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ADYNOVATE® (RURIOCTOCOG ALFA PEGOL)

Takeda

0756293

ADYNOVATE®
(RURIOCTOCOG ALFA PEGOL)

1 NAME OF THE MEDICINE

ADYNOVATE POWDER AND SOLVENT FOR SOLUTION FOR INJECTION 250IU/2ML
ADYNOVATE POWDER AND SOLVENT FOR SOLUTION FOR INJECTION 500IU/2ML

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ADYNOVATE 250 and 500 International Units (IU).

ADYNOVATE [rurioctocog alfa pegol, Recombinant Coagulation Factor VIII (rch), PEGylated] is supplied in single-use vials containing nominal potencies of 250 and 500IU per vial with a diluent vial containing sterile water for injections for reconstitution to 2 mL.

The 2 mL diluent of water for injections is available for ADYNOVATE 250 and 500 IU.

The amounts of the inactive ingredients are constant in all strengths.

Excipient(s) with known effect

Each vial of ADYNOVATE contains 0.45 mmol (10 mg) sodium, see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for injection with diluent.

ADYNOVATE is formulated as a sterile, non-pyrogenic, white to off-white, lyophilised powder for intravenous injection after reconstitution with water for injections.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ADYNOVATE is a long-acting antihaemophilic factor (recombinant) indicated in haemophilia A (congenital factor VIII deficiency) patients for:

- Control and prevention of bleeding episodes
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Perioperative management (surgical prophylaxis)

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Previously untreated patients

The safety and efficacy of ADYNOVATE in previously untreated patients have not yet been established. No data are available.

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels (by one-stage clotting or chromogenic assays) is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

Dosage

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

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

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

On demand treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. The required dose is determined using the following formula:

Required units (IU) = body weight (kg) x desired factor VIII rise (%) x 0.5

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

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period.

The following Table 1 can be used to guide dosing in bleeding episodes and surgery:

Table 1 Guide for dosing in bleeding episodes and surgery

Degree of haemorrhage/ type of surgical procedure	Factor VIII level required (% or IU/dL)	Frequency of doses (hours)/ duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 – 40	Repeat injections every 12 to 24 hours for at least 1 day, until the bleeding episode, as indicated by pain, is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 – 60	Repeat injections every 12 to 24 hours for 3 – 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60 – 100	Repeat injections every 8 to 24 hours until threat is resolved.
Surgery		
Minor Including tooth extraction	30 – 60	Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.
Major	80 – 100 (pre- and postoperative)	Repeat injections every 8 to 24 hours (6 to 24 hours for patients under the age of 6) until adequate wound healing then continue therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).

Prophylaxis

For long term prophylaxis, the recommended dose is 40 to 50 IU per kg bodyweight of ADYNOVATE twice weekly in 3 to 4 day intervals. Dose and/or frequency should be adjusted to provide the necessary coverage to prevent bleeding. In some cases, doses up to 60 IU per kg can be used.

Paediatric population

On demand treatment dosing in paediatric patients (<12 years of age) does not differ from adult patients. Higher doses or more frequent dosing may be required in some children.

For prophylactic therapy in patients under the age of 12, the recommended dose is 40 to 60 IU per kg bodyweight of ADYNOVATE twice weekly in 3 to 4 day intervals. In some cases, doses up to 80 IU per kg can be used.

Method of administration

ADYNOVATE should be administered via the intravenous route.

ADYNOVATE should be administered at room temperature not more than 3 hours after reconstitution.

Reconstituted products should be visually inspected for particulate matter and discolouration prior to administration. The solution should be clear to colourless. Do not administer if particulate matter or discolouration or cloudiness is found.

ADYNOVATE does not contain antimicrobial preservative. It is for single use in one patient only. Discard any residue.

The rate of administration should be determined to ensure the comfort of the patient up to a maximum of 10 mL/min.

After reconstitution, the solution is clear, colourless, free from foreign particles and has a pH of 6.7 to 7.3. The osmolality is ≥ 380 mOsmol/kg.

