

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

RECENT MAJOR CHANGES

Indication and Usage (1)	12/2016
Dosage and Administration (2)	12/2016

INDICATIONS AND USAGE

ADYNOVATE, Antihemophilic Factor (Recombinant), PEGylated, 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.

(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)
 - Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL)
- Routine prophylaxis: Administer 40-50 IU per kg body weight 2 times a week (Starting dose of 55 IU per kg body weight 2 times a week patients <12 years of age with a maximum of 70 IU per kg).
- 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 lyophilized powder in single-use vials containing nominally (approximately) 250, 500, 750, 1000, 1500 or 2000 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, are possible. 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 subjects in the clinical studies were headache and nausea. (6)

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.

To report SUSPECTED ADVERSE REACTIONS, contact Baxalta US Inc. at 1-800-999-1785 or FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>

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

Revised: 12/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ADYNOVATE, Antihemophilic Factor (Recombinant), PEGylated, 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.

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 bleeding is resolved.

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

Perioperative Management

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

Table 2: Dosing for Perioperative Management

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

Routine Prophylaxis

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

2.2 Preparation and Reconstitution

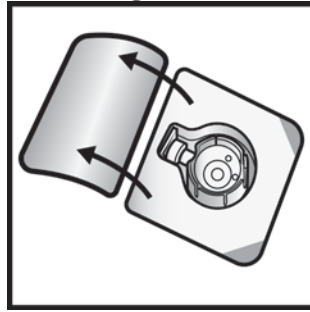
Preparation

Use aseptic technique (clean and germ free) and a flat work surface during the reconstitution procedure.

Reconstitution

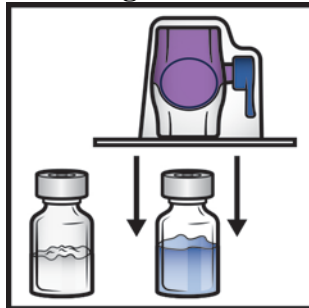
1. Allow the vials of ADYNOVATE and diluent to reach room temperature before use.
2. Remove plastic caps from the ADYNOVATE and diluent vials.
3. Cleanse rubber stoppers with a sterile alcohol prep pad and allow to dry prior to use.
4. Open the BAXJECT II Hi-Flow device package by peeling away the lid, without touching the inside (Figure A). Do not remove the device from the package.

Figure A



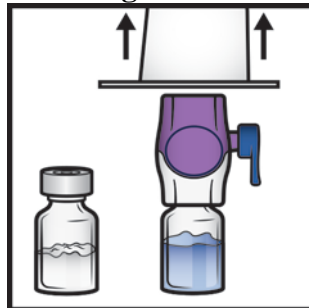
5. Turn the package over. Press straight down to fully insert the clear plastic spike through the diluent vial stopper (Figure B).

Figure B



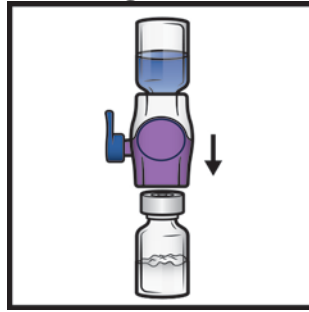
6. Grip the BAXJECT II Hi-Flow package at its edge and pull the package off the device (Figure C). Do not remove the blue cap from the BAXJECT II Hi-Flow device. Do not touch the exposed purple plastic spike.

Figure C



7. Turn the system over so that the diluent vial is on top. Quickly insert the purple plastic spike fully into the ADYNOVATE vial stopper by pushing straight down (Figure D). The vacuum will draw the diluent into the ADYNOVATE vial.

Figure D



8. Swirl gently until ADYNOVATE is completely dissolved. Do not refrigerate after reconstitution.
9. If the dose requires more than one vial of ADYNOVATE, reconstitute each vial using the above steps. Use a different BAXJECT II Hi-Flow device to reconstitute each vial of ADYNOVATE and diluent.

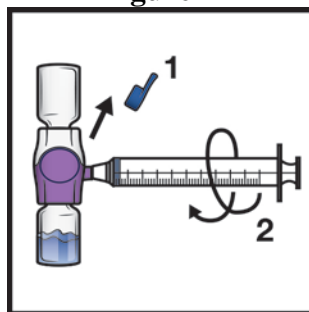
2.3 Administration

- 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:

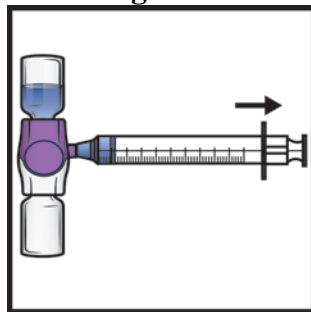
1. Remove the blue cap from the BAXJECT II Hi-Flow device. Connect the syringe to the BAXJECT II Hi-Flow device (Figure E). Use of a Luer-lock syringe is recommended. Do not inject air.

