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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADYNOVATE® safely and effectively. See full prescribing information for ADYNOVATE.

ADYNOVATE, (Antihemophilic Factor, Recombinant, PEGylated) Lyophilized Powder for Solution for Intravenous Injection

Initial U.S. Approval: 2015

INDICATIONS AND USAGE

ADYNOVATE, Antihemophilic Factor (Recombinant), PEGylated, is a human antihemophilic factor indicated in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes. (1)
- Perioperative management. (1)
- Routine prophylaxis to reduce the frequency of bleeding episodes. (1)

Limitations of Use

ADYNOVATE is not indicated for the treatment of von Willebrand disease. (1)

DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

- One unit per kilogram body weight will raise the factor VIII level by 2% international units per deciliter (IU per dL). Each vial of ADYNOVATE is labeled with the actual amount of recombinant factor VIII present in IU. (2.1)
- On-demand treatment and control of bleeding episodes and perioperative management:
 - *Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg).* (2.1)
 - *Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL)* (2.1)

Routine prophylaxis:

- Administer 40-50 IU/kg body weight twice weekly in adults and adolescents (12 years and older). (2.1)
- Administer 55 IU/kg twice weekly in children (<12 years) with a maximum of 70 IU/kg. (2.1)
- Adjust the dose and dosing intervals based on the patient's clinical response. (2.1)
- Inject intravenously over a period of less than or equal to 5 minutes (maximum infusion rate 10 mL per min). (2.3)

DOSAGE FORMS AND STRENGTHS

ADYNOVATE is available as a white to off-white lyophilized powder in single-dose vials containing nominally (approximately) 250, 500, 750, 1000, 1500, 2000, or 3000 international units. (3)

CONTRAINDICATIONS

Do not use in patients who have had prior anaphylactic reaction to ADYNOVATE, the parent molecule (ADVATE®), mouse or hamster protein, or excipients of ADYNOVATE. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, have been reported. Should symptoms occur, discontinue treatment with ADYNOVATE and administer appropriate treatment. (5.1)
- Development of factor VIII neutralizing antibodies (inhibitors) may occur. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures factor VIII inhibitor concentration. (5.2, 5.3)

ADVERSE REACTIONS

The most common adverse reactions reported in ≥1% of patients were cough, headache, diarrhea, vomiting, rash, nausea, urticaria, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pediatric Use: Higher clearance, a shorter half-life and lower incremental recovery of factor VIII has been observed in children (<12 years). Dose adjustment or more frequent dosing based on per kg body weight may be needed in this population. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ADYNOVATE® is indicated in adult and pediatric patients 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.

Limitations 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

- Each vial label of ADYNOVATE states the actual factor VIII potency in international units. This may be more or less than the nominal vial potency/content. 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 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/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.

2.2 Preparation and Reconstitution

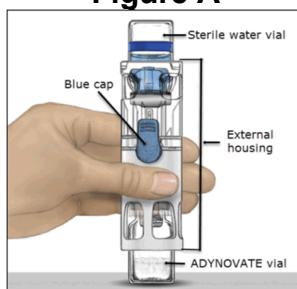
Preparation

- 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

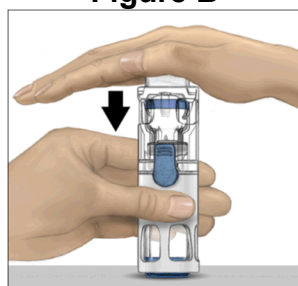
1. Allow the ADYNOVATE package to reach room temperature before use.
2. Open the package by peeling away the lid. Remove ADYNOVATE from the package and verify that the expiration date on the label has not passed and the potency unit number is same as expected. Inspect parenteral drug products for discoloration 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.