Preparation and reconstitution

Use aseptic technique.

Using the BAXJECT III system

Do not use if the lid is not completely sealed on the blister.

1. If the product is still stored in a refrigerator, take the sealed blister (contains powder and diluent vials preassembled with the system for reconstitution) from the refrigerator and let it reach room temperature.
2. Wash your hands thoroughly using soap and warm water.
3. Open the ADYNOVATE package by peeling away the lid. Remove the BAXJECT III system from the blister.
4. Place ADYNOVATE on a flat surface with the diluent vial on top (Figure 1). 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 2). Do not tilt the system until the transfer is complete.
6. Verify that the diluent transfer is complete. Swirl gently until all material is dissolved (Figure 3). 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.

Figure 1

Figure 2

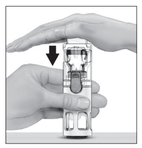

Figure 3

Administration

- Remove the blue cap from the BAXJECT III device. Connect the syringe to the BAXJECT III device. Use of a Luer-lock syringe is recommended. Do not inject air.
- Turn the system upside down (ADYNOVATE vial now on top). Draw the factor concentrate into the syringe by pulling the plunger back slowly.
- Disconnect the syringe; attach a suitable needle and inject 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 over a period of less than or equal to 5 minutes (maximum infusion rate 10 mL per min).

4.3 CONTRAINDICATIONS

Known life-threatening hypersensitivity reaction, including anaphylaxis, to the parent molecule ADVATE (octocog alfa), mouse or hamster protein, or other constituents of ADYNOVATE.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

Hypersensitivity reactions can occur following administration of ADYNOVATE. Allergic-type hypersensitivity reactions including anaphylaxis have been reported with factor VIII concentrates. Immediately discontinue administration and initiate treatment as clinically appropriate if hypersensitivity reactions occur.

Inhibitor formation

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

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

Cardiovascular events

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

Catheter-related complications in treatment

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

Excipient related considerations

After reconstitution this medicinal product contains 0.45 mmol sodium (10 mg) per vial. To be taken into consideration by patients on a controlled sodium diet.

It is strongly recommended that every time ADYNOVATE is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Use in the elderly

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

Paediatric use

The listed precautions apply both to adults and children.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of ADYNOVATE on fertility have not been established.

Use in pregnancy (Category B2)

The safety of ADYNOVATE for use in pregnant women has not been established. Animal reproduction studies with recombinant factor VIII, including ADYNOVATE, have not been conducted. Healthcare professionals should balance the potential risks and only prescribe ADYNOVATE if clearly needed.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

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

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions

The safety of ADYNOVATE has been evaluated in 6 multi-centre, prospective, open label clinical trials and 1 ongoing study in 365 previously treated and untreated patients with severe haemophilia A (factor VIII < 1% of normal), who received at least one dose of ADYNOVATE. Table 2 lists the adverse reactions reported during clinical studies.

Table 2 Adverse reaction reported for ADYNOVATE

MedDRA System Organ Class	Preferred MedDRA Term (Version 19.0)	Number and Rate by Subject[a] (N=365) n (%)	Frequency Category[c]	Number and Rate by Infusion[b] (N=74,487) n (%)	Frequency Category[c]
BLOOD AND LYMPHATIC DISORDERS	Factor VIII inhibition	1 (0.274)	Uncommon	1 (0.001)	Very Rare
GASTROINTESTINAL DISORDERS	Diarrhea	25 (6.849)	Common	31 (0.042)	Rare
	Nausea	8 (2.192)	Common	11 (0.015)	Rare
EYE DISORDERS	Ocular Hyperaemia	3 (0.822)	Uncommon	3 (0.004)	Very Rare
IMMUNE SYSTEM DISORDERS	Hypersensitivity[d]	2 (0.548)	Uncommon	2 (0.003)	Very Rare
NERVOUS SYSTEM DISORDERS	Headache	41 (11.233)	Very Common	67 (0.090)	Rare
	Dizziness	7 (1.918)	Common	7 (0.009)	Very Rare
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash	10 (2.740)	Common	11 (0.015)	Rare
	Urticaria	7 (1.918)	Common	7 (0.009)	Very Rare
	Drug Eruption	1 (0.274)	Uncommon	1 (0.001)	Very Rare

