ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 500 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 1 000 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 2 000 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 3 000 IU / 5 ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADYNOVI 250 IU / 5 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 50 IU/ml after reconstitution with 5 ml solvent.

ADYNOVI 500 IU / 5 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 100 IU/ml after reconstitution with 5 ml solvent.

ADYNOVI 1 000 IU / 5 ml powder and solvent for solution for injection

Each vial contains nominally 1 000 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 200 IU/ml after reconstitution with 5 ml solvent.

ADYNOVI 2 000 IU / 5 ml powder and solvent for solution for injection

Each vial contains nominally 2 000 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 400 IU/ml after reconstitution with 5 ml solvent.

ADYNOVI 3 000 IU / 5 ml powder and solvent for solution for injection

Each vial contains nominally 3 000 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 600 IU/ml after reconstitution with 5 ml solvent.

The potency (International Units) is determined using the chromogenic assay. The specific activity of ADYNOVI is approximately 3 800-6 000 IU/mg protein.

Rurioctocog alfa pegol (PEGylated human coagulation factor VIII (rDNA)) is a protein that has 2 332 amino acids with a molecular weight of approximately 280 kDa, conjugated with a 20 kDa polyethylene glycol (PEG). It is produced by recombinant DNA technology in 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 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 patients 12 years and above 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 ADYNOVI 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 (World Health Organization) 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 ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency (see sections 5.1, 5.2).

Paediatric population

On demand treatment dosing in paediatric patients (12 to 18 years of age) is the same as for adult patients. Prophylactic treatment for patients from 12 to <18 years is the same as for adult patients. Currently available data in patients below 12 years are described in sections 4.8, 5.1 and 5.2. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency (see sections 5.1, 5.2).

Method of administration

ADYNOVI 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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with ADYNOVI. 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 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 pro-coagulant 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 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with 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 ADYNOVI 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

This medicinal product contains up to 12.42 mg sodium per vial, equivalent to 0.62% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Depending on the body weight and posology, the patient could receive more than one vial. This should be taken into consideration by patients on a controlled sodium diet.

It is strongly recommended that every time that ADYNOVI 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

ADYNOVI has no or negligible 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 ADYNOVI. 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 (see section 5.1).

Tabulated list of adverse reactions

The safety of ADYNOVI was evaluated in 365 previously treated patients with severe haemophilia A (factor VIII less than 1% of normal), who received at least one dose of ADYNOVI in 6 completed multi-centre, prospective, open label clinical trials and 1 ongoing clinical trial.

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 ADYNOVI

MedDRA Standard System Organ Class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon (PTPs)*
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylactic reaction**	Not known
Nervous system disorders	Headache	Very common
	Dizziness	Common
Eye disorders	Ocular hyperaemia	Uncommon
Vascular disorders	Flushing	Uncommon
Gastrointestinal disorders	Diarrhoea	Common
	Nausea	Common
Skin and subcutaneous tissue disorders	Rash	Common
	Rash pruritic	Uncommon
	Urticaria	Common
Investigations	Eosinophil count increased	Uncommon
Injury, poisoning and procedural complications	Infusion related reaction	Uncommon
* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients. Frequencies presented were calculated using all adverse events, related and unrelated. ** Adverse reaction identified in post-marketing surveillance.		

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 ADYNOVI.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. The safety of ADYNOVI was evaluated in 38 subjects < 6 years and 34 subjects 6 to < 12 years of age having accumulated a total of 2 880 exposure days (EDs) and 2 975 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 listed in Appendix V

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 sex-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 ADYNOVI were evaluated in a pivotal multi-centre, 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 ADYNOVI. Twenty-five of the 137 subjects were adolescents (12 to less than 18 years of age).

Immunogenicity

None of the subjects who participated in one or more of 6 completed clinical trials in previously treated patients (PTPs) developed persistent neutralizing (inhibitory) antibodies against FVIII of ≥ 0.6 BU/mL (based on the Nijmegen modification of the Bethesda assay). One patient developed a transient FVIII inhibitor at the lowest limit of positivity (0.6 BU) during personalized prophylaxis targeting a FVIII level of 8-12%.

From an ongoing study in previously untreated patients < 6 years with severe hemophilia A, preliminary reports on 9 cases of FVIII inhibitor development associated with treatment with ADYNOVI were received.

Prophylactic treatment

Subjects received either prophylactic treatment (n = 120) with ADYNOVI at a dose of 40-50 IU per kg twice weekly or on-demand treatment (n = 17) with ADYNOVI 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 trials.

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 ADYNOVI 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 ADYNOVI.

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 ADYNOVI 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 1 320 IU/kg (median: 490 IU/kg). The median total dose for major surgeries was 553 IU/kg (range: 248-1 394 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.

The European Medicines Agency has deferred the obligation to submit results of studies with ADYNOVI in one or more subsets of the paediatric population in the treatment of congenital factor VIII deficiency. See 4.2 for information on paediatric use.

Long-term prophylaxis treatment in paediatric and adult subjects

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

Table 3: Annualized bleed rate (ABR) by prophylactic regimen (ITT population)

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

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

Of note, ABR is not comparable between different factor concentrates and between different clinical trials.

Long-term haemostatic efficacy was evaluated in 910 bleeding episodes treated with ADYNOVI and was rated excellent or good in 88.5% of bleeding episodes. Across age categories and for both the fixed-dose and the PK-tailored dose regimen, >85% of bleed treatments were rated excellent or good. The majority of bleeding episodes were treated with one (74.0%) or two (15.4%) infusions.

Personalized prophylaxis PROPEL clinical trial in adolescents and adult subjects

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

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

The primary endpoint of the study, proportion of subjects who had a total ABR of 0 during the second 6-month period, was not reached in the ITT patient population (p= 0.0545) but was reached in the per-protocol population (p = 0.0154). The proportions of randomized subjects with total ABRs, spontaneous ABRs and spontaneous annualized joint bleeding rates (AJBRs) of 0 during the second 6-month study period in the Per Protocol population are presented in Table 4.

Table 4: Annualized bleed rate (ABR) of 0, second 6-month study period

	Proportion of Subjects Without Bleedings in 6 Months [Point Estimate- 95% Confidence Interval]	
	ITT Population	
	1-3% Trough Level (N=57)	**8-12% Trough Level (N=58)**
Total ABR of 0	0.421 [0.292; 0.549]	0.621[0.491; 0.750]
Spontaneous ABR of 0	0.596 [0.469; 0.724]	0.760 [0.645; 0.875]
Spontaneous AJBR of 0	0.649 [0.525; 0.773]	0.850 [0.753; 0.947]
ABR = Annualized bleeding rate. AJBR = Annualized joint bleeding rate. ***Annualized bleeding rate determined by dividing the number of bleeds by observation period in years.***		
	Proportion of Subjects Without Bleedings in 6 Months [Point Estimate- 95% Confidence Interval]	
	Per Protocol Population	
	1-3% Trough Level (N=52)	**8-12% Trough Level (N=43)**
Total ABR of 0	0.404 [0.270; 0.549]	0.674 [0.515; 0.809]
Spontaneous ABR of 0	0.596 [0.451; 0.730]	0.814 [0.666; 0.916]
Spontaneous AJBR of 0	0.654 [0.509; 0.780]	0.907 [0.779; 0.974]
ABR = Annualized bleeding rate. AJBR = Annualized joint bleeding rate. ***Per-protocol population = all subjects who completed the second 6 months of prophylactic treatment and had no major deviations from the protocol affecting the study results.*** ***Annualized bleeding rate determined by dividing the number of bleeds by observation period in years.***		

Of note, ABR is not comparable between different factor concentrates and between different clinical trials.

Total ABRs, spontaneous ABRs and spontaneous AJBRs during the second 6-month study period are presented in Table 5.

Table 5: Annualized bleed rate (ABR) second 6-month study period

	(ITT Population)			
	1-3% Trough Level (N=57)		**8-12% Trough Level (N=53)**	
	Median	Mean (SD)	Median	Mean (SD)
Total ABR	2.0	3.6 (7.5)	0.0	1.6 (3.4)
Spontaneous ABR	0.0	2.5 (6.6)	0.0	0.7 (1.7)
Spontaneous AJBR	0.0	2.0 (6.4)	0.0	0.5 (1.7)
ABR = Annualized bleeding rate. AJBR = Annualized joint bleeding rate. ***Annualized bleeding rate determined by dividing the number of bleeds by observation period in years.***				
	Per Protocol Population			
	1-3% Trough Level (N=52)		**8-12% Trough Level (N=43)**	
	Median	Mean (SD)	Median	Mean (SD)
Total ABR	2.0	2.4 (3.2)	0.0	2.1 (4.2)
Spontaneous ABR	0.0	1.6 (2.6)	0.0	0.8 (2.4)
Spontaneous AJBR	0.0	1.0 (1.8)	0.0	0.7 (2.2)
ABR = Annualized bleeding rate. AJBR = Annualized joint bleeding rate. *Per-protocol population = all subjects who completed the second 6 months of prophylactic treatment and had no major deviations from the protocol affecting the study results.* *Annualized bleeding rate determined by dividing the number of bleeds by observation period in years.*				

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

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of ADYNOVI 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 ADYNOVI. Plasma factor VIII activity was measured by the one stage clotting assay and chromogenic assay.