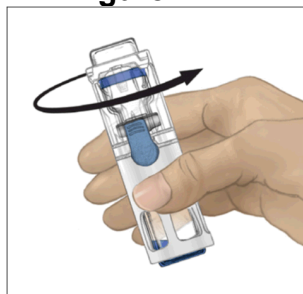
Figure B



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



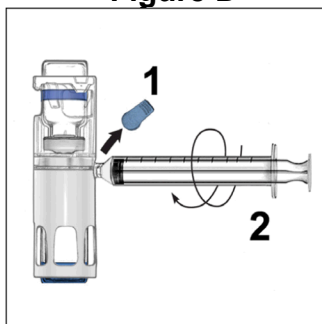
2.3 Administration

- 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:

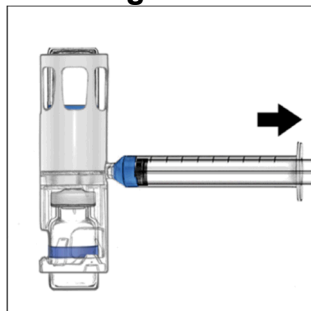
1. Remove the blue cap from the housing. Connect the syringe to the system (Figure D). Do not inject air into the ADYNOVATE.

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. If a patient is to receive more than one ADYNOVATE - BAXJECT® III system or a combination of an ADYNOVATE - BAXJECT II and an ADYNOVATE - BAXJECT III system, the contents may be drawn into the same syringe.
4. Administer ADYNOVATE intravenously over a period of less than or equal to 5 minutes (maximum infusion rate 10 mL per min).

3 DOSAGE FORMS AND STRENGTHS

ADYNOVATE is available as a white to off-white lyophilized powder in single-dose vials containing nominally (approximately) 250, 500, 750, 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 labeled 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 including anaphylaxis, have been reported with ADYNOVATE. Hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, pruritus, and nausea and vomiting. 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

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 pooled safety database described in this section reflects exposure of ADYNOVATE in 478 previously treated patients (PTPs) and previously untreated patients (PUPs) with severe hemophilia A (factor VIII less than 1% of normal), who received at least one dose of ADYNOVATE in 7 clinical studies [see *Immunogenicity (12.6)* and *Clinical Studies (14)*]. The total number of infusions within the safety database is 92173. [Table 3](#) lists the adverse reactions reported during clinical studies.

The most common adverse reactions ($\geq 1\%$ of patients) were cough, headache, diarrhea, vomiting, rash, nausea, urticaria, and dizziness.

Table 3: Adverse Reactions Reported for ADYNOVATE*

MedDRA System Organ Class	Adverse Reaction	Number of Patients n (%) (N=478)
Gastrointestinal Disorders	Diarrhea	38 (8%)
	Vomiting	26 (5%)
	Nausea	8 (2%)
Respiratory, Thoracic and Mediastinal Disorders	Cough	50 (10%)
Eye Disorders	Ocular Hyperaemia	3 (0.6%)
Immune System Disorder	Hypersensitivity ^a	2 (0.4%)
Nervous System Disorders	Headache	41 (9%)
	Dizziness	7 (1%)
Skin and Subcutaneous Tissue Disorders	Rash	16 (3%)
	Urticaria	9 (2%)
	Rash Pruritic	1 (0.2%)
	Eyelid Rash	1 (0.2%)
Vascular Disorders	Flushing	1 (0.2%)
Investigations	Eosinophil Count Increased	2 (0.4%)
Injury, Poisoning and Procedural Complications	Infusion Related Reaction	2 (0.4%)

^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.

* Pooled safety analysis from 7 clinical studies.

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 patients. Administration of ADYNOVATE continued and both cases resolved.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Immune System Disorders: Anaphylactic Reaction

8 USE IN SPECIFIC POPULATIONS

8.1 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 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.

8.2 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.

8.4 Pediatric Use

The safety and efficacy of ADYNOVATE have been established in pediatric patients. The use of ADYNOVATE for routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management was supported by five clinical studies which included 115 previously treated pediatric patients 1 to 16 years of age (78 patients <12 years of age). The safety and efficacy of ADYNOVATE in routine prophylaxis and the treatment of bleeding episodes were comparable between pediatric patients and adults. [see *Adverse Reactions* (6), *Clinical Pharmacology* (12), and *Clinical Studies* (14)]

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. [see *Clinical Pharmacology* (12.3)]

8.5 Geriatric Use

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

11 DESCRIPTION

ADYNOVATE, Antihemophilic 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-dose vials containing nominal (approximate) potencies of 250, 500, 750, 1000, 1500, 2000, or 3000 international units (IU). Each vial of ADYNOVATE is labeled 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, 750, 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* (12.1)]. 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ADYNOVATE, a PEGylated form of recombinant antihemophilic factor (ADVATE), [see *Description (11)*], 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).

