is replacement therapy with FVIII concentrates. Treatment regimens are either on-demand therapy or prophylactic. The average $T_{1/2}$ of currently available, unmodified full-length and B-domain deleted recombinant FVIII products for adults is in the range of 10 to 14 hours and is lower in children. Thus, current prophylactic regimens require infusion of FVIII every other day or 3 times weekly to effectively prevent or reduce spontaneous BEs. Adynovate is a pegylated form of a currently registered recombinant FVIII product with an extended $T_{1/2}$ that is expected to prolong the duration of action of each dose of replacement therapy and thus reduce the frequency of infusions.

The efficacy of rurioctocog alfa pegol had been demonstrated in 4 clinical studies in children and adults with severe hemophilia A. Study 261201 demonstrated that prophylaxis treatment resulted in more than 50% reduction of ABR compared to in-demand treatment. For the control of BEs, the estimated rate of success was 96%. In children <12 years old given prophylaxis treatment, a mean ABR of 3.04 was achieved. In the perioperative setting, rurioctocog alfa pegol therapy resulted in “excellent” Global Hemostatic Efficacy Assessment Scores for all procedures, and the mean spontaneous ABR in patients on a fixed-dose, twice-weekly

regimen was reported to be 1.197. These results were within the range of those expected of FVIII in demonstrating efficacy in the prevention and control of bleeding.

The safety profile of rurioctocog alfa pegol was considered acceptable and similar to other FVIII products. The most notable safety concerns were diarrhea, nausea, headache, hypersensitivity, rash and flushing and have been adequately addressed in the package insert.

Overall, the benefit-risk profile of rurioctocog alfa pegol for on-demand treatment and control of BEs, perioperative management and routine prophylaxis to reduce the frequency of BEs in children and adults with hemophilia A was considered favorable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Adynovate, indicated in children and adults with hemophilia A (congenital FVIII deficiency) for on-demand treatment and control of BEs; perioperative management and routine prophylaxis to reduce the frequency of BEs, was deemed favorable and approval of the product registration was granted on 24 Nov 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

ADYNOVATE

Rurioctocog alfa pegol [Antihæmophilic Factor (Recombinant), PEGylated]

1 INDICATIONS AND USAGE

ADYNOVATE, Rurioctocog alfa pegol [Antihæmophilic Factor (Recombinant), PEGylated], is a human antihæmophilic factor indicated in children and adults with hæmophilia A (congenital factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitation of Use

ADYNOVATE is not indicated for the treatment of von Willebrand disease.

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

- One international unit corresponds to the activity of factor VIII contained in one millilitre of normal human plasma.
- Dosage and duration of treatment depend on the severity of factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition. Careful monitoring of replacement therapy is necessary in cases of serious or life-threatening bleeding episodes.
- Potency assignment is determined using a one-stage clotting assay. Plasma factor VIII levels can be monitored clinically using a one-stage clotting assay.
- Calculate the dose of ADYNOVATE based on the empirical finding that one international unit of ADYNOVATE per kg body weight increases the plasma factor VIII level by 2 IU per dL of plasma. Use the following formula to estimate the expected *in vivo* peak increase in factor VIII level expressed as IU per dL (or % of normal) and the dose to achieve a desired *in vivo* peak increase in factor VIII level:

Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL)

- Patients vary in their pharmacokinetic (e.g., clearance, half-life, *in vivo* recovery) and clinical response. Base the dose and frequency of ADYNOVATE on the individual clinical response.

On-demand Treatment and Control of Bleeding Episodes

A guide for dosing of ADYNOVATE for the on-demand treatment and control of bleeding episodes is provided in Table 1. Maintain plasma factor VIII activity level at or above the described plasma levels (in IU per dL or % of normal).

Table 1: Dosing for On-demand Treatment and Control of Bleeding Episodes

Type of Bleeding	Target Factor VIII Level (IU/dL or % of normal)	Dose ^a (IU/kg)	Frequency of Dosing (hours)	Duration of Therapy
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding episode.	20-40	10-20	12-24	Until the bleeding is resolved
Moderate Muscle bleeding, moderate bleeding into the oral cavity, definite hemarthroses, and known trauma.	30-60	15-30	12-24	Until the bleeding is resolved
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma.	60-100	30-50	8-24	Until the bleeding is resolved.

^a Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

Perioperative Management

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

Table 2: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (% of normal or IU/dL)	Dose (IU/kg)	Frequency of Doses (hours)	Duration of Treatment
Minor Including tooth extraction	60-100	30-50	Within one hour before surgery. Repeat after 24 hours if necessary	Single dose or repeat as needed until bleeding is resolved.
Major Intracranial, intra- abdominal, or intrathoracic surgery, joint replacement surgery	80-120 (pre- and post-operative)	40-60	Within one hour before the operation to achieve 100% activity. Repeat every 8 to 24 hours (6 to 24 hours for patients <12 years of age) to maintain FVIII activity within the target range	Until adequate wound healing

Routine Prophylaxis

Administer 40-50 IU per kg body weight 2 times per week in children and adults (12 years and older). Administer 55 IU per kg body weight 2 times per week in children (< 12 years) with a maximum of 70 IU per kg. Adjust the dose based on the patient's clinical response.