ADYNOVI 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 ADYNOVI 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 6: Pharmacokinetic parameters using the chromogenic assay (Arithmetic mean ± SD)

PK parameters	ADYNOVI Adults (18 years and older) N = 18 Dose: 45 ± 5 IU/kg	ADYNOVI Adolescents (12-<18 years) N = 8 Dose: 45 ± 5 IU/kg	ADYNOVI Paediatric patients (6-<12 years) N = 17 Dose: 50 ± 10 IU/kg	ADYNOVI 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]	2 589 ± 848	1 900 ± 841	2 259 ± 514	2 190 ± 1 593
Vss [dL/kg]	0.40 ± 0.09	0.54 ± 0.22	0.46 ± 0.04	0.54 ± 0.03
C_{max} [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 *Cynomolgus* monkey, two animals showed vacuolation in the kidney in the mid dose group (350 IU/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 ADYNOVI. Thus, it was not possible to conclude on the potential risks of PEG accumulation in various tissues/organs relevant for chronic use of ADYNOVI in the paediatric population.
No studies on genotoxicity, carcinogenicity or reproductive toxicity have been performed with ADYNOVI.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Mannitol (E421)
Trehalose dihydrate
Histidine
Glutathione
Sodium chloride
Calcium chloride dihydrate (E509)

Tris(hydroxymethyl)aminomethane
Polysorbate 80 (E433)

Solvent

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 medicinal 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 in a refrigerator (2° C - 8° C).
Do not freeze.

ADYNOVI with BAXJECT II Hi-Flow device: Keep the vial in the outer carton in order to protect from light.

ADYNOVI 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, 1 000 IU, 2 000 IU or 3 000 IU of powder.

Type I glass vial, closed with a chlorobutyl or bromobutyl rubber stopper, containing 5 ml of water for injections.

The medicinal product is provided in one of the following configurations:

- ADYNOVI with BAXJECT II Hi-Flow device: Each pack contains a powder vial, a solvent vial and a device for reconstitution (BAXJECT II Hi-Flow).
- ADYNOVI 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 discolouration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

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

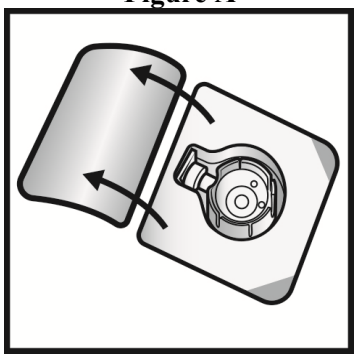


Figure B

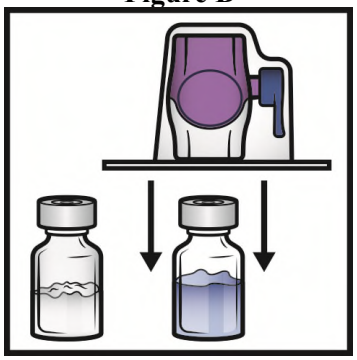


Figure C

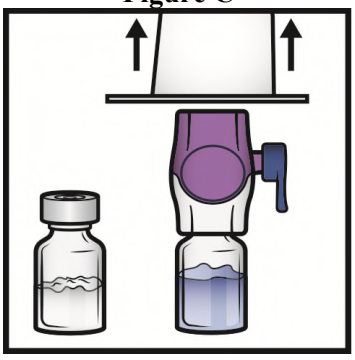


Figure D

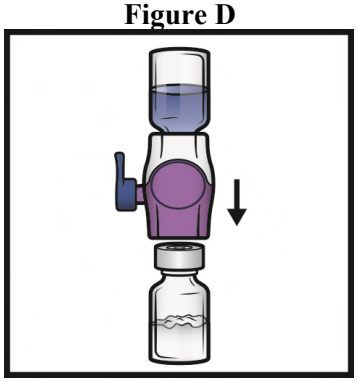


Figure E

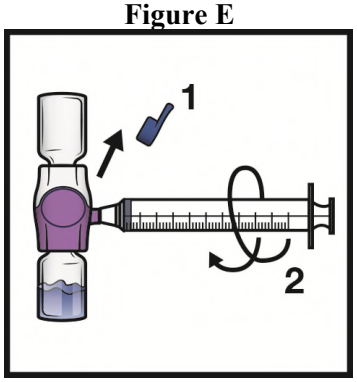
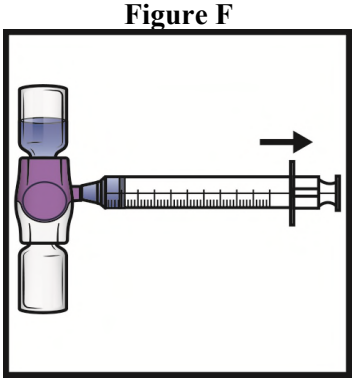


Figure F



Administration

- Visually inspect the reconstituted solution for particulate matter and discolouration prior to administration.
  - The appearance of the reconstituted solution is clear and colourless.
  - Do not use if particulate matter or discolouration 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 ADYNOVI, 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 ADYNOVI 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 ADYNOVI 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 ADYNOVI 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

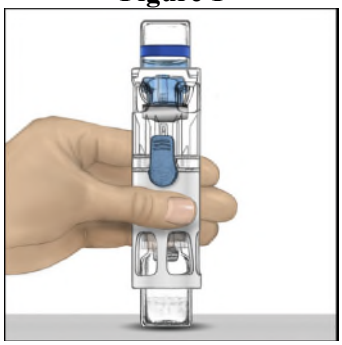


Figure 2

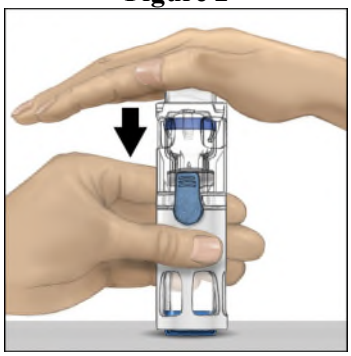


Figure 3

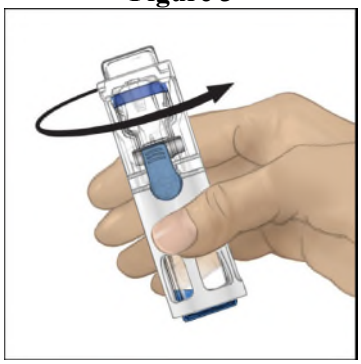


Figure 4

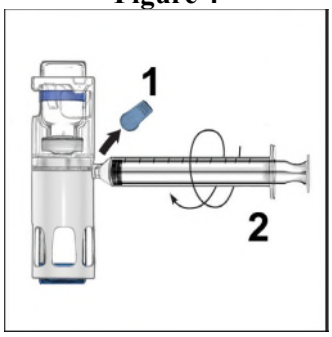
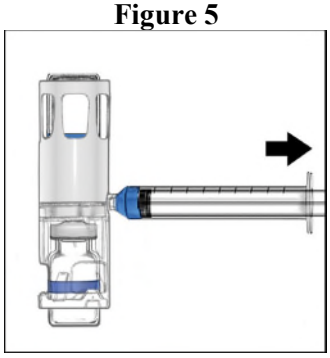


Figure 5



Administration

- Visually inspect the reconstituted solution for particulate matter and discolouration prior to administration.
  - The appearance of the reconstituted solution is clear and colourless.
  - Do not use if particulate matter or discolouration 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 (Figure 4). **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 (Figure 5).
3. Disconnect the syringe; attach a suitable needle and inject intravenously. If a patient is to receive more than one vial of ADYNOVI, 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 ADYNOVI 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

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/003
EU/1/17/1247/004
EU/1/17/1247/007
EU/1/17/1247/008
EU/1/17/1247/011
EU/1/17/1247/012
EU/1/17/1247/013
EU/1/17/1247/014
EU/1/17/1247/015
EU/1/17/1247/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 January 2018
Date of latest renewal: 09 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250 IU / 2 ml powder and solvent for solution for injection
ADYNOVI 500 IU / 2 ml powder and solvent for solution for injection
ADYNOVI 1 000 IU / 2 ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADYNOVI 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.

ADYNOVI 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.

ADYNOVI 1 000 IU / 2 ml powder and solvent for solution for injection

Each vial contains nominally 1 000 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 ADYNOVI is approximately 3 800-6 000 IU/mg protein.

Rurioctocog alfa pegol (PEGylated human coagulation factor VIII (rDNA)) is a protein that has 2 332 amino acids with a molecular weight of approximately 280 kDa, conjugated with a 20 kDa polyethylene glycol (PEG). It is produced by recombinant DNA technology in 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 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 patients 12 years and above 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 ADYNOVI 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 (World Health Organization) 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 ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency (see sections 5.1, 5.2).

Paediatric population

On demand treatment dosing in paediatric patients (12 to 18 years of age) is the same as for adult patients. Prophylactic treatment for patients from 12 to <18 years is the same as for adult patients. Currently available data in patients below 12 years are described in sections 4.8, 5.1 and 5.2. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency (see sections 5.1, 5.2).

