Summary of Product Characteristics for Adynovate _Thailand

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVATE 250 IU/ 2ml powder and solvent for solution for injection
ADYNOVATE 500 IU/ 2 ml powder and solvent for solution for injection
ADYNOVATE 750 IU / 2 ml powder and solvent for solution for injection
ADYNOVATE 1000 IU / 2 ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADYNOVATE 250 IU / 2 ml powder and solvent for solution for injection
Each vial contains nominally 250 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 125 IU/ml after reconstitution with 2 ml solvent.
ADYNOVATE 500 IU / 2 ml powder and solvent for solution for injection
Each vial contains nominally 500 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 250 IU/ml after reconstitution with 2 ml solvent.
ADYNOVATE 750 IU / 2 ml powder and solvent for solution for injection
Each vial contains nominally 750 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 375 IU/ml after reconstitution with 2 ml solvent.
ADYNOVATE 1000 IU / 2 ml powder and solvent for solution for injection
Each vial contains nominally 1000 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 500 IU/ml after reconstitution with 2 ml solvent.
The potency (International Units) is determined using the chromogenic assay. The specific activity of ADYNOVATE is approximately 4000-6500 IU/mg protein. The active substance rurioctocog alfa pegol is a covalent conjugate of the protein octocog alfa* with a 20 kDa polyethylene glycol (PEG).
* Human factor VIII produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line.
Excipient(s) with known effect
Each powder vial contains 0.45 mmol (10 mg) sodium, see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
Powder: White to off-white friable powder.
Solvent: Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in children and adults with haemophilia A (congenital factor VIII deficiency)

4.2 Posology and method of administration

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

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

Treatment monitoring
During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.
A field study has indicated that plasma factor VIII levels can be monitored using either a chromogenic substrate assay or a one stage clotting assay routinely used in clinical laboratories.

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

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

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

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

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

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

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

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

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

Prophylaxis

For long term prophylaxis, the recommended dose is 40 to 50 IU of ADYNOVATE per kg bodyweight twice weekly in 3 to 4 day intervals. The recommended starting regimen for children (< 12 years) is 40-60 IU/kg twice weekly. Adjust the dose based on clinical response to a maximum of 70 IU/kg. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency (see section 5.2).

Paediatric population

The safety and efficacy of ADYNOVATE in routine prophylaxis and the treatment of bleeding episodes were comparable between children, adolescents and adults.
Pharmacokinetic studies in children (<12 years) have demonstrated higher clearance, a shorter half-life and lower incremental recovery of factor VIII compared to adults.
Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency (see section 5.2).

Method of administration

ADYNOVATE is for intravenous use
The rate of administration should be determined to ensure the comfort of the patient up to a maximum of 10 ml/min.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to the parent molecule octocog alfa or to any of the excipients listed in section 6.1.

Known allergic reaction to mouse or hamster protein.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with ADYNOVATE. The medicinal product contains traces of mouse and hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of anaphylactic shock, standard medical treatment for shock should be implemented.

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

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

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

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

Immune tolerance induction (ITI)
No clinical data for use of ADYNOVATE in ITI are available.

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

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

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

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

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with ADYNOVATE. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions
The safety of ADYNOVATE was evaluated in 243 previously treated patients with severe haemophilia 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 2 ongoing clinical studies. The median number of exposure days to ADYNOVATE per subject was 103.5 (min-max: 1-278).

The table presented below is according to the MedDRA system organ classification (System Organ Class and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions reported for ADYNOVATE		
MedDRA Standard System Organ Class	**Adverse reactions**	**Frequency per patient**
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon (PTPs)*
Immune system disorders	Hypersensitivity	Uncommon
Nervous system disorders	Headache	Common
Vascular disorders	Flushing	Uncommon
Gastrointestinal disorders	Diarrhoea	Common
	Nausea	Common
Skin and tubcutaneous tissue disorders	Rash	Common
* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients.		

Description of selected adverse reactions

Hypersensitivity
The observed 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.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. The safety of ADYNOVATE was evaluated in 38 subjects < 6 years and 34 subjects 6 to < 12 years of age having accumulated a total of 2880 EDs and 2975 EDs respectively. The mean (SD) age was 3.3 (1.55) and 8.1 (1.92) years respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

4.9 Overdose

No symptoms of overdose with recombinant coagulation factor VIII have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII, ATC code: B02BD02.