MedDRA System Organ Class	Preferred MedDRA Term (Version 19.0)	Number and Rate by Subject[a] (N=365) n (%)	Frequency Category[c]	Number and Rate by Infusion[b] (N=74,487) n (%)	Frequency Category[c]
VASCULAR DISORDERS	Flushing	1 (0.274)	Uncommon	1 (0.001)	Very Rare
INVESTIGATIONS	Eosinophil Count Increased	2 (0.548)	Uncommon	4 (0.005)	Very Rare
INVESTIGATIONS INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Infusion Related Reaction	2 (0.548)	Uncommon	2 (0.003)	Very Rare

[a] Rate by subject = total number of subjects experiencing the AE (related and unrelated) divided by total number of subjects (N) and multiplied by 100.
[b] Rate by infusions = total number of adverse events (related and unrelated) divided by total number of infusions (N) and multiplied by 100.
Frequencies presented were calculated using all adverse events, related and unrelated.
[c] Frequency has been evaluated using the following criteria: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000).
[d] The event of Hypersensitivity was a mild transient non-serious rash, occuring in one 2-year-old patient who had developed a previous rash while on ADYNOVATE.

Description of selected adverse reactions

Immunogenicity

Inhibitor Development

Formation of neutralising antibodies (inhibitors) to factor VIII can occur following administration of factor VIII products.

Clinical trial subjects were monitored for neutralising (inhibitory) antibodies to factor VIII. None of the subjects who participated in one or more of 6 completed clinical trials in previously treated patients (PTPs) developed persistent neutralising (inhibitory) antibodies against factor VIII of ≥ 0.6 BU/mL (based on the Nijmegen modification of the Bethesda assay). One patient developed a transient FVIII inhibitor at the lowest limit of positivity (0.6 BU) during personalised prophylaxis targeting a FVIII level of 8-12%. From an ongoing study in previously untreated patients < 6 years with severe haemophilia A, preliminary reports on 9 cases of factor VIII inhibitor development associated with treatment with ADYNOVATE were received.

Binding antibodies to factor VIII, PEG-factor VII, PEG and CHO protein

Immunogenicity was also 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. No subject developed persistent treatment-emergent binding antibodies against factor VIII, PEG-factor VIII or PEG. There was no causal relationship between observed adverse events and binding antibodies except in one subject, a PUP where a causal relationship can neither be confirmed nor 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 FVIII 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 rurioctocog alfa pegol with the incidence of antibodies to other products may be misleading.

Hypersensitivity

Hypersensitivity reactions are possible with ADYNOVATE (Table 2). Allergic-type hypersensitivity reactions, including anaphylaxis, are rare complications of treatment with recombinant factor VIII, including the parent molecule, ADVATE.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Class Reactions

Adverse reactions include: Anaphylactic reaction, Hypersensitivity, Factor VIII inhibition.

Post-marketing Adverse Reactions

No additional adverse reactions, other than those from clinical trials, have been reported from post-marketing sources.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 OVERDOSE

There has been no reported clinical adverse experience that could be associated with overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ADYNOVATE is a full-length recombinant human coagulation factor VIII with an extended half-life. The therapeutic activity of ADYNOVATE is derived from its parent molecule, octocog alfa (ADVATE), which is produced by recombinant DNA technology from a Chinese hamster ovary cell line. The octocog alfa molecule is then covalently conjugated with the PEG reagent, which targets lysine residues. The PEG moiety is conjugated to the octocog alfa molecule to increase the plasma half-life through the reduction of the LRP-1 receptor-mediated clearance of the factor VIII molecule.