Method of administration

ADYNOVI 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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with ADYNOVI. 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 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 pro-coagulant 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 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with 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 ADYNOVI 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

This medicinal product contains up to 12.42 mg sodium per vial, equivalent to 0.62% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Depending on the body weight and

posology, the patient could receive more than one vial. This should be taken into consideration by patients on a controlled sodium diet.

It is strongly recommended that every time that ADYNOVI 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

ADYNOVI has no or negligible 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 ADYNOVI. 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 (see section 5.1).

Tabulated list of adverse reactions

The safety of ADYNOVI was evaluated in 365 previously treated patients with severe haemophilia A (factor VIII less than 1% of normal), who received at least one dose of ADYNOVI in 6 completed multi-centre, prospective, open label clinical trials and 1 ongoing clinical trial.

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 ADYNOVI

MedDRA Standard System Organ Class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon (PTPs)*
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylactic reaction**	Not known
Nervous system disorders	Headache	Very common
	Dizziness	Common
Eye disorders	Ocular hyperaemia	Uncommon
Vascular disorders	Flushing	Uncommon
Gastrointestinal disorders	Diarrhoea	Common
	Nausea	Common
Skin and subcutaneous tissue disorders	Rash	Common
	Rash pruritic	Uncommon
	Urticaria	Common
Investigations	Eosinophil count increased	Uncommon
Injury, poisoning and procedural complications	Infusion related reaction	Uncommon
* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients. Frequencies presented were calculated using all adverse events, related and unrelated. ** Adverse reaction identified in post-marketing surveillance.		

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 ADYNOVI.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. The safety of ADYNOVI was evaluated in 38 subjects < 6 years and 34 subjects 6 to < 12 years of age having accumulated a total of 2 880 exposure days (EDs) and 2 975 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 listed in Appendix V

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 sex-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 ADYNOVI were evaluated in a pivotal multi-centre, 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 ADYNOVI. Twenty-five of the 137 subjects were adolescents (12 to less than 18 years of age).

Immunogenicity

None of the subjects who participated in one or more of 6 completed clinical trials in previously treated patients (PTPs) developed persistent neutralizing (inhibitory) antibodies against FVIII of ≥ 0.6 BU/mL (based on the Nijmegen modification of the Bethesda assay). One patient developed a transient FVIII inhibitor at the lowest limit of positivity (0.6 BU) during personalized prophylaxis targeting a FVIII level of 8-12%.

From an ongoing study in previously untreated patients < 6 years with severe hemophilia A, preliminary reports on 9 cases of FVIII inhibitor development associated with treatment with ADYNOVI were received.

Prophylactic treatment

Subjects received either prophylactic treatment (n = 120) with ADYNOVI at a dose of 40-50 IU per kg twice weekly or on-demand treatment (n = 17) with ADYNOVI 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 trials.

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 ADYNOVI 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 ADYNOVI.

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 ADYNOVI 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 1 320 IU/kg (median: 490 IU/kg). The median total dose for major surgeries was 553 IU/kg (range: 248-1 394 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.

The European Medicines Agency has deferred the obligation to submit results of studies with ADYNOVI in one or more subsets of the paediatric population in the treatment of congenital factor VIII deficiency. See 4.2 for information on paediatric use.

Long-term prophylaxis treatment in paediatric and adult subjects

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

Table 3: Annualized bleed rate (ABR) by prophylactic regimen (ITT population)

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

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

Of note, ABR is not comparable between different factor concentrates and between different clinical trials.

Long-term haemostatic efficacy was evaluated in 910 bleeding episodes treated with ADYNOVI and was rated excellent or good in 88.5% of bleeding episodes. Across age categories and for both the fixed-dose and the PK-tailored dose regimen, >85% of bleed treatments were rated excellent or good. The majority of bleeding episodes were treated with one (74.0%) or two (15.4%) infusions.

Personalized prophylaxis PROPEL clinical trial in adolescents and adult subjects

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

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

The primary endpoint of the study, proportion of subjects who had a total ABR of 0 during the second 6-month period, was not reached in the ITT patient population (p= 0.0545) but was reached in the per-protocol population (p = 0.0154). The proportions of randomized subjects with total ABRs, spontaneous ABRs and spontaneous annualized joint bleeding rates (AJBRs) of 0 during the second 6-month study period are presented in Table 4.

Table 4: Annualized bleed rate (ABR) of 0, second 6-month study period

	Proportion of Subjects Without Bleedings in 6 Months [Point Estimate- 95% Confidence Interval]	
	ITT Population	
	1-3% Trough Level (N=57)	**8-12% Trough Level (N=58)**
Total ABR of 0	0.421 [0.292; 0.549]	0.621[0.491; 0.750]
Spontaneous ABR of 0	0.596 [0.469; 0.724]	0.760 [0.645; 0.875]
Spontaneous AJBR of 0	0.649 [0.525; 0.773]	0.850 [0.753; 0.947]
ABR = Annualized bleeding rate. AJBR = Annualized joint bleeding rate. ***Annualized bleeding rate determined by dividing the number of bleeds by observation period in years.***		
	Proportion of Subjects Without Bleedings in 6 Months [Point Estimate- 95% Confidence Interval]	
	Per Protocol Population	
	1-3% Trough Level (N=52)	**8-12% Trough Level (N=43)**
Total ABR of 0	0.404 [0.270; 0.549]	0.674 [0.515; 0.809]
Spontaneous ABR of 0	0.596 [0.451; 0.730]	0.814 [0.666; 0.916]
Spontaneous AJBR of 0	0.654 [0.509; 0.780]	0.907 [0.779; 0.974]
ABR = Annualized bleeding rate. AJBR = Annualized joint bleeding rate. ***Per-protocol population = all subjects who completed the second 6 months of prophylactic treatment and had no major deviations from the protocol affecting the study results.*** ***Annualized bleeding rate determined by dividing the number of bleeds by observation period in years.***		

Of note, ABR is not comparable between different factor concentrates and between different clinical trials.

Total ABRs, spontaneous ABRs and spontaneous AJBRs during the second 6-month study period are presented in Table 5.

Table 5: Annualized bleed rate (ABR) second 6-month study period

	(ITT Population)			
	1-3% Trough Level (N=57)		**8-12% Trough Level (N=53)**	
	Median	Mean (SD)	Median	Mean (SD)
Total ABR	2.0	3.6 (7.5)	0.0	1.6 (3.4)
Spontaneous ABR	0.0	2.5 (6.6)	0.0	0.7 (1.7)
Spontaneous AJBR	0.0	2.0 (6.4)	0.0	0.5 (1.7)
ABR = Annualized bleeding rate. AJBR = Annualized joint bleeding rate. ***Annualized bleeding rate determined by dividing the number of bleeds by observation period in years.***				
	Per Protocol Population			
	1-3% Trough Level (N=52)		**8-12% Trough Level (N=43)**	
	Median	Mean (SD)	Median	Mean (SD)
Total ABR	2.0	2.4 (3.2)	0.0	2.1 (4.2)
Spontaneous ABR	0.0	1.6 (2.6)	0.0	0.8 (2.4)
Spontaneous AJBR	0.0	1.0 (1.8)	0.0	0.7 (2.2)
ABR = Annualized bleeding rate. AJBR = Annualized joint bleeding rate. *Per-protocol population = all subjects who completed the second 6 months of prophylactic treatment and had no major deviations from the protocol affecting the study results.* *Annualized bleeding rate determined by dividing the number of bleeds by observation period in years.*				

A total of 242 bleeding episodes in 66 subjects were treated with ADYNOVI; 155 bleeds in 40 subjects in the 1-3% trough level arm and 87 bleeds in 26 subjects in the 8-12% trough level arm.

The majority of bleeds (86.0%, 208/242) were treated with 1 or 2 infusions; and bleed treatment at resolution of the bleeding episode was rated excellent or good in 84.7% (205/242) of bleeds.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of ADYNOVI 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 ADYNOVI. Plasma factor VIII activity was measured by the one stage clotting assay and chromogenic assay.

ADYNOVI 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 ADYNOVI 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 6: Pharmacokinetic parameters using the chromogenic assay (Arithmetic mean ± SD)

PK parameters	**ADYNOVI Adults (18 years and older) N = 18 Dose: 45 ± 5 IU/kg**	**ADYNOVI Adolescents (12-<18 years) N = 8 Dose: 45 ± 5 IU/kg**	**ADYNOVI Paediatric patients (6-<12 years) N = 17 Dose: 50 ± 10 IU/kg**	**ADYNOVI 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]	2 589 ± 848	1 900 ± 841	2 259 ± 514	2 190 ± 1 593
Vss [dL/kg]	0.40 ± 0.09	0.54 ± 0.22	0.46 ± 0.04	0.54 ± 0.03
C_{max} [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 *Cynomolgus* monkey, two animals showed vacuolation in the kidney in the mid dose group (350 IU/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 ADYNOVI. Thus, it was not possible to conclude on the potential risks of PEG accumulation in various tissues/organs relevant for chronic use of ADYNOVI in the paediatric population No studies on genotoxicity, carcinogenicity or reproductive toxicity have been performed with ADYNOVI.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Mannitol (E421)
Trehalose dihydrate
Histidine
Glutathione
Sodium chloride
Calcium chloride dihydrate (E509)
Tris(hydroxymethyl)aminomethane
Polysorbate 80 (E433)

Solvent

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 medicinal 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 in a refrigerator (2° C - 8° C).
Do not freeze.