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

Rurioctocog alfa pegol, is a pegylated recombinant human factor VIII with an extended half-life. Rurioctocog alfa pegol is a covalent conjugate of octocog alfa consisting of 2,332 amino acids with polyethylene glycol (PEG) reagent (MW 20 kDa). The therapeutic activity of rurioctocog alfa pegol is derived from octocog alfa, which is produced by recombinant DNA technology from a Chinese hamster ovary cell line. Octocog alfa is then covalently conjugated with the PEG reagent. The PEG moiety is conjugated to octocog alfa to increase the plasma half-life.

Clinical efficacy and safety

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

Prophylactic treatment

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 median dosing interval was 3.6 days and the mean dose (SD) was 48.7 (4.4) IU/kg. 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.

In the per-protocol population, i.e. dosed according to the protocol specific dosing requirements, a total of 101 subjects received a twice a week regimen in the prophylaxis arm, and 17 subjects were treated episodically in the on-demand arm. The median annualised bleed rate (ABR) in the on-demand treatment arm was 41.5 compared to 1.9 while on a twice a week prophylaxis regimen. The median joint ABR (Q1 ; Q3) in the on-demand arm was 38.1 (24.5 ; 44.6) compared to 0.0 (0.0 ; 2.0) while on prophylaxis, and the median spontaneous ABR was 21.6 (11.2 ; 33.2) on the on-demand arm compared to 0.0 (0.0 ; 2.2) while on prophylaxis. Results for the full-analysis population were similar to those for the per-protocol population. Of note, ABR is not comparable between different factor concentrates and between different clinical studies.

Forty out of 101 subjects (40%) experienced no bleeding episodes, 58 out of 101 subjects (57%) experienced no joint bleeding episodes, and 58 out of 101 subjects (57%) experienced no spontaneous bleeding episodes in the prophylaxis arm. All subjects in the on-demand arm experienced a bleeding episode, including a joint or spontaneous bleeding episode.

Treatment of bleeding episodes

A total of 518 bleeding episodes were treated with ADYNOVATE in the per-protocol population. 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 32.0 (Interquartile Range (IQR): 21.5) IU per kg. Overall, 95.9% of bleeding episodes were controlled with 1 to 2 infusions and 85.5% were controlled with only 1 infusion. Of the 518 bleeding episodes, 96.1% were rated excellent (full relief of pain and cessation of objective signs of bleeding after a single infusion) or good (definite pain relief and/or improvement in signs of bleeding after a single infusion) in their response to treatment with ADYNOVATE.

Paediatric population < 12 years of age

A total of 66 PTPs with severe haemophilia A were dosed (32 subjects aged < 6 years and 34 subjects aged 6 to < 12 years) in the paediatric study. The prophylactic regimen was 40 to 60 IU/kg of ADYNOVATE twice a week. The mean dose (SD) was 54.3 (6.3) IU/kg and the median frequency of infusions per week was 1.87. The median overall ABR was 2.0 (IQR: 3.9) for the 65 subjects in the per-protocol population and the median ABRs for spontaneous and joint bleeding episodes were both 0 (IQR: 1.9). Twenty four out of 65 subjects (37%) experienced no bleeding episodes, 47 out

of 65 subjects (72%) experienced no joint bleeding episodes, and 43 out of 65 subjects (66%) experienced no spontaneous bleeding episodes on prophylaxis.

Of the 70 bleeding episodes observed during the paediatric study, 82.9% were controlled with 1 infusion and 91.4% were controlled with 1 or 2 infusions. Control of bleeding was rated excellent (full relief of pain and cessation of objective signs of bleeding after a single infusion) or good (definite pain relief and/or improvement in signs of bleeding after a single infusion) in 63 out of 70 (90.0%) bleeding episodes.

Perioperative management (surgical prophylaxis)
A total of 21 major surgical procedures and 5 additional minor surgeries were performed and assessed in 21 unique subjects in the surgery study. For major surgeries, the preoperative loading dose ranged from 36 IU/kg to 109 IU/kg (median: 63 IU/kg); and postoperative total dose ranged from 186 IU/kg to 1320 IU/kg (median: 490 IU/kg). The median total dose for major surgeries was 553 IU/kg (range: 248-1394 IU/kg) and the median total dose of minor surgeries was 106 IU/kg (range: 76-132 IU/kg).