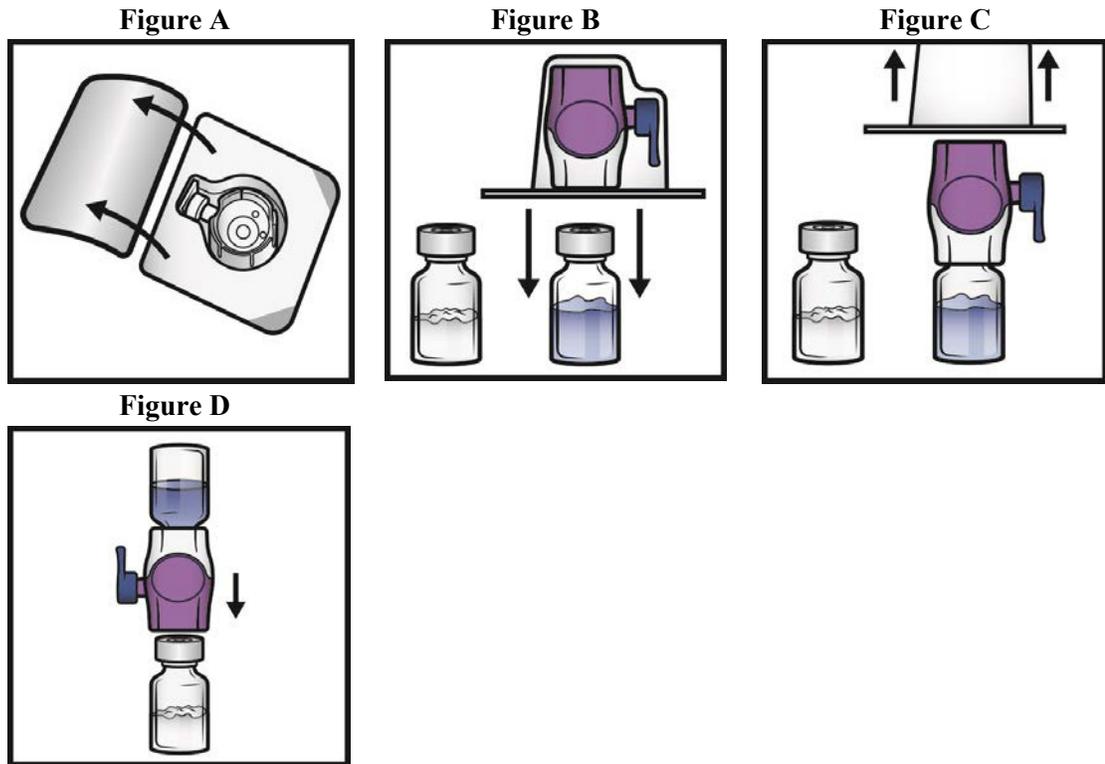
2.2 Preparation and Reconstitution

Preparation and reconstitution using the BAXJECT II Hi-Flow device

For reconstitution, use only the diluent vial and the reconstitution device provided in the pack.

1. Use antiseptic technique (clean and germ-free conditions) and a flat work surface during the reconstitution procedure.
2. Allow the vials of ADYNOVATE and diluent to reach room temperature (between 15 °C and 25 °C) before use.
3. Remove plastic caps from the ADYNOVATE and diluent vials.
4. Clean rubber stoppers with an alcohol swab and allow to dry prior to use.
5. Open the BAXJECT II Hi-Flow device package by peeling away the lid, without touching the inside (Figure A). Do not remove the device from the package.
6. Turn the package over. Press straight down to fully insert the clear plastic spike through the diluent vial stopper (Figure B).
7. Grip the BAXJECT II Hi-Flow package at its edge and pull the package off the device (Figure C). Do not remove the blue cap from the BAXJECT II Hi-Flow

- device. Do not touch the exposed purple plastic spike.
- Turn the system over so that the diluent vial is on top. Quickly insert the purple plastic spike fully into the ADYNOVATE vial stopper by pushing straight down (Figure D). The vacuum will draw the diluent into the ADYNOVATE vial.
 - Swirl gently until the ADYNOVATE is completely dissolved. Do not shake. Do not refrigerate after reconstitution.



Preparation and reconstitution using the BAXJECT III system

Preparation

- Do not remove ADYNOVATE or diluent vials from the external housing.
- Examine the packaging containing ADYNOVATE to ensure no damage or peeling of the lid is evident. Do not use if the lid is not completely sealed on the blister.
- Use aseptic technique (clean and germ-free) and a flat work surface during the reconstitution procedure.