Pharmacodynamic effects

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a X-chromosomal linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Clinical trials

The safety, efficacy, and PK of ADYNOVATE were evaluated in a multicentre, open-label, prospective, non-randomised, 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 study, with a median reduction of 33.7% (approximately one more day between doses). One hundred eighteen (118) 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 total dose to treat all bleeding episodes in the per-protocol population was 30.9 (Q1: 21.6; Q3: 45.3) IU per kg. 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 summarised in Table 3.

Table 3 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 episodes	1 infusions:	85.4%	85.9%	83.8%
	2 infusions:	10.8%	10.8%	11.0%
	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] annualised 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 4). In the per-protocol population, the median [mean] annualised 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 4 Annualised 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-study 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 Study 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 study. The prophylactic regimen was 40 to 60 IU/kg of ADYNOVATE twice a week. 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 study, 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 study were unchanged as compared to the previously conducted prophylaxis study in adolescent and adult subjects.

Long-Term Prophylaxis Treatment in Paediatric and Adult Subjects

The long-term safety and efficacy of ADYNOVATE in prophylaxis and treatment of bleeding episodes was evaluated in 216 paediatric and adult PTPs with severe haemophilia A who had either previously participated in other ADYNOVATE studies or were naive to ADYNOVATE. In the treated population, subjects received a fixed-dose twice-weekly regimen of 40 to 50 IU/kg if aged ≥ 12 years or of 40 to 60 IU/kg if aged < 12 years. The dose was adjusted up to 80 IU/kg twice weekly if required to maintain factor VIII trough levels of > 1%. Subjects that opted for a personalised (pharmacokinetically-tailored) prophylactic regimen received doses up to 80 IU/kg per infusion that targeted factor VIII trough levels of ≥ 3% at least twice weekly. ABR per prophylactic regimen, bleeding site and etiology are presented in Table 5.

Table 5 Annualised Bleed Rate by Prophylactic Regimen (ITT Population)

Bleeding Site Etiology	Twice-Weekly (N=186)	Every 5 Days (N=56)	Every 7 Days (N=15)	PK-tailored[a] (N=25)
	Mean [Point Estimate 95% Confidence Interval]			
Overall	2.2 [1.85 – 2.69]	2.1 [1.54 – 2.86]	2.7 [1.44 – 5.20]	2.6 [1.70 – 4.08]
Joint	1.2 [0.96 – 1.58]	1.1 [0.81 – 1.55]	2.0 [0.90 – 4.62]	1.4 [0.91 – 2.17]
Spontaneous	1.2 [0.92 – 1.56]	1.3 [0.87 – 2.01]	1.8 [0.78 – 4.06]	1.0 [0.54 – 1.71]

Point estimates and 95% confidence intervals obtained from a generalised linear model fitting a negative binomial distribution with logarithmic link function.
Subjects receiving doses in multiple regimens are included in summaries for multiple regimens.
Includes all subjects in the study (adults and paediatric subjects < 18 years. For Twice Weekly and PK-tailored dosing no subjects < 12 years were included in Every 5 & 7 Days dosing.
ITT = intent to treat; N = Number of subjects included in the analysis
[a] Targeting factor VIII activity trough levels of ≥ 3% of normal

Long-term haemostatic efficacy was evaluated in 910 bleeding episodes treated with ADYNOVATE and was rated excellent or good in 88.5% of bleeding episodes. Across age categories and for both

the fixed-dose and the PK-tailored dose regimen, > 85% of bleed treatments were rated excellent or good. The majority of bleeding episodes were treated with one (74.0%) or two (15.4%) infusions.

Personalised Prophylaxis PROPEL Clinical Trial in Adolescents and Adult Subjects

The safety and efficacy of ADYNOVATE was evaluated in a prospective, randomised, open-label multicentre study in 121 (115 randomised) adolescents (12-18 years old) and adult PTPs with severe haemophilia A for a 12 months treatment period. The study compared 2 PK-guided prophylactic dosing regimens of ADYNOVATE that targeted factor VIII trough levels of 1-3% dosed twice weekly (N=57) or 8-12% dosed every other day (N=58), by assessing the proportions of subjects achieving a total ABR of 0 in the second 6-month study period as the primary efficacy endpoint.