Perioperative haemostatic efficacy was rated as excellent (blood loss less than or equal to that expected for the same type of procedure performed in a non-haemophilic patient, and required blood components for transfusions less than or similar to that expected in non-haemophilic population) for all 26 (21 major, 5 minor) procedures. The median (IQR) observed intraoperative blood loss (n = 14) was 10.0 (20.0) ml compared to the predicted average blood loss (n = 14) of 150.0 (140.0) ml for major orthopaedic surgeries.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of ADYNOVATE were evaluated in a crossover study with octocog alfa in 26 subjects (18 adults and 8 adolescents) and in 22 subjects (16 adults and 6 adolescents) after 6 months of treatment with ADYNOVATE. Plasma factor VIII activity was measured by the one stage clotting assay and chromogenic assay.

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

Paediatric Pharmacokinetics
Pharmacokinetic parameters calculated from 39 subjects less than 18 years of age (intent-to-treat analysis) are available for 14 children (2 to less than 6 years), 17 older children (6 to less than 12 years) and 8 adolescent subjects (12 to < 18 years of age). The half-life extension in the paediatric population was 1.3 to 1.5 fold using both the one stage clotting and chromogenic assays. The mean clearance (based on body weight) of ADYNOVATE was higher and the mean half-life was lower in children less than 12 years of age than adults.
A higher dose may be required in children less than 12 years of age, see section 4.2.

Table 3: Pharmacokinetic parameters using the chromogenic assay (Arithmetic mean ± SD)

PK parameters	ADYNOVATE Adults (18 years and older) N = 18 Dose: 45 ± 5 IU/kg	ADYNOVATE Adolescents (12-<18 years) N = 8 Dose: 45 ± 5 IU/kg	ADYNOVATE Paediatric patients (6-<12 years) N = 17 Dose: 50 ± 10 IU/kg	ADYNOVATE Paediatric patients (< 6 years) N = 14 Dose: 50 ± 10 IU/kg
Design	Individual PK with full sampling[a]		Population PK with sparse sampling[b]	
Terminal half-life [h]	15.01 ± 3.89	13.80 ± 4.01	11.93 ± 2.58	12.99 ± 8.75
MRT [h]	19.70 ± 5.05	17.73 ± 5.44	17.24 ± 3.73	18.74 ± 12.60
CL [mL/(kg·h)][d]	2.16 ± 0.75	2.58 ± 0.84	2.80 ± 0.67	3.49 ± 1.21
Incremental recovery [(IU/dL)/(IU/kg)]	2.87 ± 0.61	2.34 ± 0.62	na[c] (2.19± 0.40)	na[c] (1.90 ± 0.27)
$AUC_{0\text{-}Inf}$ [IU·h/dL]	2589 ± 848	1900 ± 841	2259 ± 514	2190 ± 1593
Vss [dL/kg]	0.40 ± 0.09	0.54 ± 0.22	0.46 ± 0.04	0.54 ± 0.03
Cmax [IU/dL]	145 ± 29	117 ± 28	na[c] (130 ± 24)	na[c] (117 ± 16)

Abbreviations: C_{max}: maximum observed activity; AUC: area under the curve; MRT: mean residence time; CL: clearance; V_{ss}: body weight adjusted volume of distribution at steady-state,

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

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

[c] NA, Not applicable, as Incremental Recovery and C_{max} in children were determined by individual PK. Results for Incremental Recovery and C_{max} determined by individual PK in parenthesis.

[d] The clearance value of 12.18 ml/(kg·h) for subject 122001 in age group 12 to < 18 years was not included in the analysis of clearance.

5.3 Preclinical safety data

In the repeat dose toxicity study in *Cynomologous* monkey, two animals showed vacuolation in the kidney in the mid dose group (350IU/kg). The vacuolations did not recover after 2 weeks. The human relevance of kidney vacuolation observed in the preclinical study is unknown.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Mannitol
Trehalose dihydrate
Histidine
Glutathione
Sodium chloride
Calcium chloride dihydrate
Tris(hydroxymethyl)aminomethane
Polysorbate 80

Solvent
Sterilised water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
2 years.