Figure E



2. Turn the system upside down (ADYNOVATE vial now on top). Draw the factor concentrate into the syringe by pulling the plunger back slowly (Figure F).

Figure F



3. If a patient is to receive more than one vial of ADYNOVATE, the contents of multiple vials may be drawn into the same syringe.
4. Disconnect the syringe; attach a suitable needle.
5. Inject 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 with 2 mL or 5 mL of Sterile Water for Injection, USP is a lyophilized powder in single-use vials containing nominally (approximately) 250, 500, 750, 1000, or 1500 International Units (IU, units). ADYNOVATE with 5 mL of Sterile Water for Injection, USP is a lyophilized powder in single-use vials containing nominally (approximately) 2000 IU. 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 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.

5.2 Neutralizing Antibodies

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

5.3 Monitoring Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

Table 3: Adverse Reactions Reported for ADYNOVATE

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

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

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

6.2 Immunogenicity

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

Immunogenicity also was evaluated by measuring the development of binding IgG and IgM antibodies against factor VIII, PEGylated (PEG)-factor VIII, PEG and Chinese hamster ovary (CHO) protein using validated ELISA assays. The majority of subjects (238/243) with at least one infusion of ADYNOVATE did not develop a persistent binding antibody response to any of these antigens. Twenty-eight subjects in total showed pre-existing antibodies to factor VIII (n=3), PEG-factor VIII (n=25) and/or PEG (n=3) prior to the first exposure to ADYNOVATE. Thirteen subjects who tested negative at screening developed transient antibodies against factor VIII (n= 6), PEG-FVIII (n= 8) at one or two consecutive study visits. Antibodies were transient and not detectable at subsequent visits. Five subjects showed positive results for binding antibodies at study completion or at the time of data 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.

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.

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. ADYNOVATE should be given to a pregnant woman only if clearly needed.

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

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. [see *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 subjects aged 65 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-use vials containing nominal (approximate) potencies of 250, 500, 750, 1000, 1500, or 2000 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 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 multi-center, prospective, open label clinical trial and compared with ADVATE in 26 subjects prior to initiation of prophylactic treatment with ADYNOVATE and in 22 subjects after 6 months of treatment with ADYNOVATE. A single dose of 45 IU/kg was utilized for both products. The PK parameters, as shown in Table 4, were based on plasma coagulation factor VIII activity measured by the one-stage clotting assay and are presented by age groups.

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

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

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

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

^b 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).

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

Original Safety and Efficacy Clinical Trial

The safety, efficacy, and PK of ADYNOVATE were evaluated in a multicenter, open-label, prospective, non-randomized, two-arm clinical trial that compared the efficacy of a twice weekly prophylactic treatment regimen to on-demand treatment and determined 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 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 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 subjects remained on the starting recommended regimen without dose adjustment, and 2 subjects increased their dose to 60 IU/kg during prophylaxis due to bleeding in target joints.

On-demand Treatment and Control of Bleeding Episodes

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

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

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

Bleeding Episode Etiology		All	Joint	Non-joint
Number of bleeds treated		591	455	136
Number of infusions to treat bleeding 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] annualized bleed rate (ABR) in the on-demand treatment arm was 41.5 [40.8] compared to 1.9 [4.7] while on a twice a week prophylaxis regimen (Table 6). In the per-protocol population, the median [mean] annualized bleed rate (ABR) in the on-demand treatment arm was 41.5 [40.8] compared to 1.9 [3.7] while on a twice a week prophylaxis regimen. Using a negative binomial

model to estimate the ABR, there was a significant reduction in the ABR ($p < 0.0001$) for subjects in the prophylaxis arm compared to the on-demand arm.

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

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

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

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

Of the 70 bleeding episodes observed during the 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 subjects.

Perioperative Management Clinical Trial

Eleven major surgical procedures (3 knee replacements, 2 arthroscopic synovectomies, 1 cyst extirpation, 1 port placement, 1 gastric band placement, and 3 multiple tooth extractions including 1 radicular cyst removal) and 4 additional minor surgeries (1 synoviorthesis, 1 radiosynovectomy, 1 tooth extraction, 1 dermatological surgery)

were performed in 15 subjects. The preoperative loading dose ranged from 36 IU/kg to 99 IU/kg (median: 65 IU/kg) and the total postoperative dose ranged from 177 IU/kg to 769 IU/kg (median: 305 IU/kg). The median total dose for major surgeries was 362 IU/kg (range: 237-863 IU/kg) and the median total dose for minor surgeries was 97 IU/kg (range: 73-119 IU/kg).