The average prophylactic doses administered in the 1-3% and 8-12 % trough arms were 3,866.1 IU/kg per year [mean (SD) infusions/week = 2.3 (0.58)] and 7,532.8 IU/kg per year [(mean (SD) infusions/week = 3.6 (1.18)], respectively. After dose adjustment during the first 6-month period of prophylaxis, median trough levels in the second 6-month period (based on the one-stage clotting assay and calculated to the end of the planned infusion interval) ranged from 2.10 IU/dL to 3.00 IU/dL in the 1-3% trough level arm and from 10.70 IU/dL to 11.70 IU/dL in the 8-12 % trough level arm, demonstrating that dosing in the 2 prophylaxis regimens was generally adequate to achieve and maintain the desired factor VIII trough levels.

The primary endpoint of the study, proportion of subjects who had a total ABR of 0 during the second 6 month period, was not reached in the ITT patient population (p=0.0545) but was reached in the per-protocol population (nominal p value of 0.0154). The proportions of randomised subjects with total ABRs of 0 during the second 6-month study period and the secondary efficacy outcome measures, spontaneous ABRs and spontaneous annualised joint bleeding rates (AJBRs) of 0 during the second 6-month study period, are presented in Table 6.

Table 6 Annualised Bleed Rate (ABR) of 0, Second 6-month Study Period

	Proportion of Subjects Without Bleedings in 6 Months [Point Estimate 95% Confidence Interval]	
	ITT Population	
	1-3% Trough Level (N=57)	8-12% Trough Level (N=58)
Total ABR of 0	0.421 [0.292; 0.549]	0.621 [0.491; 0.750]
Spontaneous ABR of 0	0.596 [0.469; 0.724]	0.760 [0.645; 0.875]
Spontaneous AJBR of 0	0.649 [0.525; 0.773]	0.850 [0.753; 0.947]

ABR = Annualised bleeding rate, AJBR = Annualised joint bleeding rate.
Annualised bleeding rate determined by dividing the number of bleeds by observation period in years.

	Proportion of Subjects Without Bleedings in 6 Months [Point Estimate 95% Confidence Interval]	
	Per Protocol Population	
	1-3% Trough Level (N=52)	8-12% Trough Level (N=43)
Total ABR of 0	0.404 [0.270; 0.549]	0.674 [0.515; 0.809]
Spontaneous ABR of 0	0.596 [0.451; 0.730]	0.814 [0.666; 0.916]
Spontaneous AJBR of 0	0.654 [0.509; 0.780]	0.907 [0.779; 0.974]

ABR = Annualised bleeding rate, AJBR = Annualised joint bleeding rate.
Per-protocol population = all subjects who completed the second 6 months of prophylactic treatment and had no major deviations from the protocol affecting the study results.
Annualised bleeding rate determined by dividing the number of bleeds by observation period in years.

The secondary efficacy outcome measures (total ABRs, spontaneous ABRs and spontaneous AJBRs during the second 6-month study period), are presented in Table 7.

Table 7 Annualised Bleed Rate (ABR), Second 6-month Study Period

	ITT Population			
	1-3% Trough Level (N=57)		8-12% Trough Level (N=53)	
	Median	Mean (SD)	Median	Mean (SD)
Total ABR	2.0	3.6 (7.5)	0.0	1.6 (3.4)
Spontaneous ABR	0.0	2.5 (6.6)	0.0	0.7 (1.7)
Spontaneous AJBR	0.0	2.0 (6.4)	0.0	0.5 (1.7)

ABR = Annualised bleeding rate, AJBR = Annualised joint bleeding rate.
Annualised bleeding rate determined by dividing the number of bleeds by observation period in years.

