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Rurioctocog Alfa Pegol (PEGylated Recombinant Human FVIII) ADYNOVATE®

0748755

For the use of registered medical practitioner or hospital or laboratory only.

Rurioctocog Alfa Pegol (PEGylated Recombinant Human FVIII)

ADYNOVATE®

1. NAME OF THE MEDICINAL PRODUCT
Rurioctocog Alfa Pegol (PEGylated Recombinant Human FVIII) - 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU & 2000 IU
Adynovate®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Rurioctocog Alfa Pegol (PEGylated Recombinant Human FVIII) - Adynovate® 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, 750, 1000, 1500 & 2000 international units (IU). Each vial of Adynovate® is labeled with Nominal 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. The full list of active and inactive ingredients of the drug product is shown below in Table 1:

Table 1: Composition of Adynovate® drug product (without reconstitution)

Component	Quality Standard	Function	Component Quantity per Vial					
			Strength (nominal) 250 IU	Strength (nominal) 500 IU	Strength (nominal) 750 IU	Strength (nominal) 1000 IU	Strength (nominal) 1500 IU	Strength (nominal) 2000 IU
Rurioctocog alfa pegol - PEGylated recombinant human FVIII	In-house specification	Active Pharmaceutical Ingredient (API)	250 IU	500 IU	750 IU	1000 IU	1500 IU	2000 IU
Mannitol	USP, EP,JP	Bulking Agent	160 mg	160 mg	160 mg	160 mg	160 mg	160 mg
Trehalose dihydrate	NF, EP, JP	Bulking Agent	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg
Sodium chloride	USP, EP,JP	Tonicity modifier	26.3 mg	26.3 mg	26.3 mg	26.3 mg	26.3 mg	26.3 mg
Histidine	USP, EP,JP	Buffering agent	7.8 mg	7.8 mg	7.8 mg	7.8 mg	7.8 mg	7.8 mg
Tromethamine / Trometamol [Tris(hydroxymethyl)-Aminomethane]	USP, EP,JP	Buffering agent	6.1 mg	6.1 mg	6.1 mg	6.1 mg	6.1 mg	6.1 mg
Calcium chloride dihydrate	USP, EP,JP	Stabilizing agent	1.2 mg	1.2 mg	1.2 mg	1.2 mg	1.2 mg	1.2 mg
Polysorbate 80	NF, EP,JP	Surfactant	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Glutathione	EP, JP	Antioxidant	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg

USP/NF = United States Pharmacopoeia/National Formulary; Ph.Eur. = European Pharmacopoeia; JP = Japanese Pharmacopoeia

A 5 mL (5 ml for 2000 IU) or 2 mL (2 mL for 250, 500, 750, 1000, and 1500 IU strengths only) solvent per vial is required for reconstitution.
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, refer Table 2:

Table 2: Composition of excipients after reconstitution with either 2 ml or 5 ml

Stabilizer and Excipient	2 mL Reconstitution (for 250, 500, 750, 1000, 1500 IU) Target (per mL)	5 mL Reconstitution (for 2000 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 2800 - 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). The therapeutic activity of Adynovate® is derived from its parent drug substance, Advate [Antihemophilic 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.

3. PHARMACEUTICAL FORM
Adynovate® is a sterile, non-pyrogenic, white to off-white lyophilized powder in single-use vials containing nominally (approximately) 250, 500, 750, 1000, 1500 and 2000 IU. The 250-1500 IU strengths comes with 2 ml Sterile Water for Injection (sWFI); the 2000 IU strengths comes with 5 ml of sWFI.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Adynovate® is a human antihemophilic factor indicated in children and adults with Hemophilia 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.

4.2 Dosage and Administration
For intravenous use after reconstitution only.
4.2.1 Dose
- Each vial label of Adynovate® states the nominal factor VIII potency in international units. One international unit corresponds to the activity of factor VIII contained in one milliliter 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 3. Maintain plasma factor VIII activity level at or above the described plasma levels (in IU per dL or % of normal).

Table 3: 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 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 4. Consideration should be given to maintain a factor VIII activity at or above the target range.

Table 4: Dosing for Perioperative Management

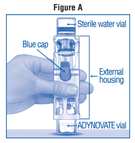
Type of Surgery	Factor VIII Level Required (% of normal or IU/dL)	Dose (IU/kg)	Frequency of Doses (hours)	Duration of Treatment
Minor Including tooth extraction	60-100	30-50	Within one hour before surgery. Repeat after 24 hours if necessary	Single dose or repeat as needed until bleeding is resolved.
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/ kg body weight twice weekly in adults and adolescents (12 years and older). Administer 55 IU per kg body weight two times per week in children (< 12 years) with a maximum of 70 IU/kg. Adjust the dose and dosing intervals based on the patient's clinical response.