Before opening the product may be stored at room temperature (up to 30° C) for a period of up to 3 months. The end of the 3-month storage at room temperature should be recorded on the product carton. This date should never exceed the one initially mentioned on the outer carton. At the end of this period the product shall not be put back in the refrigerator, but shall be used or discarded.

After reconstitution
Chemical and physical in-use stability has been demonstrated for 3 hours at a temperature not above 30° C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Do not refrigerate.

6.4 Special precautions for storage

Store refrigerated (2°to 8° C).
Do not freeze.
ADYNOVATE with BAXJECT II Hi-Flow device: Keep the vial in the outer carton in order to protect from light.
ADYNOVATE in BAXJECT III system: Keep the sealed blister in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial, closed with a chlorobutyl rubber stopper, containing 250 IU, 500 IU, 750 IU or 1000 IU of powder.
Type I glass vial, closed with a chlorobutyl rubber stopper, containing 2 ml of sterilised water for injections.
The medicinal product is provided in one of the following configurations:

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

6.6 Special precautions for disposal and other handling

The reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Solutions that are cloudy or have deposits should not be used.
After reconstitution, the solution has a pH of 6.7 to 7.3. The osmolality is ≥ 380 mOsmol/kg.

Preparation and reconstitution using the BAXJECT II Hi-Flow device:

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

1. Use antiseptic technique (clean and low-germ conditions) and a flat work surface during the reconstitution procedure.
2. Allow the vials of powder and solvent to reach room temperature (between 15 °C and 25 °C) before use.
3. Remove plastic caps from the powder and solvent vials.
4. Clean rubber stoppers with an alcohol wipe and allow to dry prior to use.
5. Open the BAXJECT II Hi-Flow device package by peeling away the lid, without touching the inside (Figure A). Do not remove the device from the package.
6. Turn the package over. Press straight down to fully insert the clear plastic spike through the solvent vial stopper (Figure B).
7. Grip the BAXJECT II Hi-Flow package at its edge and pull the package off the device (Figure C). Do not remove the blue cap from the BAXJECT II Hi-Flow device. Do not touch the exposed purple plastic spike.
8. Turn the system over so that the solvent vial is on top. Quickly insert the purple plastic spike fully into the powder vial stopper by pushing straight down (Figure D). The vacuum will draw the solvent into the powder vial.
9. Swirl gently until the powder is completely dissolved. Do not refrigerate after reconstitution.