ADYNOVI with BAXJECT II Hi-Flow device: Keep the vial in the outer carton in order to protect from light.

ADYNOVI 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, or 1 000 IU of powder.

Type I glass vial, closed with a chlorobutyl or bromobutyl rubber stopper, containing 2 ml of water for injections.

The medicinal product is provided in one of the following configurations:

- ADYNOVI with BAXJECT II Hi-Flow device: Each pack contains a powder vial, a solvent vial and a device for reconstitution (BAXJECT II Hi-Flow).
- ADYNOVI 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 discolouration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

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

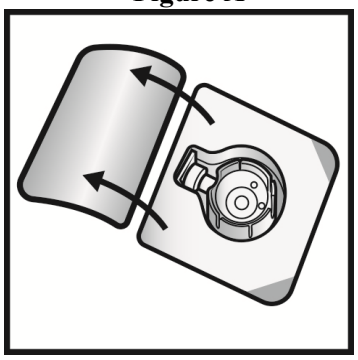


Figure B

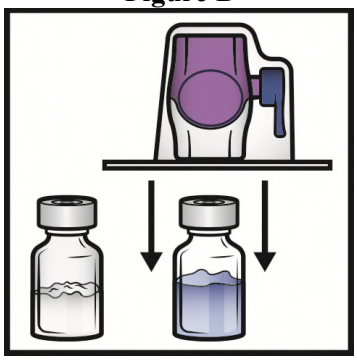


Figure C

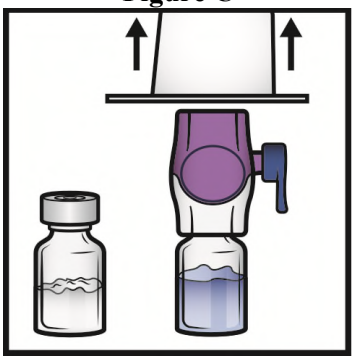


Figure D

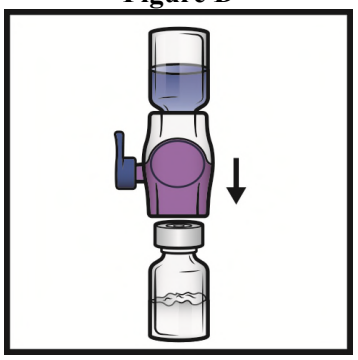


Figure E

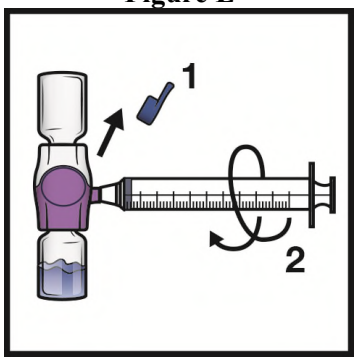
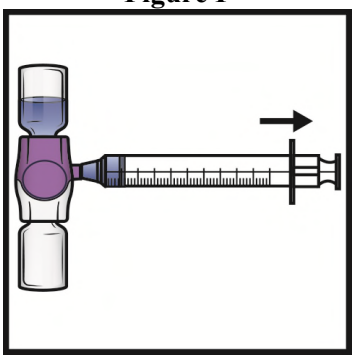


Figure F



Administration

- Visually inspect the reconstituted solution for particulate matter and discolouration prior to administration.
  - The appearance of the reconstituted solution is clear and colourless.
  - Do not use if particulate matter or discolouration 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 ADYNOVI, 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 ADYNOVI 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 ADYNOVI 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 ADYNOVI 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

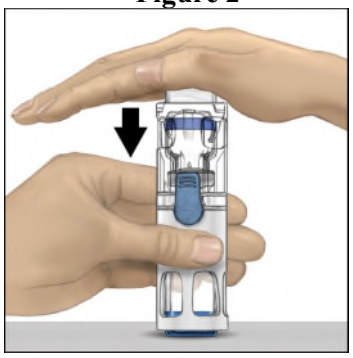


Figure 3

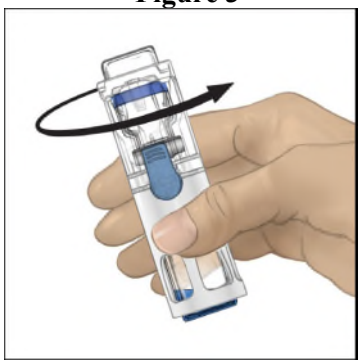


Figure 4

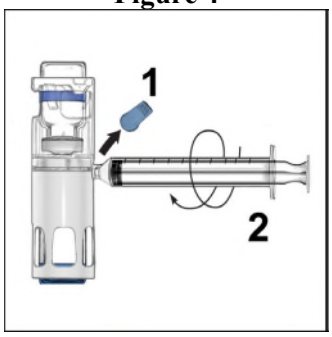
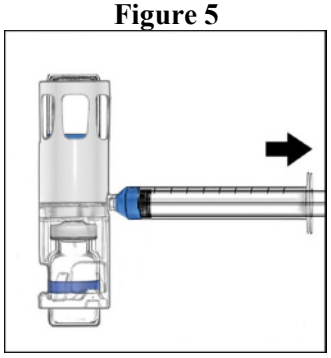


Figure 5



<u>Administration</u>

- Visually inspect the reconstituted solution for particulate matter and discolouration prior to administration.
  - The appearance of the reconstituted solution is clear and colourless.
  - Do not use if particulate matter or discolouration 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 (Figure 4). **Do not draw air into the syringe.** Connect the syringe to the BAXJECT III device. Use of a Luer-lock syringe is recommended.
2. <u>Turn the system upside down</u> (powder vial now on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Figure 5).
3. Disconnect the syringe; attach a suitable needle and inject intravenously. If a patient is to receive more than one vial of ADYNOVI, 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 ADYNOVI 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

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A-1221 Vienna
Austria
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/001
EU/1/17/1247/002
EU/1/17/1247/005
EU/1/17/1247/006
EU/1/17/1247/009
EU/1/17/1247/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 January 2018
Date of latest renewal: 09 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Baxalta US Inc
1700 Rancho Conejo Boulevard
Thousand Oaks
California
CA-91320
UNITED STATES

Name and address of the manufacturer(s) responsible for batch release

Baxalta Belgium Manufacturing SA
Boulevard Rene Branquart 80
B-7860 Lessines
BELGIUM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation safety study (PASS): In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a post-authorisation safety study according to an agreed protocol.	Q3/Q4 2030

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU rurioctocog alfa pegol, 50 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 vial with 5 ml solvent, 1 BAXJECT II Hi-Flow device.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 250 IU / 5 ml powder for solution for injection

rurioctocog alfa pegol
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 500 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU rurioctocog alfa pegol, 100 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 vial with 5 ml solvent, 1 BAXJECT II Hi-Flow device.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 500 IU / 5 ml powder for solution for injection

rurioctocog alfa pegol
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 1 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1 000 IU rurioctocog alfa pegol, 200 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 vial with 5 ml solvent, 1 BAXJECT II Hi-Flow device.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 1 000 IU / 5 ml powder for solution for injection

rurioctocog alfa pegol
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 000 IU

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 2 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 2 000 IU rurioctocog alfa pegol, 400 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 vial with 5 ml solvent, 1 BAXJECT II Hi-Flow device.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 2 000 IU / 5 ml powder for solution for injection

rurioctocog alfa pegol
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 000 IU

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 3 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 3 000 IU rurioctocog alfa pegol, 600 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 vial with 5 ml solvent, 1 BAXJECT II Hi-Flow device.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 3 000 IU / 5 ml powder for solution for injection

rurioctocog alfa pegol
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 000 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ADYNOVI
Water for injections
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU rurioctocog alfa pegol, 50 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial and 1 vial with 5 ml solvent preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use after reconstitution.
Use within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder and solvent vials preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

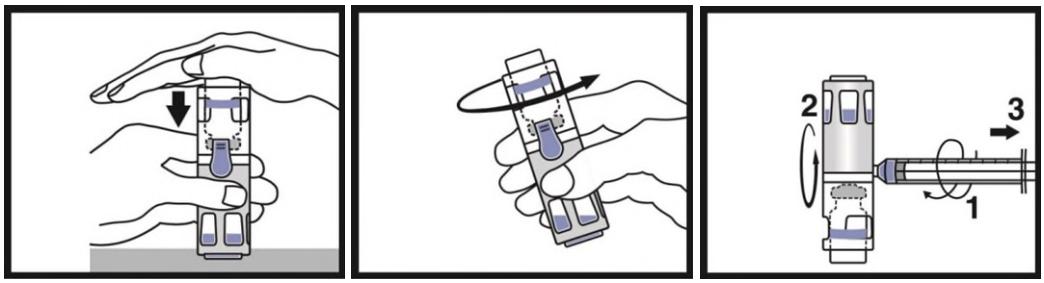
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 250

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 500 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU rurioctocog alfa pegol, 100 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial and 1 vial with 5 ml solvent preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 500 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use after reconstitution.
Use within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder and solvent vials preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 500