4.2.2 Preparation and Reconstitution
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.

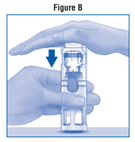
Reconstitution
1. Allow the Adynovate® package to reach room temperature before use.
2. Open the package by peeling away the lid. Remove Adynovate® from the package and verify that the expiration date on the label has not passed and the potency unit number is same as expected. Inspect parenteral drug products for discoloration and particulate matter. The Adynovate® powder should be white to off-white in color and the diluent free from foreign particles. Do not use if the criteria are not met.
3. Place the Adynovate® on a flat surface with the diluent vial on top (Figure A). The diluent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.

Figure A



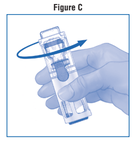
4. With one hand holding the Adynovate® housing, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the Adynovate® vial (Figure B). Do not tilt the system until the transfer is complete.

Figure B



5. Verify that diluent transfer is complete. Swirl gently until the powder is completely dissolved (Figure C). Do not shake. Do not refrigerate after reconstitution.

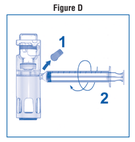
Figure C



4.2.3 Administration
- Visually inspect the reconstituted Adynovate® solution for particulate matter and discoloration prior to administration, whenever solution and container permit. The final Adynovate® solution should be clear and colorless. Do not use if particulate matter or discoloration is observed.
- Administer Adynovate® as soon as possible, but no later than 3 hours after reconstitution.

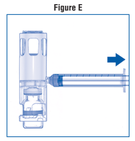
Administration Steps:
1. Remove the blue cap from the housing. Connect the syringe to the system (Figure D). Do not inject air into the Adynovate® .

Figure D



2. Turn the system upside down (Adynovate® vial now on top). Draw the Adynovate® solution into the syringe by pulling the plunger back slowly (Figure E).

Figure E



3. Disconnect the syringe, attach a suitable needle, and inject intravenously as instructed.
4. Administer Adynovate® intravenously over a period of less than or equal to 5 minutes (maximum infusion rate 10 mL per min).

4.3 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).
4.4 Special warnings and precautions for use
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, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.
Hypervolemia/Hemodilution
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.

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.

4.5 Interaction with other Medicinal products and other forms of interaction
No interactions of Antihemophilic Factor (Recombinant), PEGylated (Rurioctocog Alfa Pegol), **Adynovate®** product with other medicinal products have been reported.

4.6 Pregnancy and lactation
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 fetal harm when administered to a pregnant woman or can affect reproduction capacity.

In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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.

4.6.1 Use in Specific Populations (Pediatric and Geriatric Use)
Pediatric Use
Safety and efficacy studies have been performed in 91 previously treated, pediatric 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 pediatric trial. The safety and efficacy of Adynovate® in routine prophylaxis and the treatment of bleeding episodes were comparable between children and adults.
Pharmacokinetic 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.
Geriatric Use
Clinical studies of Adynovate® did not include subjects aged 65 and over.

4.7 Effects on ability to drive and use machines
Adynovate® has no influence on the ability to drive and use machines.
4.8 Undesirable Effects
Adverse Reactions
The most common adverse reactions (≥1% of subjects) reported in the clinical studies were headache, diarrhea, rash, nausea, dizziness and urticaria.

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 365 previously treated patients (PTPs) and 6 previously untreated patients (PUPs) with severe hemophilia A (factor VIII less than 1% of normal), who received at least one dose of Adynovate in 6 completed multi-center, prospective, open label clinical studies and 1 ongoing clinical studies. The total number of infusions within the safety database is 74487. Table 5 lists the adverse reactions reported during clinical studies.