12.2 Pharmacodynamics

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.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of ADYNOVATE were evaluated in a multicenter, prospective, open-label clinical trial (Study 1) [see *Clinical Studies (14)*] and compared with ADVATE in 26 patients prior to initiation of prophylactic treatment with ADYNOVATE and in 22 patients 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.

Pediatric Pharmacokinetics

Pharmacokinetic parameters calculated from 39 patients <18 years of age (intent-to-treat analysis) are available for 14 children (2 to <6 years), 17 older children (6 to <12 years) from Study 2 [see *Clinical Studies (14)*] and 8 adolescent patients (12 to <18 years of age) from Study 1 [see *Clinical Studies (14)*], 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	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 \pm 2.43	12.4 \pm 1.67	13.43 \pm 4.05	14.69 \pm 3.79
MRT [h]	17.0 \pm 3.50	17.8 \pm 2.42	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) ^d	2.27 \pm 0.84
Incremental Recovery [(IU/dL)/(IU/kg)]	1.89 \pm 0.49	1.95 \pm 0.47	2.12 \pm 0.60	2.66 \pm 0.68
AUC _{0-Inf} [IU·h/dL]	1947 \pm 757	2012 \pm 495	1642 \pm 752	2264 \pm 729
V _{ss} [dL/kg]	0.56 \pm 0.12	0.54 \pm 0.09	0.56 \pm 0.18	0.43 \pm 0.11
C _{max} [IU/dL]	115 \pm 30	115 \pm 33	95 \pm 25	122 \pm 29
T _{max} [h]	c	c	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.

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

^b Individual PK with 12 post-infusion samples.

^c T_{max} could not be calculated for patients 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 patient whose clearance estimate was 11.8 mL/(kg·h). Median including all patients is 2.78 mL/(kg·h).

Incremental recovery was further evaluated in 99 patients (PUP) <6 years of age in a prospective, uncontrolled, open-label, multicenter trial. Incremental recovery remained relatively stable over time of treatment with mean (SD) incremental recovery values (1-stage clotting method) of 1.670 (0.594) (IU/dL)/(IU/kg) (n=99), 1.617 (0.640) (IU/dL)/(IU/kg) (n=47), 1.805 (0.593) (IU/dL)/(IU/kg) (n=87), and 1.873 (0.440) (IU/dL)/(IU/kg) (n=89), at baseline, visit 3 (ED 15 \pm 1), visit 6 (ED 40 \pm 3), and trial completion/termination (ED 100 to 110), respectively.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (FVIII, PEG FVIII, PEG, CHO) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies to ADYNOVATE in the studies described below with the incidence of anti-drug antibodies in studies with other products.

Immunogenicity was evaluated during 7 clinical trials with ADYNOVATE in 365 previously treated patients and 120 previously untreated patients with severe hemophilia A.

Previously Treated Patients

In 6 clinical studies with previously treated patients, immunogenicity was evaluated by monitoring neutralizing (inhibitory) antibodies to FVIII and 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.

Two previously treated patients developed a transient low titer FVIII inhibitor at 0.6 BU/mL with ADYNOVATE, only one of which was confirmed with repeat testing. Both of these patients continued treatment without change in the dose of ADYNOVATE.

Out of 365 patients, thirty-six patients 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 patients 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. 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 pharmacokinetic parameters. There was no causal relationship between observed adverse events and binding antibodies except in one patient where a causal relationship cannot be ruled out based on available data. No patient had pre-existing or treatment-emergent antibodies to CHO protein.