Reconstitution

- Allow the ADYNOVATE package to reach room temperature (between 15°C and 25°C) before use.
- Wash your hands thoroughly using soap and warm water.
- Open the package by peeling away the lid. Remove the BAXJECT III system from the package.
- Place ADYNOVATE on a flat surface with the diluent vial on top (Figure E). The diluent vial has a blue stripe. Do not remove the blue cap until instructed in a later

step.

5. With one hand holding ADYNOVATE in the BAXJECT III system, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the ADYNOVATE vial (Figure F). Do not tilt the system until the transfer is complete.
6. Verify the diluent transfer is complete. Swirl gently until all material is dissolved (Figure G). Do not shake. Be sure that the ADYNOVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution, the solution should be clear, colourless and free from foreign particles. Do not refrigerate after reconstitution.

Figure E

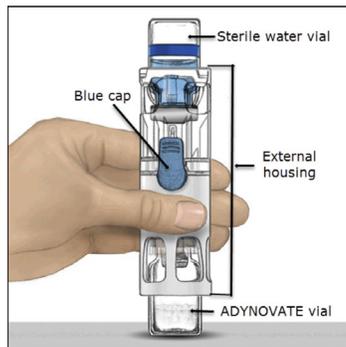


Figure F

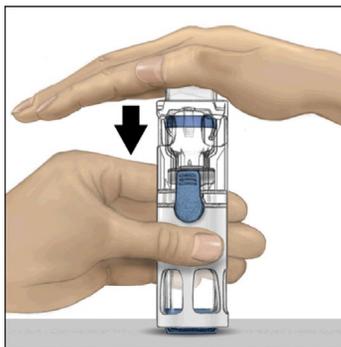
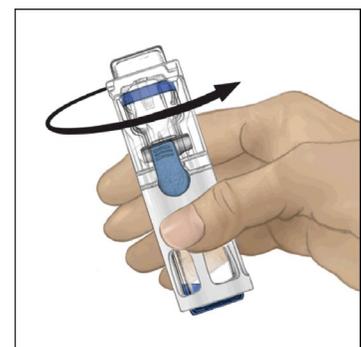


Figure G



Administration

- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration.
 - The appearance of the reconstituted solution is clear and colourless.
 - Do not use if particulate matter or discoloration is observed.
- Administer as soon as possible, but no later than 3 hours after reconstitution.

Administration steps for BAXJECT II Hi-Flow device

1. Remove the blue cap from the BAXJECT II Hi-Flow device (Figure H). Connect the syringe to the BAXJECT II Hi-Flow device. Use of a Luer-lock syringe is recommended. **Do not inject air.**
2. Turn the system upside down (ADYNOVATE vial now on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Figure I).
3. Disconnect the syringe; attach the infusion set needle to the syringe and inject the reconstituted solution intravenously. If a patient is to receive more than one vial of ADYNOVATE, the contents of multiple vials may be drawn into the same syringe.

A separate BAXJECT II Hi-Flow device is required to reconstitute each vial of ADYNOVATE with the diluent.

- Administer over a period of up to 5 minutes (maximum infusion rate 10 ml per min).

Figure H

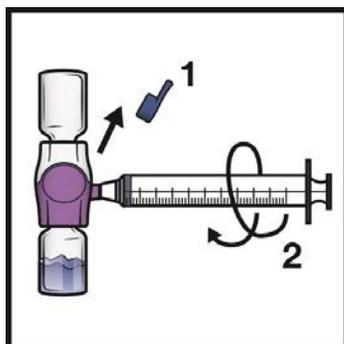
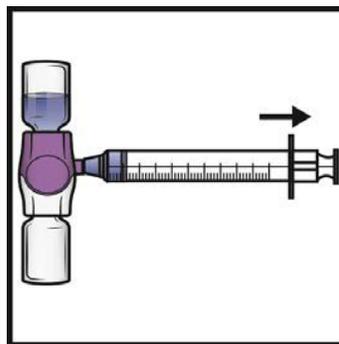


Figure I



Administration steps for BAXJECT III system:

- Remove the blue cap from the BAXJECT III system. Connect the syringe to the system (Figure J). Use of a Luer-lock syringe is recommended. **Do not inject air.**
- Turn the system upside down (ADYNOVATE vial now on top). Draw the reconstituted solution into the syringe by pulling plunger back slowly (Figure K).
- Disconnect the syringe, attach the infusion set needle to the syringe, and inject the reconstituted solution intravenously. If a patient is to receive more than one vial of ADYNOVATE, the contents of multiple vials may be drawn into the same syringe.
- Administer ADYNOVATE intravenously over a period of less than or equal to 5 minutes (maximum infusion rate 10 mL per min).