Table 5: Adverse Reactions Reported for Adynovate®

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects n (%) (N=365)
Gastrointestinal Disorders	Diarrhea	25 (6.8%)
	Nausea	8 (2.2%)
Eye Disorders	Ocular Hyperaemia	3 (0.8%)
Immune System Disorder	Hypersensitivity[a]	2 (0.5%)
Nervous System Disorders	Headache	41 (11.2%)
	Dizziness	7 (1.9%)
Skin and Subcutaneous Tissue Disorders	Rash	10 (2.7%)
	Urticaria	7 (1.9%)
	Drug Eruption	1 (0.3%)
Vascular Disorders	Flushing	1 (0.27%)
Investigations	Eosinophil Count Increased	2 (0.5%)
Injury, Poisoning and Procedural Complications	Infusion Related Reaction	2 (0.5%)

[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 216 subjects. Administration of Adynovate® continued and both cases resolved.
Immunogenicity
Clinical trial subjects were monitored for neutralizing (inhibitory) antibodies to FVIII. Of the 6 completed clinical trials in previously treated patients (PTPs), in the randomized controlled trial comparing different dosing regimens of Adynovate, one previously treated patient developed a transient low titer FVIII inhibitor at 0.6 BU while receiving more frequent dosing with Adynovate. In a continuation study with Adynovate, one patient developed a transient low titer (0.6BU) FVIII inhibitor. Repeat testing did not confirm the presence of inhibitor. Both of these subjects continued treatment without change in the dose of Adynovate.

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. Persistent treatment-emergent binding antibodies against FVIII, PEG-FVIII or PEG were not detected. Out of 365 subjects, thirty six subjects in total showed pre-existing antibodies to factor VIII (n=5), PEG-factor VIII (n=31) and/or PEG (n=6) prior to the first exposure to Adynovate. Twenty four subjects who tested negative at screening developed transient antibodies against factor VIII (n= 10), PEG-FVIII (n= 16) and/or PEG (n=3) at one or two consecutive study visits. Antibodies were transient and not detectable at subsequent visits. Two subjects showed positive results for binding antibodies at study completion or at the time of data cutoff. 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 cutoff 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.

From an ongoing study in previously untreated patients < 6 years with severe hemophilia A, 9 cases of FVIII inhibitor development associated with treatment with Adynovate were reported.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Manufacturer/Importer and via the national reporting system. The physician should discuss the risks and benefits of this product with the patient.
4.9 Overdose
No symptoms of overdose with Adynovate® have been reported.

5. PHARMACOLOGICAL PROPERTIES
Mechanism of Action
Adynovate® , a PEGylated form of recombinant antihemophilic factor (Advate), temporarily replaces the missing coagulation factor VIII needed for effective hemostasis in congenital hemophilia 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).
5.1 Pharmacodynamic Properties
Hemophilia 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 hemophilia A patients.

5.2 Pharmacokinetic Properties
The pharmacokinetics (PK) of Adynovate® were evaluated in a multi-center, prospective, open label clinical trial and compared with Adate 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 6, 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.
Pediatric 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 6. 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 6: Pharmacokinetic Parameters (Arithmetic Mean ± SD)

PK Parameters	Pediatric Population PK with Sparse Sampling[a]		Adult and Adolescent Individual PK with Full Sampling[b]	
	<6 years N=14	6 to <12 years N=17	12 to <18 years N = 8	≥18 years N = 18
Terminal half-life [h]	11.8 ± 2.43	12.4 ± 1.67	13.43 ± 4.05	14.69 ± 3.79
MRT [h]	17.0 ± 3.50	17.8 ± 2.42	17.96 ± 5.49	20.27 ± 5.23
CL [mL/(kg·h)]	3.53 ± 1.29	3.11 ± 0.76	3.87 ± 3.31 (2.73 ± 0.93)[c]	2.27 ± 0.84

Rurioctocog Alfa Pegol (PEGylated Recombinant Human FVIII)

ADYNOVATE®

Patient Information

Rurioctocog Alfa Pegol (PEGylated Recombinant Human FVIII) - Adynovate®

This leaflet summarizes important information about Adynovate®. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about Adynovate®. If you have any questions after reading this, ask your healthcare provider.

What is the most important information I need to know about Adynovate®?

Do not attempt to do an infusion to yourself unless you have been taught how by your healthcare provider or hemophilia center.

You must carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing Adynovate® so that your treatment will work best for you.

What is Adynovate®?

Adynovate® is an injectable medicine that is used to help treat and control bleeding in children and adults with hemophilia A (congenital Factor VIII deficiency). Your healthcare provider may give you Adynovate® when you have surgery.

Adynovate® can reduce the number of bleeding episodes when used regularly (prophylaxis).

Adynovate® is not used to treat von Willebrand disease.

Who should not use Adynovate®?

You should not use Adynovate® if you:

- Are allergic to mice or hamster protein
- Are allergic to any ingredients in Adynovate® or ADVATE

Tell your healthcare provider if you are pregnant or breastfeeding because Adynovate® may not be right for you.

How should I use Adynovate®?

Adynovate® is given directly into the bloodstream.