Previously Untreated Patients

In the clinical study with previously untreated patients, immunogenicity was evaluated by monitoring neutralizing (inhibitory) antibodies to FVIII and by measuring the development of binding IgG and IgM antibodies against factor VIII, PEGylated (PEG)-factor VIII, and PEG using validated ELISA assays.

Of the 120 dosed patients, 100 patients were evaluable for inhibitor development. Of these, 11 (11%) patients developed confirmed FVIII inhibitors after mean (SD) exposure days of 7.6 (4) to ADYNOVATE.

Of the 11 patients who developed inhibitors, 6 (55%) developed high titer inhibitors (>5 BU/mL) and 5 (45%) developed low titer inhibitors (≤5 BU/mL).

Of the 120 patients, 4 patients (3%) had preexisting IgG binding antibodies to FVIII, 13 patients (11%) had preexisting IgM binding antibodies to PEG, 11 patients (9%) had preexisting IgG binding antibodies to PEG FVIII, and 7 patients (6%) had preexisting IgM binding antibodies to PEGFVIII. Of the 120 patients, 59 patients developed transient binding non-neutralizing antibodies to FVIII, PEG FVIII, and PEG after exposure to ADYNOVATE. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of ADYNOVATE over the treatment duration.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

The efficacy of ADYNOVATE was evaluated in 4 clinical studies, as described below.

Study 1

The safety, efficacy, and PK of ADYNOVATE were evaluated in a multicenter, open-label, prospective, non-randomized, two-arm clinical trial (Study 261201, NCT01736475) that compared the efficacy of a twice weekly prophylactic treatment regimen to on-demand treatment and determined hemostatic efficacy in the treatment of bleeding episodes. A total of 137 male PTPs (12 to 65 years of age) with severe hemophilia A received at least one infusion with ADYNOVATE. Twenty-five of the 137 patients were adolescents (12 to less than 18 years of age).

Patients 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%) patients previously treated prophylactically prior to enrollment, 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 patients remained on the starting recommended regimen without dose adjustment, and 2 patients 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 patients) occurred in the on-demand arm and 157 (n=61 patients) 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 patients 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 patients) occurred in the on-demand arm and 230 bleeding episodes (n=75 patients) 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 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 patients (treated population) received a twice a week regimen in the prophylaxis arm, and an additional 17 patients 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 patients 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 patients 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 patients 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 patients (38%) experienced no bleeding episodes and 68 out of 120 patients (57%) experienced no joint bleeding episodes in the prophylaxis arm. Of those patients who were compliant to regimen (per-protocol population), 40 out of 101 patients (40%) experienced no bleeding episodes. All patients in the on-demand arm experienced a bleeding episode, including a joint bleeding episode.

Study 2

Routine Prophylaxis Clinical Trial in Pediatric Patients (<12 years of age)

The safety and efficacy of ADYNOVATE was evaluated in a total of 73 pediatric PTPs with severe hemophilia A, of which 66 patients were dosed (32 patients aged <6 years and 34 patients aged 6 to <12 years) in a separate pediatric clinical trial (Study 261202, NCT02210091). 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 patients 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 patients 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 pediatric 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 pediatric clinical trial were unchanged as compared to the previously conducted prophylaxis clinical trial in adolescent and adult patients.

Study 3

An extension study (Study 261302, NCT01945593) in adult and pediatric patients evaluated the safety and efficacy of prophylactic treatment regimen in 216 previously treated patients with severe hemophilia A. Majority had completed the adult and adolescent study or the pediatric study. Similar efficacy was noted in this extension study.

Study 4

Perioperative Management Clinical Trial

The safety and efficacy of ADYNOVATE in PTPs (aged 12 to 65 years) with severe hemophilia A, who were undergoing elective surgical or other invasive procedures, was evaluated in a multicenter, open-label clinical trial (Study 261204, NCT01913405). In this clinical trial 21 major surgical procedures comprising of 14 orthopedic, and 7 non-orthopedic procedures, and 5 additional minor surgeries were performed in 21 patients. The preoperative loading dose ranged from 36 IU/kg to 99 IU/kg (median: 60 IU/kg) and the total post-operative dose ranged from 23 IU/kg to 769 IU/kg (median: 183 IU/kg). The median total dose (including all administrations from pre-surgical PK and loading doses to post-hospital follow up) was 629 IU/kg (range: 464-1,457 IU/kg) for major orthopedic surgeries, 489 IU/kg (range: 296-738 IU/kg) for major non-orthopedic surgeries.