	Per Protocol Population			
	1-3% Trough Level (N=52)		8-12% Trough Level (N=43)	
	Median	Mean (SD)	Median	Mean (SD)
Total ABR	2.0	2.8 (3.0)	0.0	1.2 (2.4)
Spontaneous ABR	0.0	1.7 (2.5)	0.0	0.6 (1.5)
Spontaneous AJBR	0.0	1.2 (2.0)	0.0	0.4 (1.4)

ABR = Annualised bleeding rate, AJBR = Annualised joint bleeding rate.
Per-protocol population = all subjects who completed the second 6 months of prophylactic treatment and had no major deviations from the protocol affecting the study results.
Annualised bleeding rate determined by dividing the number of bleeds by observation period in years.

A total of 242 bleeding episodes in 66 subjects were treated with ADYNOVATE; 155 bleeds in 40 subjects in the 1-3% trough level arm and 87 bleeds in 26 subjects in the 8-12% trough level arm. The majority of bleeds (86.0%, 208/242) were treated with 1 or 2 infusions; and bleed treatment at resolution of the bleeding episode was rated excellent or good in 84.7% (205/242) of bleeds.

Perioperative Management Study

A total of 21 major surgical procedures and 5 additional minor surgeries were performed and assessed in 21 unique subjects in the surgery study. For major surgeries, the preoperative loading dose ranged from 36 IU/kg to 109 IU/kg (median: 63 IU/kg); and postoperative total dose ranged from 186 IU/kg to 1320 IU/kg (median: 490 IU/kg). The median total dose for major surgeries was 553 IU/kg (range: 248-1394 IU/kg) and the median total dose of minor surgeries was 106 IU/kg (range: 76-132 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 26 (21 major, 5 minor) procedures. The median (IQR) observed intraoperative blood loss (n=14) was 10.0 (20.0) mL compared to the predicted average blood loss (n=14) of 150.0 (140.0) mL for major orthopaedic surgeries.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of ADYNOVATE was evaluated in a crossover study with ADVATE in 26 subjects (18 adults and 8 adolescents) and in 22 subjects (16 adults and 6 adolescents) after 6 months of treatment with ADYNOVATE. A single dose of 45 ± 5 IU/kg was utilised for both products. In the paediatric study, a single dose of 60 ± 5 IU/kg was utilised for both ADVATE and

ADYNOVATE to evaluate PK in 31 paediatrics subjects (< 6 years and 6 to < 12 years of age). Plasma factor VIII activity was measured by the one-stage clotting assay and chromogenic assay as shown in Table 8 to Table 11.

ADYNOVATE has an extended half-life of 1.4 to 1.5-fold compared to recombinant full-length human coagulation factor VIII (ADVATE) in the adolescent and adult population, as determined based on one-stage clotting and chromogenic assays, respectively. The half-life extension in the paediatric population was 1.3 to 1.5-fold using both the one stage clotting and chromogenic assays. An increase in AUC and a decrease in clearance as compared to the parent molecule, ADVATE, were also observed. Incremental recovery was comparable with both products. The change in PK parameters was similar in both the adult and adolescent populations and between one-stage clotting and chromogenic substrate assays.

Table 8 Pharmacokinetic Parameters in Adults Using the One-stage Clotting Assay (Arithmetic mean ± SD)

PK Parameters	ADVATE N = 18	ADYNOVATE N = 18
Design	Individual PK with Full Sampling[a]	
Terminal half-life [h]	10.83 ± 2.08	14.69 ± 3.79
MRT [h]	13.41 ± 3.00	20.27 ± 5.23
CL [mL/(kg•h)]	3.88 ± 1.24	2.27 ± 0.84
Incremental Recovery [(IU/dL)/(IU/kg)]	2.57 ± 0.43	2.66 ± 0.68
$AUC_{0\text{-}Inf}$ [IU•h/dL]	1286 ± 390	2264 ± 729
Vss [dL/kg]	0.50 ± 0.11	0.43 ± 0.11
C_{max} [IU/dL]	117 ± 20	122 ± 29
T_{max} [h]	0.33 ± 0.19	0.46 ± 0.29

Abbreviations: CI: confidence interval; C_{max}: maximum observed activity; AUC: area under the curve; MRT: mean residence time; CL: clearance; V_{ss}: body weight adjusted volume of distribution at steady-state, T_{max}: time to reach the maximum concentration
[a] Individual PK with 12 post-infusion samples.