You may infuse Adynovate® at a hemophilia treatment center, at your healthcare provider's office or in your home. You should be trained on how to do infusions by your healthcare provider or hemophilia treatment center. Many people with hemophilia A learn to infuse their Adynovate® by themselves or with the help of a family member.

Your healthcare provider will tell you how much Adynovate® to use based on your individual weight, level of physical activity, the severity of your hemophilia A, and where you are bleeding.

Reconstituted product (after mixing dry product with wet diluent) must be used within 3 hours and cannot be stored or refrigerated. Discard any Adynovate® left in the vial at the end of your infusion as directed by your healthcare professional.

You may have to have blood tests done after getting Adynovate® to be sure that your blood level of factor VIII is high enough to clot your blood.

Call your healthcare provider right away if your bleeding does not stop after taking Adynovate®.

What should I tell my healthcare provider before I use Adynovate®?

You should tell your healthcare provider if you:

- Have or have had any medical problems.
- Take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
- Have any allergies, including allergies to mice or hamsters.
- Are breastfeeding. It is not known if Adynovate® passes into your milk and if it can harm your baby.
- Are pregnant or planning to become pregnant. It is not known if Adynovate® may harm your unborn baby.
- Have been told that you have inhibitors to factor VIII (because Adynovate® may not work for you).

What are the possible side effects of Adynovate®?

You can have an allergic reaction to Adynovate®.

Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, lightheadedness, dizziness, nausea or fainting.

The common side effects of Adynovate® are headache, diarrhea, rash, nausea, dizziness and hives

These are not all the possible side effects with Adynovate®. You can ask your healthcare provider for information that is written for healthcare professionals.

What are the Adynovate® dosage strengths?

Adynovate® with 2 mL or 5 mL Sterile Water for Injection in a BAXJECT III system comes in Six different dosage strengths: 250 International Units (IU), 500 IU, 750 IU, 1000 IU, 1500 IU, and 2000 IU. The actual strength will be imprinted on the label and on the box. The six different strengths are color coded, as follows:

Light Blue	Dosage strength of approximately 250 International Units per vial (with 2 mL sWFI)
Pink	Dosage strength of approximately 500 International Units per vial (with 2 mL sWFI)
Red	Dosage strength of approximately 750 International Units per vial (with 2 mL sWFI)
Light Green	Dosage strength of approximately 1000 International Units per vial (with 2 mL sWFI)
Purple	Dosage strength of approximately 1500 International Units per vial (with 2 mL sWFI)
Orange	Dosage strength of approximately 2000 International Units per vial (with 5 mL sterile Water For Injection)

Always check the expiration date printed on the box. Do not use the product after the expiration date printed on the box.

How do I store Adynovate®?

- Do not freeze.
- Store at refrigerated temperature 2°C to 8°C (36°F to 46°F).
- May store at room temperature not to exceed 30°C (86°F) for up to 3 months.
  - o Write the date on the carton when Adynovate® is removed from refrigeration.
  - o After storage at room temperature, do not return product back to the refrigerator.
- Do not use beyond the expiration date printed on the carton or vial.
- Store Adynovate® in the original box and protect from extreme exposure to light.

What else should I know about Adynovate® and Hemophilia A?

Your body may form inhibitors to Factor VIII. An inhibitor is part of the body's normal defense system. If you form inhibitors, it may stop Adynovate® from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to Factor VIII.

Medicines are sometimes prescribed for purposes other than those listed here. Do not use Adynovate® for a condition for which it is not prescribed. Do not share Adynovate® with other people, even if they have the same symptoms that you have.

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PK Parameters	Pediatric Population PK with Sparse Sampling[a]		Adult and Adolescent Individual PK with Full Sampling[b]	
	<6 years N=14	6 to <12 years N=17	12 to <18 years N = 8	≥18 years N = 18
Incremental Recovery [(IU/dL)/(IU/kg)]	1.89 ± 0.49	1.95 ± 0.47	2.12 ± 0.60	2.66 ± 0.68
$AUC_{0\text{-}Inf}$ [IU·h/dL]	1947 ± 757	2012 ± 495	1642 ± 752	2264 ± 729
Vss [dL/kg]	0.56 ± 0.12	0.54 ± 0.09	0.56 ± 0.18	0.43 ± 0.11
C_{max} [IU/dL]	115 ± 30	115 ± 33	95 ± 25	122 ± 29
T_{max} [h]	c	c	0.26 ± 0.10	0.46 ± 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.

[a] Population PK model with 3 post-infusion samples based on randomized drawing schedule.

[b] Individual PK with 12 post-infusion samples.