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

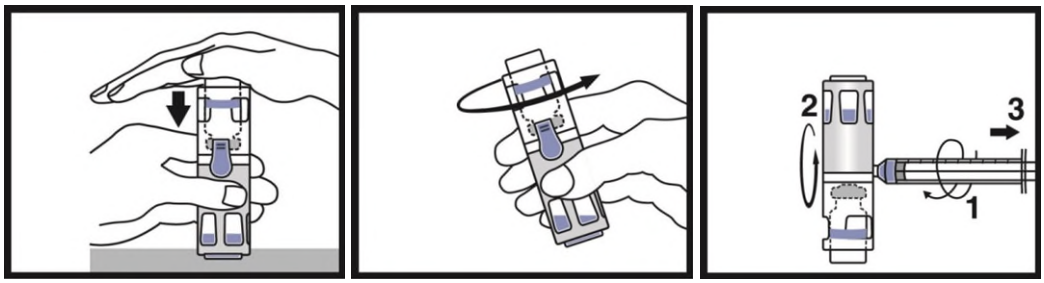
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 500

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 1 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1 000 IU rurioctocog alfa pegol, 200 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial and 1 vial with 5 ml solvent preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 1 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use after reconstitution.
Use within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder and solvent vials preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 1 000

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

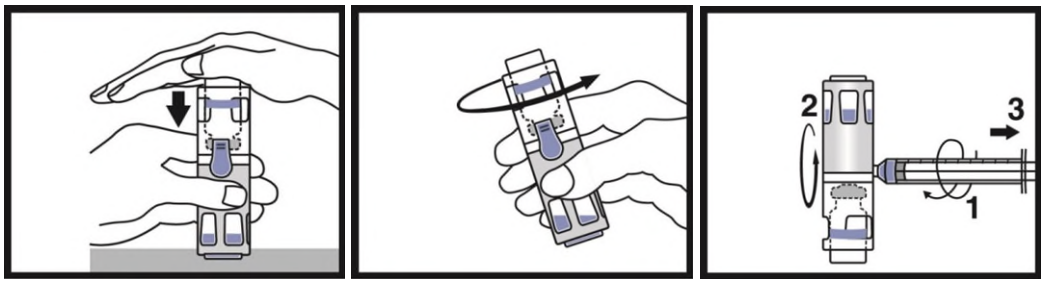
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 1 000

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 2 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 2 000 IU rurioctocog alfa pegol, 400 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial and 1 vial with 5 ml solvent preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 2 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use after reconstitution.
Use within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder and solvent vials preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 2 000

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

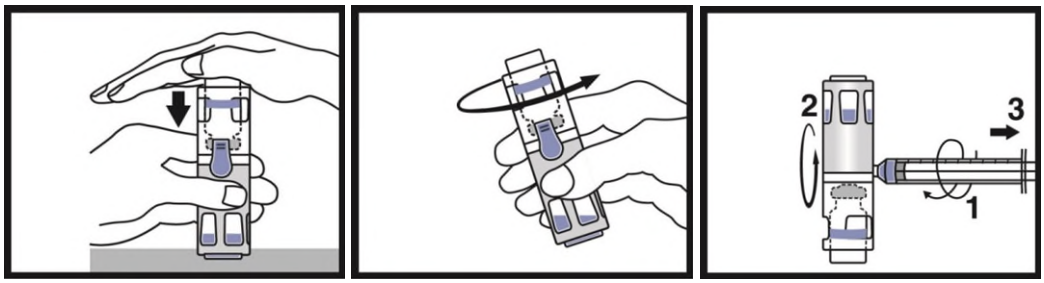
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 2 000

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 3 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 3 000 IU rurioctocog alfa pegol, 600 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial and 1 vial with 5 ml solvent preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 3 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use after reconstitution.
Use within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder and solvent vials preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 3 000

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

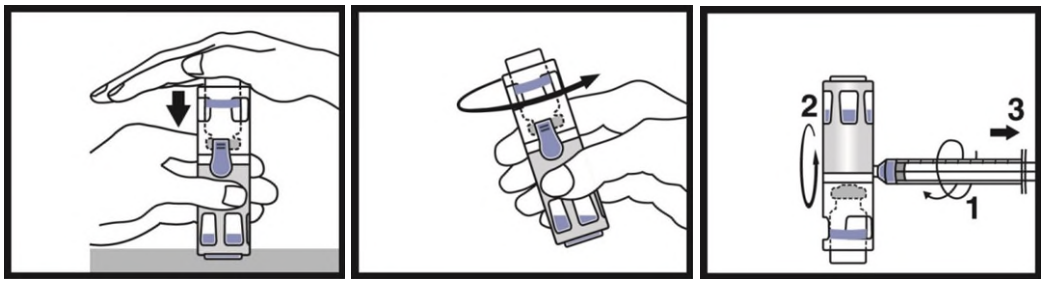
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 3 000

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ADYNOVI
Water for injections
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU rurioctocog alfa pegol, 125 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 vial with 2 ml solvent, 1 BAXJECT II Hi-Flow device.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 250 IU / 2 ml powder for solution for injection

rurioctocog alfa pegol
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 500 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU rurioctocog alfa pegol, 250 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 vial with 2 ml solvent, 1 BAXJECT II Hi-Flow device.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 500 IU / 2 ml powder for solution for injection

rurioctocog alfa pegol
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 1 000 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1 000 IU rurioctocog alfa pegol, 500 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 vial with 2 ml solvent, 1 BAXJECT II Hi-Flow device.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 1 000 IU / 2 ml powder for solution for injection

rurioctocog alfa pegol
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 000 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II HI-FLOW DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ADYNOVI
Water for injections
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU rurioctocog alfa pegol, 125 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial and 1 vial with 2 ml solvent preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use after reconstitution.
Use within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder and solvent vials preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 250

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

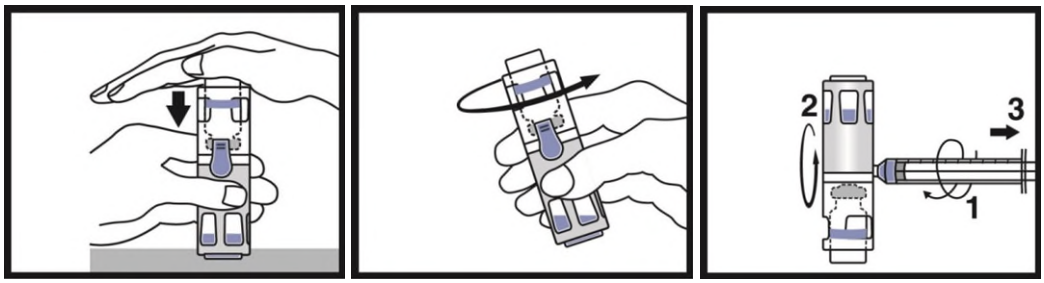
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 250

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 500 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU rurioctocog alfa pegol, 250 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial and 1 vial with 2 ml solvent preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 500 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use after reconstitution.
Use within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder and solvent vials preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 500

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

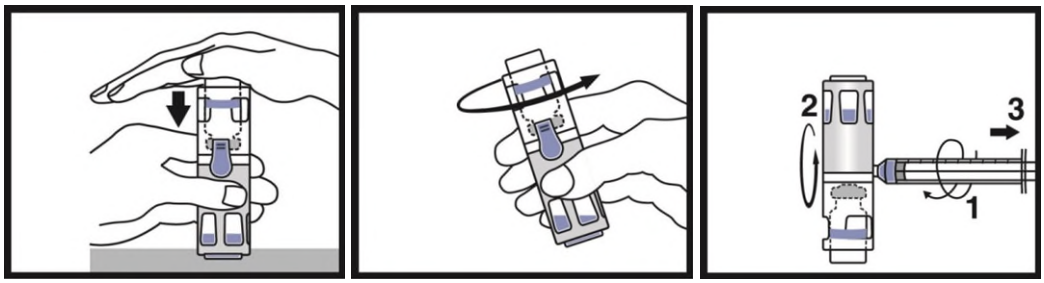
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 500

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 1 000 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1 000 IU rurioctocog alfa pegol, 500 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial and 1 vial with 2 ml solvent preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

End of 3-month room temperature storage:

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1247/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADYNOVI 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 1 000 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use after reconstitution.
Use within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder and solvent vials preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADYNOVI 1 000

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH

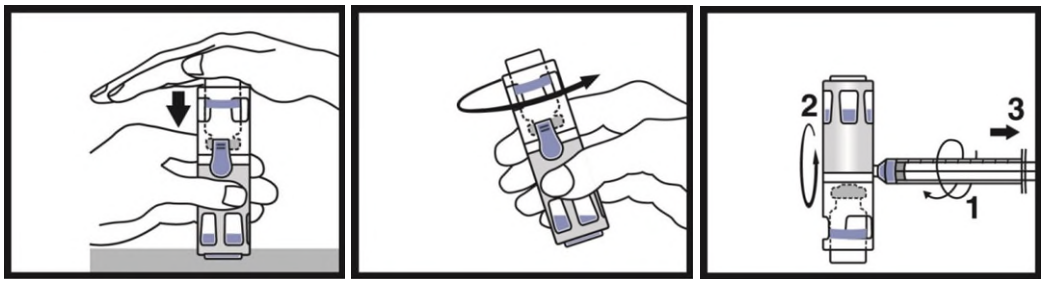
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADYNOVI 1 000

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ADYNOVI
Water for injections
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ADYNOVI 250 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 500 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 1 000 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 2 000 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 3 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADYNOVI is and what it is used for

ADYNOVI contains the active substance rurioctocog alfa pegol, pegylated human coagulation factor VIII. The human coagulation factor VIII has been modified to prolong its duration of action. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn lack of factor VIII), it is missing or not working properly.