Perioperative 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, and required blood components for transfusions less than or similar to that expected in non-hemophilic population) for all 15 (11 major, 4 minor) procedures. The median (QR) observed intraoperative blood loss (n=10) was 10.0 (Q1: 5.0, Q3: 50.0) mL compared to the predicted average blood loss (n=11) of 50.0 (Q1: 6.0, Q3: 150.0) mL for major surgeries.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ADYNOVATE is supplied in packages comprised of a single-use vial containing nominally (approximately) 250, 500, 750, 1000, 1500, or 2000 international units (IU) of factor VIII potency, a diluent vial containing 2 mL or 5 mL of sterile Water for Injection (sWFI), a BAXJECT II Hi-Flow Needleless Transfer Device, and one Terumo Microbore Infusion set (2 mL only). 2000 IU will only be supplied with 5 mL Sterile Water for Injection. Components not made with natural rubber latex.

Nominal Strength	Potency Color Code	Carton NDC (Includes 2 mL sWFI Diluent)	Carton NDC (Includes 5 mL sWFI Diluent)
250 IU	Light Blue	0944-4132-02	0944-4252-02
500 IU	Pink	0944-4133-02	0944-4254-02
750 IU	Red	0944-4135-02	0944-4260-02
1000 IU	Light Green	0944-4134-02	0944-4256-02
1500 IU	Purple	0944-4136-02	0944-4262-02
2000 IU	Orange		0944-4258-02

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

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 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.

17 PATIENT COUNSELING INFORMATION

Advise 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.
- Advise patients to consult with their physicians or healthcare provider prior to travel. While traveling, advise patients to bring an adequate supply of ADYNOVATE based on their current regimen of treatment.

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

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FDA-Approved Patient Labeling Patient Information

ADYNOVATE [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 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 and nausea. 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 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
Pink	Dosage strength of approximately 500 International Units per vial
Red	Dosage strength of approximately 750 International Units per vial
Light Green	Dosage strength of approximately 1000 International Units per vial
Purple	Dosage strength of approximately 1500 International Units per vial
Orange	Dosage strength of approximately 2000 International Units per vial (*available only with 5 mL Sterile Water for Injection)

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 vials in their original box and protect them 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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**FDA-Approved Patient Labeling
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.

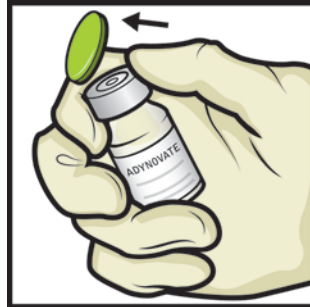
Your healthcare provider may need to take blood tests from time to time.

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 vials with the ADYNOVATE concentrate and the Sterile Water for Injection, USP (diluent) 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.
 - If you are using more than one vial of ADYNOVATE, make sure you mix each vial of ADYNOVATE with the Sterile Water for Injection, USP that is provided in the box.
 - Inspect the contents of the product and diluent vials. 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.

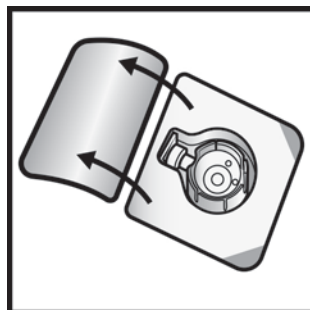
2. Remove caps from the ADYNOVATE concentrate and diluent vials to expose the centers of the rubber stoppers.



3. Disinfect the stoppers with a sterile alcohol prep pad (or other suitable solution suggested by your healthcare provider or hemophilia center) by rubbing the stoppers firmly for several seconds and allow them to dry prior to use. Place the vials on a flat surface.

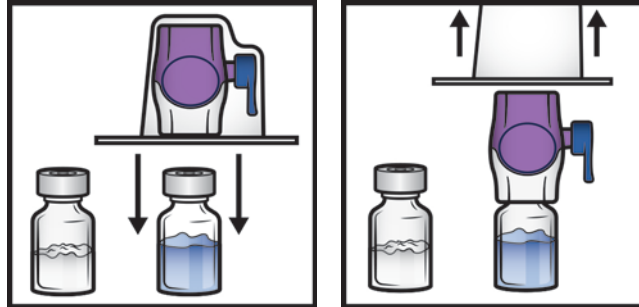


4. Open the BAXJECT II Hi-Flow device package by completely peeling away the lid, without touching the inside of the package. Do not remove the BAXJECT II Hi-flow device from the package.