Figure J

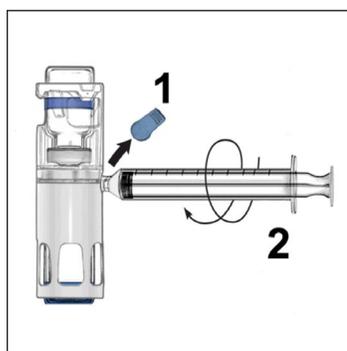
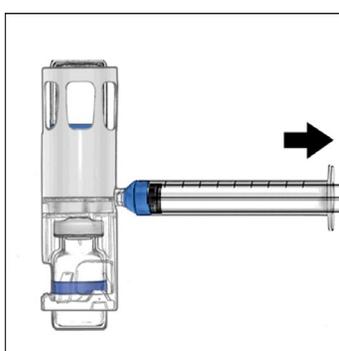


Figure K



It is strongly recommended that every time ADYNOVATE is administered, the name and batch number of the product are recorded. Peel-off labels are provided on the ADYNOVATE vial (with BAXJECT II Hi-Flow device) and on the blister (with BAXJECT III system).

3 DOSAGE FORMS AND STRENGTHS

ADYNOVATE is a lyophilized powder in single-use vials containing nominally

(approximately) 250, 500, 1000, 1500, 2000, and 3000 International Units (IU, units). The 250-1500 IU strengths come with 2 mL Sterile Water for Injection (sWFI); the 2000 and 3000 IU strengths come with 5 mL of sWFI. The actual factor VIII potency/content is labelled on each ADYNOVATE vial.

The potency assignment employs a factor VIII concentrate standard that is referenced to a WHO (World Health Organization) international standard for factor VIII concentrates and is evaluated by appropriate methodology to ensure accuracy of the results.

4 CONTRAINDICATIONS

ADYNOVATE is contraindicated in patients who have had prior anaphylactic reaction to ADYNOVATE, to the parent molecule (ADVATE), mouse or hamster protein, or excipients of ADYNOVATE (e.g. Tris, mannitol, trehalose, glutathione, and/or polysorbate 80).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions are possible with ADYNOVATE. Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with other recombinant antihemophilic factor VIII products, including the parent molecule, ADVATE. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnoea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

5.2 Neutralizing Antibodies

Formation of neutralizing antibodies (inhibitors) to factor VIII can occur following administration of ADYNOVATE. Monitor patients regularly for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. Perform an assay that measures factor VIII inhibitor concentration if the plasma factor VIII level fails to increase as expected, or if bleeding is not controlled with expected dose.

5.3 Monitoring Laboratory Tests

- Monitor plasma factor VIII activity by performing a validated one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained [see *Dosage and Administration (2)*].
- Monitor for the development of factor VIII inhibitors. Perform the Bethesda inhibitor assay to determine if factor VIII inhibitor is present. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with the expected dose of ADYNOVATE, use Bethesda Units (BU) to determine inhibitor levels.

6 ADVERSE REACTIONS

The most common adverse reactions ($\geq 1\%$ of subjects) reported in the clinical studies were headache and nausea.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ADYNOVATE was evaluated in 237 previously treated patients (PTPs) and 6 previously untreated patients (PUPs) with severe haemophilia A (factor VIII less than 1% of normal), who received at least one dose of ADYNOVATE in 3 completed multi- centre, prospective, open label clinical studies and 4 ongoing clinical studies. The median duration of participation per subject was 401 (min-max: 3-1034) days and the median number of exposure days to ADYNOVATE per subject was 111 (min-max: 1-322). Table 3 lists the adverse reactions reported during clinical studies.

Table 3: Adverse Reactions Reported for ADYNOVATE

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects n (%) (N=243)	Rate of AEs per 100 Infusions (N=30865)
Gastrointestinal Disorders	Diarrhoea	1 (0.4%)	0.003
	Nausea	2 (0.8%)	0.006
Immune System Disorder	Hypersensitivity ^a	1 (0.4%)	0.003
Nervous System Disorders	Headache	5 (2.1%)	0.026
Skin and Subcutaneous Tissue Disorders	Rash	1 (0.4%)	0.003
Vascular Disorders	Flushing	1 (0.4%)	0.003

^a The event of hypersensitivity was a mild transient non-serious rash, occurring in one 2-year old patient who had developed a previous rash while on ADYNOVATE.

Two cases of acute pancreatitis, with no precipitating cause identified in one case, were reported in adults during an extension study of the clinical trial which evaluated 137 subjects. Administration of ADYNOVATE continued and both cases resolved.

6.2 Immunogenicity

The risk of the development of factor VIII inhibitors with the use of ADYNOVATE was evaluated in 3 completed and 4 ongoing clinical trials. Subjects consisted of adolescent and adult (n= 148 with ≥ 150 prior EDs) and paediatric PTPs [(< 6 years of age with ≥ 50 prior EDs (n= 32), ≥ 6 years of age with ≥ 150 prior EDs (n= 57)], and paediatric PUPs (n=6). In 191 adult and paediatric PTPs who were treated for at least 50 exposure days with ADYNOVATE, the factor VIII inhibitor frequency was 0 (95% CI of 0 to 0.019). One PUP subject from an ongoing study, who received at least one infusion of ADYNOVATE, developed neutralizing antibodies to factor VIII.