Figure A

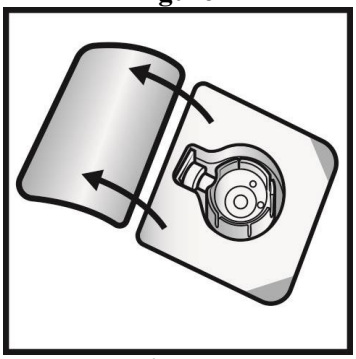


Figure B

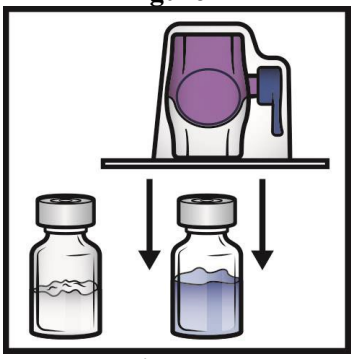


Figure C

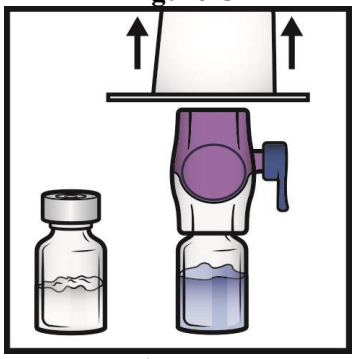


Figure D

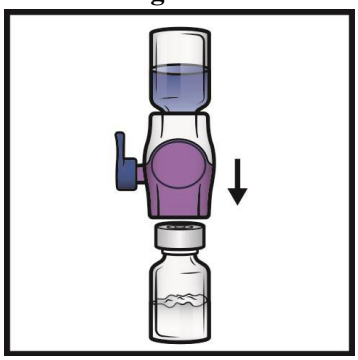


Figure E

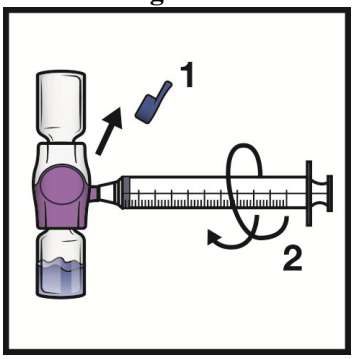
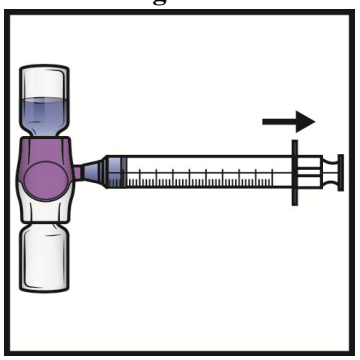


Figure F



Administration

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

Administration Steps:

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

2. Turn the system upside down (powder vial now on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Figure F).
3. Disconnect the syringe; attach a suitable needle and inject intravenously. If a patient is to receive more than one vial of ADYNOVATE, the contents of multiple vials may be drawn into the same syringe.
   A separate BAXJECT II Hi-Flow device is required to reconstitute each vial of ADYNOVATE with the solvent.
4. Administer over a period of up to 5 minutes (maximum infusion rate 10 ml per min).

It is strongly recommended that every time ADYNOVATE is administered, the name and batch number of the product are recorded. Peel-off labels are provided on the powder vial.

Reconstitution with the BAXJECT III system
Do not use if the lid is not completely sealed on the blister

1. If the product is still stored in a refrigerator, take the sealed blister (contains powder and solvent vials preassembled with the system for reconstitution) from the refrigerator and let it reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Open the ADYNOVATE blister by peeling away the lid. Remove the BAXJECT III system from the blister.
4. Place the powder vial on a flat surface with the solvent vial on top (Figure 1). The solvent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.
5. With one hand holding the powder vial in the BAXJECT III system, press down firmly on the solvent vial with the other hand until the system is fully collapsed and the solvent flows down into the powder vial (Figure 2). Do not tilt the system until the transfer is complete.
6. Verify that the solvent transfer is complete. Swirl gently until all material is dissolved (Figure 3). Be sure that the powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from particles.

Figure 1

Figure 2

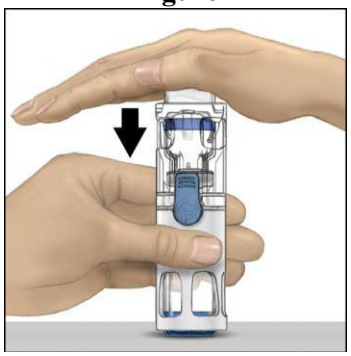
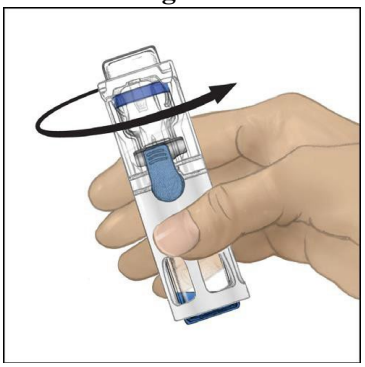


Figure 3



Administration

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

Administration Steps:

1. Remove the blue cap from the BAXJECT III device. **Do not draw air into the syringe.** Connect the syringe to the BAXJECT III device. Use of a Luer-lock syringe is recommended.
2. Turn the system upside down (powder vial now on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly.

3. Disconnect the syringe; attach a suitable needle and inject intravenously. If a patient is to receive more than one vial of ADYNOVATE, the contents of multiple vials may be drawn into the same syringe.
4. Administer over a period of up to 5 minutes (maximum infusion rate 10 ml per min).

It is strongly recommended that every time ADYNOVATE is administered, the name and batch number of the product are recorded. Peel-off labels are provided on the blister.

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

7. MARKETING AUTHORISATION HOLDER

Takeda (Thailand), Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

Adynovate 250 IU: 1C 15150/63 (NBC)
Adynovate 500 IU: 1C 15151/63 (NBC)
Adynovate 750 IU: 1C 15152/63 (NBC)
Adynovate 1000 IU: 1C 15153/63 (NBC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 Nov 2020

10. DATE OF REVISION OF THE TEXT

15 Dec 2020