ADYNOVI is used for the treatment and prevention of bleeding in patients from 12 years of age with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII).

2. What you need to know before you use ADYNOVI

Do not use ADYNOVI

- if you are allergic to rurioctocog alfa pegol, octocog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

It is important to keep a record of the batch number of your ADYNOVI. So, every time you get a new package of ADYNOVI, note down the date and the batch number (which is on the packaging after *{abbreviation used for batch number}*) and keep this information in a safe place.

Talk to your doctor before using ADYNOVI.

There is a rare risk that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ADYNOVI. You should be aware of the early signs of allergic reactions such as rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, general feeling of being unwell, and dizziness. These could be early symptoms of anaphylactic shock; additional symptoms may include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.

If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

If you suffer from cardiac disease, please inform your doctor, as there is an increased risk of blood clotting (coagulation) complications.

Patients developing factor VIII inhibitors
The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child´s bleeding is not being controlled with ADYNOVI, tell your doctor immediately.

Catheter-related complications
If you require a central venous access device (CVAD), risk of CVAD-related complications including local infections, presence of bacteria in the blood and catheter site thrombosis should be considered.

Children and adolescents

ADYNOVI can be used only in adolescents and adults (12 years and above). The listed warnings and precautions also apply to adolescents.

Other medicines and ADYNOVI

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Haemophilia A occurs only rarely in women. Therefore no experience regarding the use of ADYNOVI during pregnancy and breast-feeding is available.

Driving and using machines

ADYNOVI has no or negligible influence on the ability to drive or use machines.

ADYNOVI contains sodium

ADYNOVI contains up to 12.42 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.62% of the recommended maximum daily dietary intake of sodium for an adult. Depending on your body weight and your dose of ADYNOVI, you could receive multiple vials. This should be taken into consideration if you are on a low salt diet.

3. How to use ADYNOVI

Treatment with ADYNOVI will be started and supervised by a doctor who is experienced in the care of patients with haemophilia A.

Your doctor will calculate your dose of ADYNOVI depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. The frequency of administration will depend on how well ADYNOVI is working for you. Usually, the replacement therapy with ADYNOVI is a life-long treatment.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Prevention of bleeding
The usual dose of ADYNOVI is 40 to 50 IU per kg body weight, administered 2 times per week.

Treatment of bleeding
The dose of ADYNOVI is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.
If you think that the effect of ADYNOVI is insufficient, talk to your doctor.
Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Use in children and adolescents

ADYNOVI can be used only in adolescents and adults (12 years and above). The dose in adolescents is also calculated to body weight and is the same dose as for adults.

How ADYNOVI is given

ADYNOVI is usually injected into a vein (intravenously) by your doctor or nurse. You or someone else might also administer ADYNOVI as an injection, but only after receiving adequate training. Detailed instructions for self-administration are given at the end of this package leaflet.

If you use more ADYNOVI than you should

Always use ADYNOVI exactly as your doctor has told you. You should check with your doctor if you are not sure. If you inject more ADYNOVI than recommended, tell your doctor as soon as possible.

If you forget to use ADYNOVI

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using ADYNOVI

Do not stop using ADYNOVI without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If **severe, sudden allergic reactions** (anaphylactic) occur, the injection **must be stopped immediately**. You must **contact your doctor immediately** if you have any of the following early symptoms of allergic reactions:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment.

For patients who have received previous treatment with Factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens your medicine may stop working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Headache

Common side effects (may affect up to 1 in 10 people)
Nausea
Diarrhoea
Rash
Dizziness
Hives

Uncommon side effects (may affect up to 1 in 100 people)
Flushing, allergic reaction (hypersensitivity)
Factor VIII inhibitors (for patients who have received previous treatment with Factor VIII (more than 150 days of treatment))
Increase in some type of white blood cells
Infusion reaction
Redness of the eye
Adverse drug reaction of the skin

Side effects with unknown frequency (frequency cannot be estimated from the available data)
Potentially life-threatening reactions (anaphylaxis)

Additional side effects in children

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

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADYNOVI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

During the shelf life the powder vial may be kept at room temperature (up to 30 °C) for a single period not exceeding 3 months. In this case, this medicine expires at the end of this 3-month period or the expiry date printed on the product vial, whichever is earlier. Please record the end of the 3-month storage at room temperature on the outer carton. The product may not be returned to refrigerated storage after storage at room temperature. Do not refrigerate the solution after preparation.

Use the product within 3 hours once the powder is completely dissolved.

The product is for single use only. Discard any unused solution appropriately.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADYNOVI contains

- The active substance is rurioctocog alfa pegol (pegylated human coagulation factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, 1 000, 2 000 or 3 000 IU rurioctocog alfa pegol.
- The solvent vial contains 5 ml of water for injections.
- The other ingredients are mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane and polysorbate 80. See section 2 “ADYNOVI contains sodium”.

What ADYNOVI looks like and contents of the pack

ADYNOVI is provided as a powder and solvent for solution for injection (powder for solution for injection). The powder is a white to off-white crumbly powder. The solvent is a clear, colourless solution. After reconstitution, the solution is clear, colourless and free from foreign particles.

Each pack contains one powder vial, one solvent vial and a device for reconstitution (BAXJECT II Hi-Flow).

Marketing Authorisation Holder

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna

Manufacturer

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This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

Instructions for preparation and administration

Use only the solvent and the reconstitution device for preparation of the solution that are provided with each package of ADYNOVI. The powder must not be mixed with other medicinal products or solvents or used with other reconstitution devices.

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

Instructions for reconstitution

- Do not use after the expiry date stated on the labels and carton.
- Do not use if the BAXJECT II Hi-Flow device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.

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

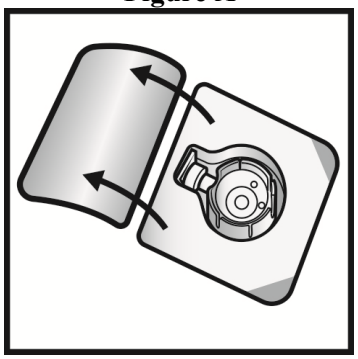


Figure B

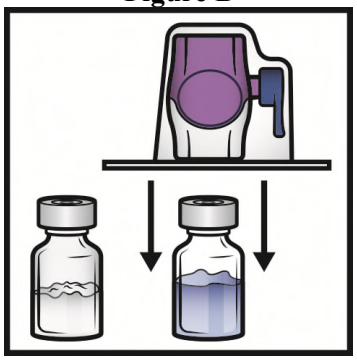


Figure C

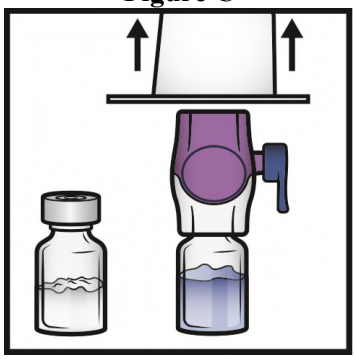


Figure D

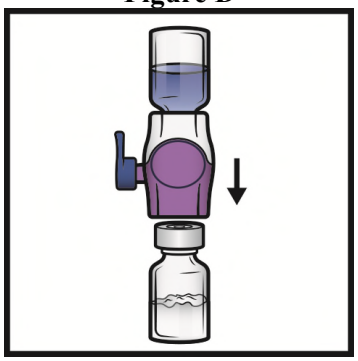


Figure E

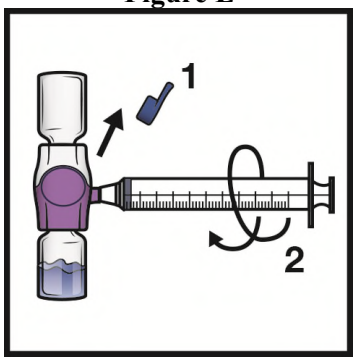
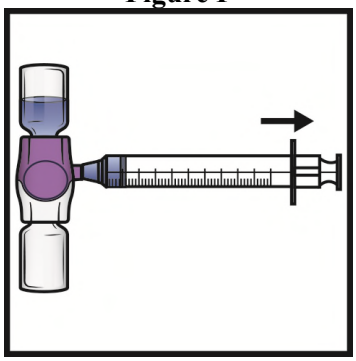


Figure F



Instructions for injection

Important note:

- Inspect the prepared solution for particulate matter and discolouration prior to administration (the solution should be clear, colourless and free from particles).
  Do not use ADYNOVI if the solution is not fully clear or not completely dissolved.

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 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 (Figure F).
3. Disconnect the syringe; attach a suitable needle and inject intravenously. If a patient is to receive more than one vial of ADYNOVI, 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 ADYNOVI with the solvent.
4. Administer over a period of up to 5 minutes (maximum infusion rate 10 ml per min).
5. Discard any unused solution appropriately.