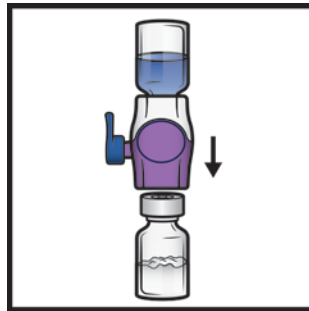


5. Turn the package with the BAXJECT II Hi-Flow device upside down and place it over the top of the diluent vial. Fully insert the clear plastic spike of the device into the center of the diluent vial's stopper by pushing straight down. Grip the package at its edge and lift it off the device. Be careful not to touch the purple plastic spike. Do

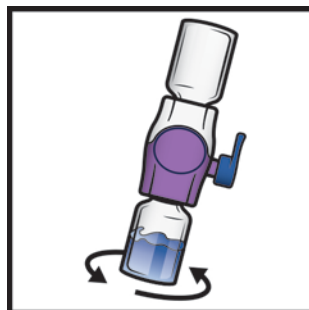
not remove the blue cap from the BAXJECT II Hi-Flow device. The diluent vial now has the BAXJECT II Hi-Flow device connected to it and is ready to be connected to the ADYNOVATE vial.



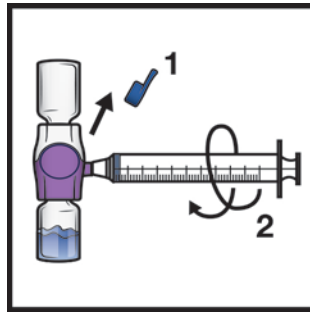
6. To connect the diluent vial to the ADYNOVATE vial, turn the diluent vial over and place it on top of the vial containing ADYNOVATE concentrate. Fully insert the purple plastic spike into the ADYNOVATE vial's stopper by pushing straight down. Diluent will flow into the ADYNOVATE vial. This should be done right away to keep the liquid free of germs.



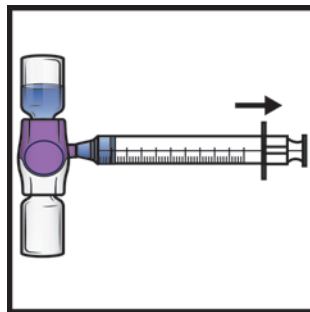
7. Swirl the connected vials gently and continuously until the ADYNOVATE is completely dissolved. Do not shake.



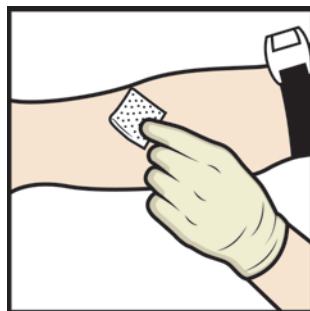
8. Take off the blue cap from the BAXJECT II Hi-Flow device and connect the syringe. Use of a Luer-lock syringe is recommended. Be careful to not inject air.



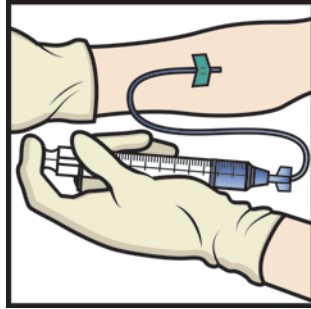
9. Turn over the connected vials so that the ADYNOVATE vial is on top. Draw the ADYNOVATE solution into the syringe by pulling back the plunger slowly. Disconnect the syringe from the vials. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the needle 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. The ADYNOVATE solution should look clear and colorless. If not, do not use it and notify Baxalta immediately.



10. If you are using more than one vial of ADYNOVATE, the contents of more than one vial may be drawn into the same syringe (Following Steps 1-9). You will need a separate BAXJECT II Hi-Flow device to mix each additional vial of ADYNOVATE. Apply a tourniquet and get the injection site ready by wiping the skin well with a sterile alcohol prep pad (or other suitable solution suggested by your healthcare provider or hemophilia center).



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



12. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.
13. Do not recap the needle. Place it with the used syringe in a hard-walled Sharps container for proper disposal.
14. Remove the peel-off label from the ADYNOVATE vial 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.



15. Dispose of the used vials and BAXJECT II Hi-Flow device in your hard-walled sharps container without taking them apart. 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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