Table 9 Pharmacokinetic Parameters in Adults Using the Chromogenic Assay (Arithmetic mean ± SD)

PK Parameters	ADVATE N = 18	ADYNOVATE N = 18
Design	Individual PK with Full Sampling[a]	
Terminal half-life [h]	10.43 ± 3.41	15.01 ± 3.90
MRT [h]	13.00 ± 3.87	19.70 ± 5.05
CL [mL/(kg•h)]	3.95 ± 1.37	1.97 ± 0.70
Incremental Recovery [(IU/dL)/(IU/kg)]	2.74 ± 0.39	3.16 ± 0.68
AUC0-Inf [IU•h/dL]	1281 ± 424	2589 ± 849
Vss [dL/kg]	0.48 ± 0.14	0.37 ± 0.08
Cmax [IU/dL]	125 ± 17	145 ± 29
Tmax [h]	0.26 ± 0.12	0.32 ± 0.16

Abbreviations: CI: confidence interval; C_{max}: maximum observed activity; AUC: area under the curve; MRT: mean residence time; CL: clearance; V_{ss}: body weight adjusted volume of distribution at steady-state, T_{max}: time to reach the maximum concentration
[a] Individual PK with 12 post-infusion samples.

Paediatric Pharmacokinetics

Pharmacokinetic parameters calculated from 39 subjects less than 18 years of age (intent-to-treat analysis) are available for 14 children (1 to less than 5 years), 17 older children (6 to less than 12 years) and 8 adolescent subjects (12 to < 18 years of age), as shown in Table 10. The mean clearance (based on body weight) of ADYNOVATE was higher and the mean half-life was lower in children less than 12 years of age than adults.

A higher dose may be required in children less than 12 years of age.

Table 10 Summary of Pharmacokinetic Parameters of ADYNOVATE for Paediatrics using the One-Stage Clotting Assay

Parameter (mean ± standard deviation)	Paediatric Study		Pivotal Study in adolescents and adults
	< 6 years (n=14)	6 to < 12 years (n=17)	12 to < 18 years (n=8)
Design	Population PK with Sparse Sampling[a]		Individual PK with Full Sampling[b]
Terminal half-life [h]	11.8 ± 2.43	12.4 ± 1.67	13.43 ± 4.05
MRT [h]	17.0 ± 3.50	17.8 ± 2.42	17.96 ± 5.49
CL [mL/(kg•h)]	3.53 ± 1.29	3.11 ± 0.76	3.87 ± 3.31 (2.73 ± 0.93)[d]
Incremental Recovery [(IU/dL)/(IU/kg)]	1.89 ± 0.49	1.95 ± 0.47	2.12 ± 0.60
$AUC_{0\text{-}Inf}$ [IU•h/dL]	1947 ± 757	2012 ± 495	1642 ± 752
V_{ss} [dL/kg]	0.56 ± 0.12	0.54 ± 0.09	0.56 ± 0.18
C_{max} [IU/dL]	115 ± 30	115 ± 33	95 ± 25
T_{max} [h]	-[c]	-[c]	0.26 ± 0.10

Abbreviations: CI: confidence interval; C_{max}: maximum observed activity; AUC: area under the curve; MRT: mean residence time; CL: clearance; V_{ss}: body weight adjusted volume of distribution at steady-state, T_{max}: time to reach the maximum concentration
[a] Population PK model with 3 post-infusion samples based on randomised drawing schedule.
[b] Individual PK with 12 post-infusion samples.
[c] T_{max} could not be calculated for subjects in the paediatric study as only one sample was drawn (15-30 minutes post-infusion) within the first 3 hours of the infusion
[d] Estimated 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).