[c] Tmax could not be calculated for subjects in the pediatric 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).

5.3 Preclinical Safety Data

Nonclinical Toxicology: *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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Name of Excipient	Quality Standard	Component Quantity per Vial					
		Strength (nominal) 250 IU	Strength (nominal) 500 IU	Strength (nominal) 750 IU	Strength (nominal) 1000 IU	Strength (nominal) 1500 IU	Strength (nominal) 2000 IU
Mannitol	USP, EP,JP	160 mg	160 mg	160 mg	160 mg	160 mg	160 mg
Trehalose dihydrate	NF, EP, JP	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg
Sodium chloride	USP, EP,JP	26.3 mg	26.3 mg	26.3 mg	26.3 mg	26.3 mg	26.3 mg
Histidine	USP, EP,JP	7.8 mg	7.8 mg	7.8 mg	7.8 mg	7.8 mg	7.8 mg
Tromethamine / Trometamol [Tris(hydroxymethyl)-Aminomethane]	USP, EP,JP	6.1 mg	6.1 mg	6.1 mg	6.1 mg	6.1 mg	6.1 mg
Calcium chloride dihydrate	USP, EP,JP	1.2 mg	1.2 mg	1.2 mg	1.2 mg	1.2 mg	1.2 mg
Polysorbate 80	NF, EP,JP	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Glutathione	EP, JP	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg

6.2 Incompatibilities

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at refrigerated temperature of **2°C to 8°C** (36°F to 46°F), including partial room temperature storage of up to 3 months at not more than 30°C.

- The drug product reconstituted with either 2 ml or 5 ml is stable at controlled room temperature for up to 24 hours post reconstitution using samples within product shelf life. The reconstituted product should be used within 3 hours to avoid the risk of microbial contamination.
- 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.

6.5 Nature and contents of container

The Adynovate® is supplied with Baxject III configuration

Primary Packaging Materials

Primary packaging materials are the same for all dosage strengths of Adynovate® drug product. The primary packaging components utilized for Adynovate® drug product are:

- Clear and colorless 6R Type I glass vials,
- Gray, 20 mm, Flurotec® laminated butyl rubber stopper
- Aluminium crimp-cap with a polypropylene flip-off disk.

Secondary Packaging Configurations (Unit Carton)

A sealed blister pack with a Tyvek® lid with the following content:

- pre-assembled BAXJECT III system with:
  - a vial of rurioctocog alfa pegol drug product (lyophilized powder) and
  - a vial containing 2 or 5 mL reconstitution solvent (sterile water for injection)
- a package leaflet

Sterile water for injection is filled in a clear Type I, 6R (USP, Ph.Eur.) glass vial, sealed with a chlorobutyl rubber stopper with an inert coating.

6.6 Special Precautions for Disposal

Place needle, syringe and Adynovate® system in a hard-walled Sharps container for proper disposal. Do not dispose of these supplies in ordinary household trash.
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 blister.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PATIENT COUNSELING INFORMATION

Advise patients to:

- Read the patient labeling (Patient Information and Steps of Administration at Section 4.2.2. and 4.2.3).
- 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 Adynovate® therapy because this may be a sign of inhibitor development.
- 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.

8. MANUFACTURER

Manufactured by:
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Imported & Marketed by:
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9. IMPORT LICENSE NUMBER

IL/BIO-000202- RC/BIO-000188

10. CONSUMER CARE NO

0008000504087

11. DATE OF REVISION OF TEXT

June 2021

Rurioctocog Alfa Pegol (PEGylated Recombinant Human FVIII) - Adynovate®
Administration Set: Instructions for Use

Description

This Administration Set contains: Disposable syringe and butterfly needle. The kit may or may not include alcohol swab and a wound resistant strip.

Intended Use

This Administration Set is for administration of Adynovate®, which are reconstituted with the ready to use BAXJECT III system, as indicated by your treating physician and described in the package insert.

Operating Instructions

Use aseptic technique.

1. Use the syringe to withdraw the reconstituted factor from the BAXJECT III device.
2. Use the infusion set to perform venipuncture.
3. Connect the filled syringe to the infusion set and administer the coagulation factor.
4. Remove the infusion set and protect the needle.
5. Adhesive bandages may be used as appropriate.
6. Discard all used material according to your local practice.

Precautions and Symbols

For B. Braun Syringe: Re-use of single use devices creates a potential risk to patient or user. It may lead to contamination and/or impairment of functional capability. Contamination and/or limited functionality of the device may lead to injury, illness or death of the patient.
See also individual device labeling.
Do not use if the product, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.

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