Immunogenicity also was evaluated by measuring the development of binding IgG and IgM antibodies against factor VIII, PEGylated (PEG)-factor VIII, PEG and Chinese hamster ovary (CHO) protein using validated ELISA assays. The majority of subjects (238/243) with at least one infusion of ADYNOVATE did not develop a persistent binding antibody response to any of these antigens. Twenty-eight subjects in total showed pre-existing antibodies to factor VIII (n=3), PEG-factor VIII (n=25) and/or PEG (n=3) prior to the first exposure to ADYNOVATE. Thirteen subjects who tested negative at screening developed transient antibodies against factor VIII (n= 6), PEG-FVIII (n= 8) at one or two consecutive study visits. Antibodies were transient and not detectable at subsequent visits. Five subjects showed positive results for binding antibodies at study completion or at the time of data cut-off. Binding antibodies that were detected prior to exposure to ADYNOVATE, that transiently developed during the trial or were still detectable at study completion or data cut-off could not be correlated to any impaired treatment efficacy or altered PK parameters. There was no causal relationship between observed adverse events and binding antibodies except in one subject where a causal relationship cannot be ruled out based on available data. No subject had pre-existing or treatment-emergent antibodies to CHO protein.

The detection of antibodies that are reactive to factor VIII is highly dependent on many factors, including: the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ADYNOVATE with the incidence of antibodies to other products may be misleading.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

There are no data with ADYNOVATE use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with ADYNOVATE. It is unknown whether ADYNOVATE can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. ADYNOVATE should be given to a pregnant woman only if clearly needed.

7.2 Lactation

Risk Summary

There is no information regarding the presence of ADYNOVATE in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADYNOVATE and any potential adverse effects on the breastfed infant from ADYNOVATE or from the underlying maternal condition.

7.3 Paediatric Use

Safety and efficacy studies have been performed in 91 previously treated, paediatric

patients age 1 year to <18 years who received at least one dose of ADYNOVATE as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. Adolescent subjects age 12 to <18 (n=25) were enrolled in the adult and adolescent safety and efficacy trial, and subjects <12 years of age (n=66) were enrolled in a paediatric trial. The safety and efficacy of ADYNOVATE in routine prophylaxis and the treatment of bleeding episodes were comparable between children and adults [see *Clinical Studies (11)*].

Pharmacokinetic (PK) studies in children (<12 years) have demonstrated higher clearance, a shorter half-life and lower incremental recovery of factor VIII compared to adults.

Because clearance (based on per kg body weight) has been demonstrated to be higher in children (<12 years), dose adjustment or more frequent dosing based on per kg body weight may be needed in this population [see *Clinical Pharmacology (9.3)*].

7.4 Geriatric Use

Clinical studies of ADYNOVATE did not include subjects aged 65 and over.

8 DESCRIPTION

ADYNOVATE, Rurioctocog alfa pegol [Antihæmophilic Factor (Recombinant), PEGylated], is formulated as a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection. The product is supplied in single-use vials containing nominal (approximate) potencies of 250, 500, 1000, 1500, 2000, or 3000 international units (IU). Each vial of ADYNOVATE is labelled with the actual factor VIII activity in IU determined using one-stage clotting assay, using a reference material calibrated against a World Health Organization (WHO) International Standard for factor VIII concentrates. One IU, as defined by the WHO standard for blood coagulation factor VIII, human, is approximately equal to the level of factor VIII activity found in 1 mL of fresh pooled human plasma.

When reconstituted with 2 mL or 5 mL sterile water for injection, the final solution contains the following excipients and stabilizers in targeted amounts per mL of reconstituted product:

Stabilizer and Excipient	2 mL Reconstitution (for 250, 500, 1000, 1500 IU) Target (per mL)	5 mL Reconstitution (for 2000, 3000 IU) Target (per mL)
Tris (hydroxymethyl) aminomethane	3.05 mg	1.22 mg
Calcium Chloride	0.60 mg	0.24 mg
Mannitol	80 mg	32 mg
Sodium Chloride	13.15 mg	5.26 mg
Trehalose Dihydrate	20 mg	8 mg
Glutathione	0.2 mg	0.08 mg
Histidine	3.90 mg	1.56 mg
Polysorbate 80	0.25 mg	0.10 mg

ADYNOVATE contains no preservative. The specific activity of ADYNOVATE is 2700 - 8000 IU/mg protein.

ADYNOVATE is a recombinant full-length human coagulation factor VIII (2,332 amino acids with a molecular weight (MW) of 280 kDa) covalently conjugated with one or more molecules of polyethylene glycol (MW 20 kDa) [*see Clinical Pharmacology (9.1)*]. The therapeutic activity of ADYNOVATE is derived from its parent drug substance, ADVATE [Antihæmophilic Factor (Recombinant)], which is produced by recombinant DNA technology from the CHO cell line. ADVATE is purified from the culture medium using a series of chromatography columns. The purification process includes an immunoaffinity chromatography step in which a monoclonal antibody directed against factor VIII is employed to selectively isolate the factor VIII from the medium. The production process includes a dedicated, viral inactivation solvent-detergent treatment step. The ADVATE molecule is then covalently conjugated with the polyethylene glycol, which mainly targets lysine residues.