The following information is intended for healthcare professionals only:

On demand treatment
In 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 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 ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Paediatric population
On demand treatment dosing in paediatric patients (12 to 18 years of age) is the same as for adult patients. Prophylactic treatment for patients from 12 to <18 years is the same as for adult patients. The long-term safety of ADYNOVI in children below 12 years has not yet been established. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Package leaflet: Information for the user

ADYNOVI 250 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 500 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 1 000 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 2 000 IU / 5 ml powder and solvent for solution for injection
ADYNOVI 3 000 IU / 5 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADYNOVI is and what it is used for

ADYNOVI contains the active substance rurioctocog alfa pegol, pegylated human coagulation factor VIII. The human coagulation factor VIII has been modified to prolong its duration of action. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn lack of factor VIII), it is missing or not working properly.

ADYNOVI is used for the treatment and prevention of bleeding in patients from 12 years of age with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII).

2. What you need to know before you use ADYNOVI

Do not use ADYNOVI

- if you are allergic to rurioctocog alfa pegol, octocog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

It is important to keep a record of the batch number of your ADYNOVI. So, every time you get a new package of ADYNOVI, note down the date and the batch number (which is on the packaging after *{abbreviation used for batch number}*) and keep this information in a safe place.

Talk to your doctor before using ADYNOVI.

There is a rare risk that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ADYNOVI. You should be aware of the early signs of allergic reactions such as rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, general feeling of being unwell, and dizziness. These could be early symptoms of anaphylactic shock; additional symptoms may include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.

If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

If you suffer from cardiac disease, please inform your doctor, as there is an increased risk of blood clotting (coagulation) complications.

Patients developing factor VIII inhibitors
The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child´s bleeding is not being controlled with ADYNOVI, tell your doctor immediately.

Catheter-related complications
If you require a central venous access device (CVAD), risk of CVAD-related complications including local infections, presence of bacteria in the blood and catheter site thrombosis should be considered.

Children and adolescents

ADYNOVI can be used only in adolescents and adults (12 years and above). The listed warnings and precautions also apply to adolescents.

Other medicines and ADYNOVI

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Haemophilia A occurs only rarely in women. Therefore no experience regarding the use of ADYNOVI during pregnancy and breast-feeding is available.

Driving and using machines

ADYNOVI has no or negligible influence on the ability to drive or use machines.

ADYNOVI contains sodium

ADYNOVI contains up to 12.42 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.62% of the recommended maximum daily dietary intake of sodium for an adult. Depending on your body weight and your dose of ADYNOVI, you could receive multiple vials. This should be taken into consideration if you are on a low salt diet.

3. How to use ADYNOVI

Treatment with ADYNOVI will be started and supervised by a doctor who is experienced in the care of patients with haemophilia A.

Your doctor will calculate your dose of ADYNOVI depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. The frequency of administration will depend on how well ADYNOVI is working for you. Usually, the replacement therapy with ADYNOVI is a life-long treatment.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Prevention of bleeding
The usual dose of ADYNOVI is 40 to 50 IU per kg body weight, administered 2 times per week.

Treatment of bleeding
The dose of ADYNOVI is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.
If you think that the effect of ADYNOVI is insufficient, talk to your doctor.
Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Use in children and adolescents

ADYNOVI can be used only in adolescents and adults (12 years and above). The dose in adolescents is also calculated to body weight and is the same dose as for adults.

How ADYNOVI is given

ADYNOVI is usually injected into a vein (intravenously) by your doctor or nurse. You or someone else might also administer ADYNOVI as an injection, but only after receiving adequate training. Detailed instructions for self-administration are given at the end of this package leaflet.

If you use more ADYNOVI than you should

Always use ADYNOVI exactly as your doctor has told you. You should check with your doctor if you are not sure. If you inject more ADYNOVI than recommended, tell your doctor as soon as possible.

If you forget to use ADYNOVI

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using ADYNOVI

Do not stop using ADYNOVI without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If **severe, sudden allergic reactions** (anaphylactic) occur, the injection **must be stopped immediately**. You must **contact your doctor immediately** if you have any of the following early symptoms of allergic reactions:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment.

For patients who have received previous treatment with Factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens your medicine may stop working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Headache

Common side effects (may affect up to 1 in 10 people)
Nausea
Diarrhoea
Rash
Dizziness
Hives

Uncommon side effects (may affect up to 1 in 100 people)
Flushing, allergic reaction (hypersensitivity)
Factor VIII inhibitors (for patients who have received previous treatment with Factor VIII (more than 150 days of treatment))
Increase in some type of white blood cells
Infusion reaction
Redness of the eye
Adverse drug reaction of the skin

Side effects with unknown frequency (frequency cannot be estimated from the available data)
Potentially life-threatening reactions (anaphylaxis)

Additional side effects in children

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

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADYNOVI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the blister in the outer carton in order to protect from light.

During the shelf life the powder vial may be kept at room temperature (up to 30 °C) for a single period not exceeding 3 months. In this case, this medicine expires at the end of this 3-month period or the expiry date printed on the product vial, whichever is earlier. Please record the end of the 3-month storage at room temperature on the outer carton. The product may not be returned to refrigerated storage after storage at room temperature. Do not refrigerate the solution after preparation.

Use the product within 3 hours once the powder is completely dissolved.

The product is for single use only. Discard any unused solution appropriately.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADYNOVI contains

- The active substance is rurioctocog alfa pegol (pegylated human coagulation factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, 1 000, 2 000 or 3 000 IU rurioctocog alfa pegol.
- The solvent vial contains 5 ml of water for injections.
- The other ingredients are mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane and polysorbate 80. See section 2 “ADYNOVI contains sodium”.

What ADYNOVI looks like and contents of the pack

ADYNOVI is provided as a powder and solvent for solution for injection (powder for solution for injection). The powder is a white to off-white crumbly powder. The solvent is a clear, colourless solution. After reconstitution, the solution is clear, colourless and free from foreign particles.

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This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

Instructions for preparation and administration

ADYNOVI must not be mixed with other medicinal products or solvents.

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

Instructions for reconstitution

- Do not use after the expiry date stated on the labels and carton.
- Do not use if the lid is not completely sealed on the blister
- Do not refrigerate the solution after preparation.

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 ADYNOVI 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 foreign particles.

Figure 1

Figure 2

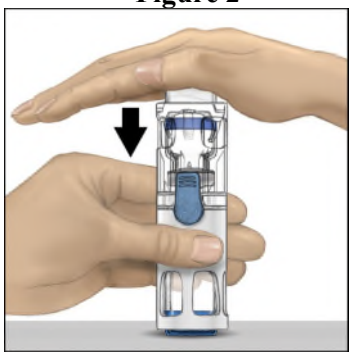


Figure 3

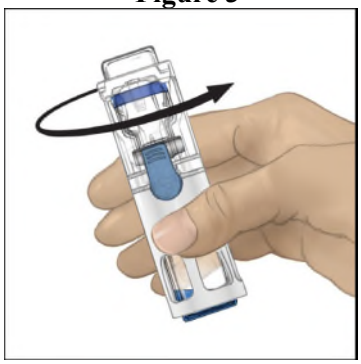


Figure 4

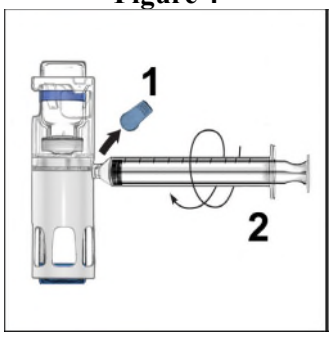
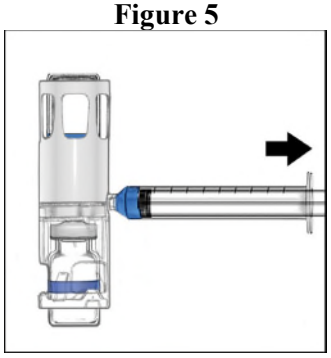


Figure 5



Instructions for injection

Antiseptic technique (clean and low-germ conditions) is required during administration.

Important note:

- Inspect the prepared solution for particulate matter and discolouration prior to administration (the solution should be clear, colourless and free from particles).
  Do not use if the solution is not fully clear or not completely dissolved.

1. Remove the blue cap from BAXJECT III (Figure 4). **Do not draw air into the syringe**.
   Connect the syringe to BAXJECT III. 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 5).
3. Disconnect the syringe; attach a butterfly needle to the syringe and inject the reconstituted solution into a vein. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute. (See section 4 "Possible side effects").
4. Discard any unused solution appropriately.

The following information is intended for healthcare professionals only:

On demand treatment
In 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 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 ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Paediatric population
On demand treatment dosing in paediatric patients (12 to 18 years of age) is the same as for adult patients. Prophylactic treatment for patients from 12 to <18 years is the same as for adult patients. The long-term safety of ADYNOVI in children below 12 years has not yet been established. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Package leaflet: Information for the user

ADYNOVI 250 IU / 2 ml powder and solvent for solution for injection
ADYNOVI 500 IU / 2 ml powder and solvent for solution for injection
ADYNOVI 1 000 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADYNOVI is and what it is used for

ADYNOVI contains the active substance rurioctocog alfa pegol, pegylated human coagulation factor VIII. The human coagulation factor VIII has been modified to prolong its duration of action. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn lack of factor VIII), it is missing or not working properly.