Overall hemostatic efficacy was rated as excellent (blood loss less than or equal to that expected for the same type of procedure performed in a non-hemophilic patient, for all 24 (21 major, 3 minor) procedures with available assessments.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ADYNOVATE in a BAXJECT III system is packaged with 2 mL or 5 mL of Sterile Water for Injection, one Terumo Microbore Infusion set (2 mL only), one full prescribing physician insert and one patient insert. Components not made with natural rubber latex.

ADYNOVATE is available in single-dose vials that contain the following nominal product strengths:

Nominal Strength	Potency Color Code	Carton NDC (Includes 2 mL sWFI Diluent)	Carton NDC (Includes 5 mL sWFI Diluent)
250 IU	Light Blue	0944-4622-01	
500 IU	Pink	0944-4623-01	
750 IU	Red	0944-4626-01	
1000 IU	Light Green	0944-4624-01	
1500 IU	Purple	0944-4627-01	
2000 IU	Orange		0944-4625-01
3000 IU	Silver		0944-4628-01

Actual factor VIII activity in IU is stated on the label of each ADYNOVATE carton and housing.

Storage and Handling

- Store ADYNOVATE in powder form at 2°C to 8°C (36°F to 46°F).
- Do not freeze.
- ADYNOVATE may be stored at room temperature not to exceed 30°C (86°F) 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.

17 PATIENT COUNSELING INFORMATION

Advise the patients to:

- Read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- 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.
- 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.


To enroll in the confidential, industry-wide Patient Notification System, call 1-888-873-2838.

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Patient Information
ADYNOVATE®(ah-DYE-noh-vayt)
[Antihemophilic Factor (Recombinant), PEGylated]

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 adults and children 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 cough, headache, diarrhea, vomiting, rash, nausea, hives, and dizziness. Tell your healthcare provider about any side effects that bother you or do not go away.

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 seven different dosage strengths: 250 International Units (IU), 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU. The actual strength will be imprinted on the label and on the box. The seven 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 sWFI)
Silver	Dosage strength of approximately 3000 International Units per vial (with 5 mL sWFI)

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider. 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.
 - Write the date on the carton when ADYNOVATE is removed from refrigeration.
 - 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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This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 10/2025

Instructions For Use

ADYNOVATE® **[Antihemophilic Factor (Recombinant), PEGylated]** **(For intravenous use only)**

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

Step-by-step instructions for reconstituting ADYNOVATE are found at the end of this leaflet.

Always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using ADYNOVATE. If you are unsure of the procedures, please call your healthcare provider before using.

Call your healthcare provider right away if bleeding is not controlled after using ADYNOVATE.

Your healthcare provider will prescribe the dose that you should take.

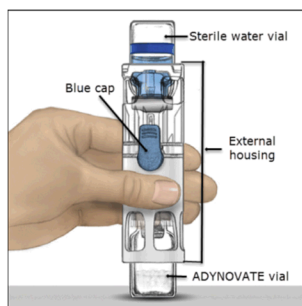
Reconstituted product (after mixing dry product with wet diluent) must be used within 3 hours and cannot be stored or refrigerated.

Your healthcare provider may need to take blood tests from time to time.

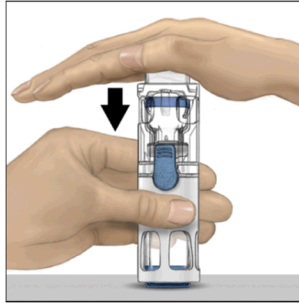
Talk to your healthcare provider before traveling. Plan to bring enough ADYNOVATE for your treatment during this time.

Dispose of all materials, including any leftover reconstituted ADYNOVATE product, in an appropriate container.