Table 11 Summary of Pharmacokinetic Parameters of ADYNOVATE for Paediatrics using the Chromogenic Assay

Parameter (mean ± standard deviation)	Paediatric Study		Pivotal Study in adolescents and adults
	< 6 years (n=14)[a]	6 to < 12 years (n=17)[a]	12 to < 18 years (n=8)[b]
Design	Population PK with Sparse Sampling[a]		Individual PK with Full Sampling[b]
Terminal half-life [h]	12.99 ± 8.75	11.93 ± 2.58	13.80 ± 4.01
MRT [h]	18.74 ± 12.60	17.24 ± 3.72	17.73 ± 5.44

Parameter (mean ± standard deviation)	Paediatric Study		Pivotal Study in adolescents and adults
	< 6 years (n=14)[a]	6 to < 12 years (n=17)[a]	12 to < 18 years (n=8)[b]
Design	Population PK with Sparse Sampling[a]		Individual PK with Full Sampling[b]
CL [mL/(kg•h)][d]	3.49 ± 1.21	2.80 ± 0.67	2.58 ± 0.84
Incremental Recovery [(IU/dL)/(IU/kg)]	NA[c] (1.90 ± 0.27)	NA[c] (2.19 ± 0.40)	2.34 ± 0.62
$AUC_{0\text{-}Inf}$ [IU•h/dL]	2190 ± 1593	2259 ± 514	1900 ± 841
V_{ss} [dL/kg]	0.54 ± 0.03	0.46 ± 0.04	0.54 ± 0.22
C_{max} [IU/dL]	NA[c] (117 ± 16)	NA[c] (130 ± 24)	117 ± 28
T_{max} [h]	-[e]	-[e]	0.26 ± 0.14

Abbreviations: CI: confidence interval; C_{max}: maximum observed activity; AUC: area under the curve; MRT: mean residence time; CL: clearance; V_{ss}: body weight adjusted volume of distribution at steady-state, T_{max}: time to reach the maximum concentration
[a] Population PK model with 3 post-infusion samples based on randomised drawing schedule.
[b] Individual PK with 12 post-infusion samples.
[c] NA, Not applicable, as Incremental Recovery and C_{max} in children were determined by individual PK. Results for Incremental Recovery and C_{max} determined by individual PK in parenthesis.
[d] The clearance value of 12.18 ml(kg.h) for subject 122001 in age group 12 to < 18 years was not included in the analysis of clearance.
[e] T_{max} could not be calculated for subjects in the paediatric study as only one sample was drawn (15-30 minutes post-infusion) within the first 3 hours of the infusion

The PK data demonstrates that ADYNOVATE has an extended circulating half-life.

5.3 PRECLINICAL SAFETY DATA

Nonclinical data are limited to 1 month exposure and no studies in juvenile animals were conducted with ADYNOVATE. Thus it was not possible to conclude on the potential risks of PEG accumulation in various tissues/organs relevant for chronic use of ADYNOVATE in the paediatric population.

Genotoxicity

No studies on genotoxicity have been performed with ADYNOVATE.

Carcinogenicity

No studies on carcinogenicity have been performed with ADYNOVATE.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Calcium chloride dihydrate
Glutathione
Histidine
Mannitol
Polysorbate 80
Sodium chloride
Trehalose dihydrate
Trometamol
Water for injections (diluent)

6.2 INCOMPATIBILITIES

Incompatibilities were not assessed as part of the registration of this medicine. ADYNOVATE must not be mixed with other medicinal products.

6.3 SHELF LIFE

Please refer to product carton.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

- 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, record the end date of the 3-month storage at room temperature 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 vial.
- Store vials in their original box and protect them from extreme exposure to light.
- After reconstitution, do not refrigerate the solution. Use the reconstituted solution immediately or within 3 hours after reconstitution. Discard any remaining solution.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pack contains a powder vial and a vial containing 2 mL diluent (both type I glass closed with chlorobutyl rubber stoppers). The product is supplied in the following configuration:

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

ADYNOVATE is comprised of 2,332 amino acids [molecular weight (MW) 280 kDa] covalently conjugated with a polyethylene glycol (PEG) reagent (MW 20 kDa).

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