The cell culture, pegylation, purification process and formulation used in the manufacture of ADYNOVATE do not use additives of human or animal origins.

9 CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

ADYNOVATE, a PEGylated form of recombinant antihæmophilic factor (ADVATE), [*see Description (8)*], temporarily replaces the missing coagulation factor VIII needed for effective hæmostasis in congenital hæmophilia A patients. ADYNOVATE exhibits an extended terminal half-life through pegylation of the parent molecule, ADVATE, which reduces binding to the physiological factor VIII clearance receptor (LRP1).

9.2 Pharmacodynamics

Hæmophilia A is a disorder characterized by a deficiency of functional coagulation factor VIII, resulting in a prolonged, patient plasma clotting time as measured by the activated partial thromboplastin time (aPTT). Treatment with ADYNOVATE normalizes the aPTT over the effective dosing period. The administration of ADYNOVATE increases plasma levels of factor VIII and can temporarily correct the coagulation defect in hæmophilia A patients.

9.3 Pharmacokinetics

The PK of ADYNOVATE were evaluated in a multi-centre, prospective, open label clinical trial and compared with ADVATE in 26 subjects prior to initiation of prophylactic treatment with ADYNOVATE and in 22 subjects after 6 months of treatment with ADYNOVATE. A single dose of 45 IU/kg was utilized for both products. The PK parameters, as shown in Table 4, were based on plasma coagulation

factor VIII activity measured by the one-stage clotting assay and are presented by age groups.

Incremental recovery was comparable between both products. The PK parameters determined after 6 months of prophylactic treatment with ADYNOVATE were consistent with the initial parameter estimates.

Paediatric Pharmacokinetics

Pharmacokinetic parameters calculated from 39 subjects <18 years of age (intent-to-treat analysis) are available for 14 children (2 to <6 years), 17 older children (6 to <12 years) and 8 adolescent subjects (12 to <18 years of age), as shown in Table 4. The mean clearance (based on body weight) of ADYNOVATE was higher and the mean half-life was lower in children <12 years of age than adults. A dose adjustment may be required in children <12 years of age.

**Table 4: Pharmacokinetic Parameters
(Arithmetic Mean \pm SD)**

PK Parameters	Paediatric		Adult and Adolescent	
	<6 years N=14	6 to <12 years N=17	12 to <18 years N = 8	\geq 18 years N = 18
Terminal half-life [h]	11.8 \pm 2.43	12.4 \pm 1.67	13.43 \pm 4.05	14.69 \pm 3.79
MRT [h]	17.0 \pm 3.51	17.8 \pm 2.40	17.96 \pm 5.49	20.27 \pm 5.23
CL [mL/(kg·h)]	3.53 \pm 1.29	3.11 \pm 0.76	3.87 \pm 3.31 (2.73 \pm 0.93) ^b	2.27 \pm 0.84
Incremental Recovery [(IU/dL)/(IU/kg)]	NA ^a (1.88 \pm 0.49)	NA ^a (1.93 \pm 0.48)	2.12 \pm 0.60	2.66 \pm 0.68
AUC _{0-Inf} [IU·h/dL]	1950 \pm 758	2010 \pm 493	1642 \pm 752	2264 \pm 729
V _{ss} [dL/kg]	0.97 \pm 0.23	1.59 \pm 0.34	0.56 \pm 0.18	0.43 \pm 0.11
C _{max} [IU/dL]	NA ^a (115 \pm 30)	NA ^a (115 \pm 33)	95 \pm 25	122 \pm 29
T _{max} [h]	-	-	0.26 \pm 0.10	0.46 \pm 0.29

Abbreviations: MRT: mean residence time; CL: clearance; CI: confidence interval; AUC: area under the curve; V_{ss}: body weight adjusted volume of distribution at steady-state; C_{max}: maximum observed activity; T_{max}: time to reach the maximum concentration.

^aNA, Not applicable as Incremental Recovery and C_{max} in children were determined by individual PK. Results determined by individual PK are contained in parenthesis

^bEstimated mean and SD calculated not including one subject whose clearance estimate was 11.8 mL/(kg·h). Median including all subjects is 2.78 mL/(kg·h).

10 NONCLINICAL TOXICOLOGY

10.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of ADYNOVATE or studies to determine the effects of ADYNOVATE on genotoxicity or fertility have not been performed.

11 CLINICAL STUDIES

Original Safety and Efficacy Clinical Trial

The safety, efficacy, and PK of ADYNOVATE were evaluated in a multi-centre, open-label, prospective, non-randomized, two-arm clinical trial that compared the efficacy of a twice weekly prophylactic treatment regimen to on-demand treatment and determined haemostatic efficacy in the treatment of bleeding episodes. A total of 137 male PTPs (12 to 65 years of age) with severe haemophilia A received at least one infusion with ADYNOVATE. Twenty-five of the 137 subjects were adolescents (12 to less than 18 years of age).