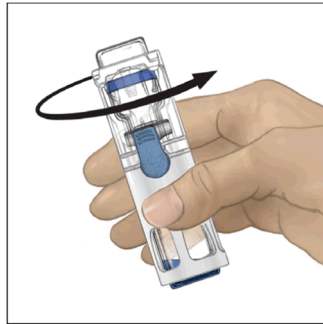
1. Prepare a clean flat surface and gather all the materials you will need for the infusion.
 - Check the expiration date, and let the ADYNOVATE warm up to room temperature.
 - Wash your hands and put on clean exam gloves. If infusing yourself at home, the use of gloves is optional.
2. Open the ADYNOVATE package by peeling away the lid. Remove the ADYNOVATE from the package and visually inspect the contents of the product and diluent vial. The ADYNOVATE powder should be white to off-white in color and the diluent should not contain particles. Do not use if discoloration or particles are seen.
3. Place on a flat surface with the diluent vial on top. The diluent vial has a blue stripe.



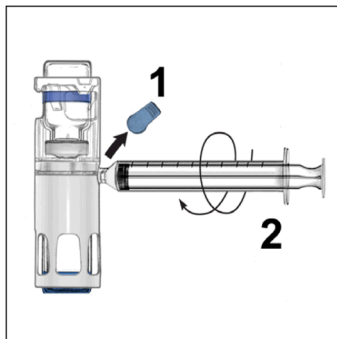
4. With one hand holding the ADYNOVATE housing, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the ADYNOVATE vial. Both vials will move into the housing when pressed. If you don't see the diluent transfer to the product vial, press the vials again to assure they are completely inserted. Do not remove the blue cap until instructed in a later step.



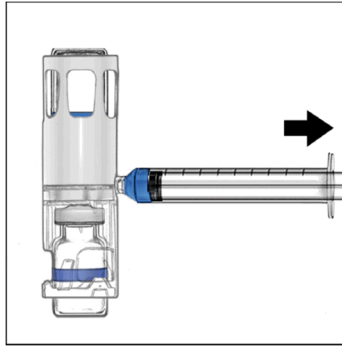
5. Swirl the ADYNOVATE gently and continuously until the ADYNOVATE is completely dissolved. Do not shake. Do not refrigerate after reconstitution. Inspect the ADYNOVATE solution for particulate matter and discoloration prior to administration. The solution should be clear and colorless in appearance. If not, do not use the solution and notify your healthcare provider immediately.



6. Take off the blue cap from the housing and connect the syringe. Be careful to not inject air into the ADYNOVATE.



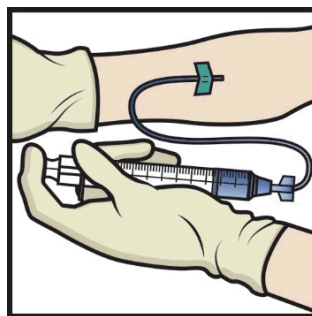
7. Turn over the ADYNOVATE so that the vial containing the ADYNOVATE solution is on top. Draw the ADYNOVATE solution into the syringe by pulling back the plunger slowly. If the solution does not draw into the syringe, be sure that both vials are pressed firmly together. The contents of more than one vial may be drawn into a single, appropriately sized syringe if you are using more than one vial of ADYNOVATE.



8. Disconnect the syringe from the system. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.
9. Apply a tourniquet and get the injection site ready by wiping the skin well with an alcohol swab (or other suitable solution suggested by your healthcare provider or hemophilia center)



10. Insert the needle into the vein and remove the tourniquet. Slowly infuse the ADYNOVATE. Do not infuse any faster than 10 mL per minute.



11. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.
12. Remove the peel-off label from blister lid and place it in your logbook. Clean any spilled blood with a freshly prepared mixture of 1 part bleach and 9 parts water, soap and water, or any household disinfecting solution.
13. Do not recap the needle. 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.


Important: Contact your healthcare provider or local hemophilia treatment center if you experience any problems.

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Revised: 10/2025