Subjects received either prophylactic treatment (n = 120) with ADYNOVATE at a dose of 40-50 IU per kg twice weekly or on-demand treatment (n = 17) with ADYNOVATE at a dose of 10-60 IU per kg for a 6-month period. The mean (SD) dose per prophylaxis infusion was 44.4 (3.9) IU per kg with a median dosing interval of 3.6 days. There were 91 out of 98 (93%) subjects previously treated prophylactically prior to enrolment, who experienced a reduction in dosing frequency during routine prophylaxis in the trial, with a median reduction of 33.7% (approximately one more day between doses). One hundred eighteen of 120 (98%) prophylaxis subjects remained on the starting recommended regimen without dose adjustment, and 2 subjects increased their dose to 60 IU/kg during prophylaxis due to bleeding in target joints.

On-demand Treatment and Control of Bleeding Episodes

A total of 518 bleeding episodes were treated with ADYNOVATE in the per-protocol population, i.e. dosed according to the protocol specific dosing requirements. Of these, 361 bleeding episodes (n=17 subjects) occurred in the on-demand arm and 157 (n=61 subjects) occurred in the prophylaxis arm. The median dose per infusion to treat all bleeding episodes in the per-protocol population was 29 (Q1: 20.0; Q3: 39.2) IU per kg. The median dose per infusion to treat a minor, moderate, or severe/major bleeding episode in the per-protocol population was 25.5 (Q1: 16.9; Q3: 37.6) IU/kg, 30.9 (Q1: 23.0; Q3: 43.1) IU/kg, or 36.4 (Q1: 29.0; Q3: 44.5) IU/kg, respectively.

A total of 591 bleeding episodes were treated with ADYNOVATE in the treated population, which was identical to the safety analysis set of subjects assigned to routine prophylaxis or on-demand treatment with ADYNOVATE and who received at least one dose of the product. Of these, 361 bleeding episodes (n=17 subjects) occurred in the on-demand arm and 230 bleeding episodes (n=75 subjects) occurred in the routine prophylaxis arm. Efficacy in control of bleeding episodes is summarized in Table 5.

Table 5: Summary of Efficacy in Control of Bleeding (Treated Population)

Bleeding Episode Etiology		All	Joint	Non-joint
Number of bleeds treated		591	455	136
Number of infusions to treat bleeding	1 infusion:	85.4%	85.9%	83.8%
	2 infusions:	10.8%	10.8%	11.0%

episodes	Total (1 or 2 infusions):	96.2%	96.7%	94.8%
Rate of success to treat bleeding episodes*	Excellent or good	95.3%	95.8%	93.4%

* Excellent defined as full relief of pain and objective signs of bleeding cessation; Good defined as definite pain relief and/or improvement in signs of bleeding; Fair defined as probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution; None defined as no improvement or condition worsened.

Routine Prophylaxis

A total of 120 subjects (treated population) received a twice a week regimen in the prophylaxis arm, and an additional 17 subjects were treated episodically in the on-demand arm. In the treated population, the median [mean] annualized bleed rate (ABR) in the on-demand treatment arm was 41.5 [40.8] compared to 1.9 [4.7] while on a twice a week prophylaxis regimen (Table 6). In the per-protocol population, the median [mean] annualized bleed rate (ABR) in the on-demand treatment arm was 41.5 [40.8] compared to 1.9 [3.7] while on a twice a week prophylaxis regimen. Using a negative binomial model to estimate the ABR, there was a significant reduction in the ABR ($p < 0.0001$) for subjects in the prophylaxis arm compared to the on-demand arm.

Table 6: Annualized Bleed Rate by Treatment for ≥ 12 years of age (Treated Population)

Bleeding Episode Etiology	On-Demand Treatment		Routine Prophylaxis Treatment	
	Median	Mean (SD)	Median	Mean (SD)
Overall	41.5	40.8 (16.3)	1.9	4.7 (8.6)
Joint	38.1	34.7 (15.1)	0.0	2.9 (8.0)
Non-Joint	3.7	6.1 (6.7)	0.0	1.8 (3.0)
Spontaneous	21.6	26.0 (19.6)	0.0	2.9 (7.1)
Traumatic	9.3	14.9 (15.3)	0.0	1.8 (3.1)

In the treated population, the median [mean] ABR for the 23 adolescent subjects age 12 to <18 years of age on routine prophylaxis was 2.1 [5.2] compared to a median [mean] ABR of 1.9 [4.6] for the 97 subjects 18 years and older. Reduction in ABR between the treatment arms was observed regardless of baseline subgroups examined, including age, presence or absence of target joints, and pre-trial treatment regimen. The majority of the bleeding episodes during prophylaxis (95%) were of minor/moderate severity. Forty-five out of 120 subjects (38%) experienced no bleeding episodes and 68 out of 120 subjects (57%) experienced no joint bleeding episodes in the prophylaxis arm. Of those subjects who were compliant to regimen (per-protocol population), 40 out of 101 subjects (40%) experienced no bleeding episodes. All subjects in the on-demand arm experienced a bleeding episode, including a joint bleeding episode.

Routine Prophylaxis Clinical Trial in Paediatric Subjects (<12 years of age)

The safety and efficacy of ADYNOVATE was evaluated in a total of 73 paediatric PTPs

with severe haemophilia A, of which 66 subjects were dosed (32 subjects aged <6 years and 34 subjects aged 6 to <12 years) in a separate paediatric clinical trial. The prophylactic regimen was 40 to 60 IU/kg of ADYNOVATE twice a week, with a mean (SD) dose of 51.1 IU/kg (5.5). The median [mean] overall ABR was 2.0 [3.61] for the 66 subjects in the treated population and the median [mean] ABRs for spontaneous and joint bleeding episodes were both 0 [1.18 and 1.12, respectively]. Of the 66 subjects treated prophylactically, 25 (38%) experienced no bleeding episodes, 44 (67%) experienced no spontaneous bleeding episodes, and 48 (73%) experienced no joint bleeding episodes.

Of the 70 bleeding episodes observed during the paediatric trial, 82.9% were controlled with 1 infusion and 91.4% were controlled with 1 or 2 infusions. Control of bleeding was rated excellent or good in 63 out of 70 (90%) bleeding episodes. The definitions of excellent or good in the paediatric clinical trial were unchanged as compared to the previously conducted prophylaxis clinical trial in adolescent and adult subjects.

Perioperative Management Clinical Trial

Eleven major surgical procedures (3 knee replacements, 2 arthroscopic synovectomies, 1 cyst extirpation, 1 port placement, 1 gastric band placement, and 3 multiple tooth extractions including 1 radicular cyst removal) and 4 additional minor surgeries (1 synoviorthesis, 1 radiosynovectomy, 1 tooth extraction, 1 dermatological surgery) were performed in 15 subjects. The preoperative loading dose ranged from 36 IU/kg to 99 IU/kg (median: 65 IU/kg) and the total postoperative dose ranged from 177 IU/kg to 769 IU/kg (median: 305 IU/kg). The median total dose for major surgeries was 362 IU/kg (range: 237-863 IU/kg) and the median total dose for minor surgeries was 97 IU/kg (range: 73-119 IU/kg).

Perioperative haemostatic efficacy was rated as excellent (blood loss less than or equal to that expected for the same type of procedure performed in a non-haemophilic patient, and required blood components for transfusions less than or similar to that expected in non-haemophilic population) for all 15 (11 major, 4 minor) procedures. The median (QR) observed intraoperative blood loss (n=10) was 10.0 (Q1: 5.0, Q3: 50.0) mL compared to the predicted average blood loss (n=11) of 50.0 (Q1: 6.0, Q3: 150.0) mL for major surgeries.

12 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- Type I glass vial, closed with a chlorobutyl rubber stopper, containing 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU or 3000 IU of powder.
- Type I glass vial, closed with a chlorobutyl rubber stopper, containing 2 mL or 5 mL of sterilised water for injections.
- Administration set containing 1 infusion set, 1 disposable syringe 10 mL, 2 sterile alcohol swabs and 2 adhesive bandages.

The medicinal product is provided in one of the following configurations:

- ADYNOVATE with BAXJECT II Hi-Flow device: Each pack contains a powder vial, a diluent vial and a device for reconstitution (BAXJECT II Hi-Flow).
- ADYNOVATE in BAXJECT III system: Each pack contains a ready to use BAXJECT III system in a sealed blister, with the powder vial and the diluent vial preassembled for reconstitution.

Storage and Handling

- Store ADYNOVATE in powder form at 2°C to 8°C.
- Do not freeze.
- ADYNOVATE may be stored at room temperature not to exceed 30°C for a period of up to 3 months not to exceed the expiration date. If stored at room temperature, write the date on the carton when ADYNOVATE is removed from refrigeration.
- After storage at room temperature, do not return the product to the refrigerator.
- Do not use beyond expiration date printed on the carton or housing.
- Store ADYNOVATE in the original box and protect from extreme exposure to light.

13 PATIENT COUNSELING INFORMATION

Advise patients to:

- Call their healthcare provider or go to the emergency department right away if a hypersensitivity reaction occurs. Early signs of hypersensitivity reactions may include rash, hives, itching, facial swelling, tightness of the chest, and wheezing. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment.
- Contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to factor VIII therapy because this may be a sign of inhibitor development.
- Advise patients to consult with their physicians or healthcare provider prior to travel. While traveling, advise patients to bring an adequate supply of ADYNOVATE based on their current regimen of treatment.

Baxalta US Inc.

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