ADYNOVI is used for the treatment and prevention of bleeding in patients from 12 years of age with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII).

2. What you need to know before you use ADYNOVI

Do not use ADYNOVI

- if you are allergic to rurioctocog alfa pegol, octocog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

It is important to keep a record of the batch number of your ADYNOVI. So, every time you get a new package of ADYNOVI, note down the date and the batch number (which is on the packaging after *{abbreviation used for batch number}*) and keep this information in a safe place.

Talk to your doctor before using ADYNOVI.

There is a rare risk that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ADYNOVI. You should be aware of the early signs of allergic reactions such as rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, general feeling of being unwell, and dizziness. These could be early symptoms of anaphylactic shock; additional symptoms may include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.

If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

If you suffer from cardiac disease, please inform your doctor, as there is an increased risk of blood clotting (coagulation) complications.

Patients developing factor VIII inhibitors
The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child´s bleeding is not being controlled with ADYNOVI, tell your doctor immediately.

Catheter-related complications
If you require a central venous access device (CVAD), risk of CVAD-related complications including local infections, presence of bacteria in the blood and catheter site thrombosis should be considered.

Children and adolescents

ADYNOVI can be used only in adolescents and adults (12 years and above). The listed warnings and precautions also apply to adolescents.

Other medicines and ADYNOVI

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Haemophilia A occurs only rarely in women. Therefore no experience regarding the use of ADYNOVI during pregnancy and breast-feeding is available.

Driving and using machines

ADYNOVI has no or negligible influence on the ability to drive or use machines.

ADYNOVI contains sodium

ADYNOVI contains up to 12.42 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.62% of the recommended maximum daily dietary intake of sodium for an adult. Depending on your body weight and your dose of ADYNOVI, you could receive multiple vials. This should be taken into consideration if you are on a low salt diet.

3. How to use ADYNOVI

Treatment with ADYNOVI will be started and supervised by a doctor who is experienced in the care of patients with haemophilia A.

Your doctor will calculate your dose of ADYNOVI depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. The frequency of administration will depend on how well ADYNOVI is working for you. Usually, the replacement therapy with ADYNOVI is a life-long treatment.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Prevention of bleeding
The usual dose of ADYNOVI is 40 to 50 IU per kg body weight, administered 2 times per week.

Treatment of bleeding
The dose of ADYNOVI is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.
If you think that the effect of ADYNOVI is insufficient, talk to your doctor.
Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Use in children and adolescents

ADYNOVI can be used only in adolescents and adults (12 years and above). The dose in adolescents is also calculated to body weight and is the same dose as for adults.

How ADYNOVI is given

ADYNOVI is usually injected into a vein (intravenously) by your doctor or nurse. You or someone else might also administer ADYNOVI as an injection, but only after receiving adequate training. Detailed instructions for self-administration are given at the end of this package leaflet.

If you use more ADYNOVI than you should

Always use ADYNOVI exactly as your doctor has told you. You should check with your doctor if you are not sure. If you inject more ADYNOVI than recommended, tell your doctor as soon as possible.

If you forget to use ADYNOVI

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using ADYNOVI

Do not stop using ADYNOVI without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If **severe, sudden allergic reactions** (anaphylactic) occur, the injection **must be stopped immediately**. You must **contact your doctor immediately** if you have any of the following early symptoms of allergic reactions:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
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- general feeling of being unwell,
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Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment.

For patients who have received previous treatment with Factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens your medicine may stop working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Headache

Common side effects (may affect up to 1 in 10 people)
Nausea
Diarrhoea
Rash
Dizziness
Hives

Uncommon side effects (may affect up to 1 in 100 people)
Flushing, allergic reaction (hypersensitivity)
Factor VIII inhibitors (for patients who have received previous treatment with Factor VIII (more than 150 days of treatment))
Increase in some type of white blood cells
Infusion reaction
Redness of the eye
Adverse drug reaction of the skin

Side effects with unknown frequency (frequency cannot be estimated from the available data)
Potentially life-threatening reactions (anaphylaxis)

Additional side effects in children

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

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADYNOVI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

During the shelf life the powder vial may be kept at room temperature (up to 30 °C) for a single period not exceeding 3 months. In this case, this medicine expires at the end of this 3-month period or the expiry date printed on the product vial, whichever is earlier. Please record the end of the 3-month storage at room temperature on the outer carton. The product may not be returned to refrigerated storage after storage at room temperature. Do not refrigerate the solution after preparation.

Use the product within 3 hours once the powder is completely dissolved.

The product is for single use only. Discard any unused solution appropriately.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADYNOVI contains

- The active substance is rurioctocog alfa pegol (pegylated human coagulation factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, or 1 000 IU rurioctocog alfa pegol.
- The solvent vial contains 2 ml of water for injections.
- The other ingredients are mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane and polysorbate 80. See section 2 “ADYNOVI contains sodium”.

What ADYNOVI looks like and contents of the pack

ADYNOVI is provided as a powder and solvent for solution for injection (powder for solution for injection). The powder is a white to off-white crumbly powder. The solvent is a clear, colourless solution. After reconstitution, the solution is clear, colourless and free from foreign particles.

Each pack contains one powder vial, one solvent vial and a device for reconstitution (BAXJECT II Hi-Flow).

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This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

Instructions for preparation and administration

Use only the solvent and the reconstitution device for preparation of the solution that are provided with each package of ADYNOVI. The powder must not be mixed with other medicinal products or solvents or used with other reconstitution devices.

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

Instructions for reconstitution

- Do not use after the expiry date stated on the labels and carton.
- Do not use if the BAXJECT II Hi-Flow device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.

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

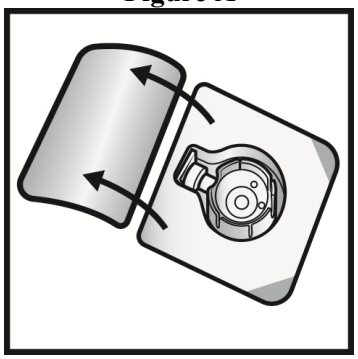


Figure B

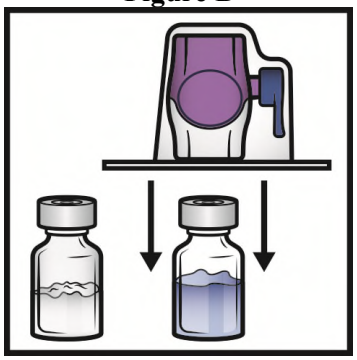


Figure C

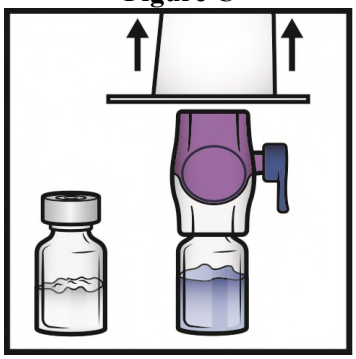


Figure D

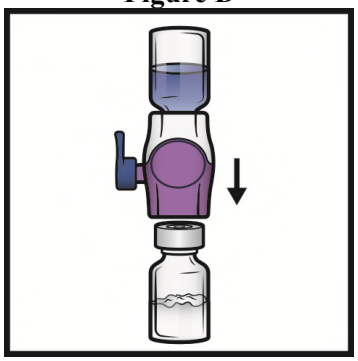


Figure E

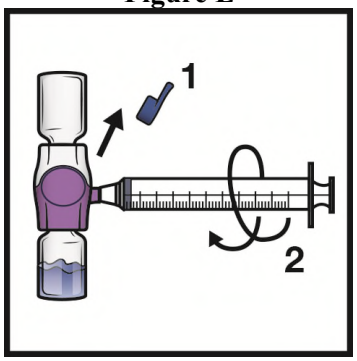
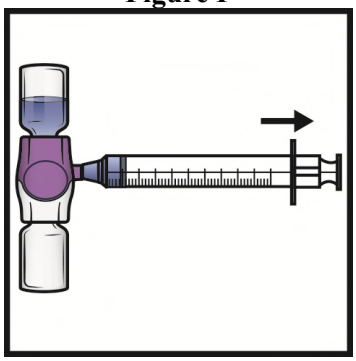


Figure F



Instructions for injection

Important note:

- Inspect the prepared solution for particulate matter and discolouration prior to administration (the solution should be clear, colourless and free from particles).
  Do not use ADYNOVI if the solution is not fully clear or not completely dissolved.

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 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 (Figure F).
3. Disconnect the syringe; attach a suitable needle and inject intravenously. If a patient is to receive more than one vial of ADYNOVI, 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 ADYNOVI with the solvent.
4. Administer over a period of up to 5 minutes (maximum infusion rate 10 ml per min).
5. Discard any unused solution appropriately.

The following information is intended for healthcare professionals only:

On demand treatment
In 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 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 ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Paediatric population
On demand treatment dosing in paediatric patients (12 to 18 years of age) is the same as for adult patients. Prophylactic treatment for patients from 12 to <18 years is the same as for adult patients. The long-term safety of ADYNOVI in children below 12 years has not yet been established. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Package leaflet: Information for the user

ADYNOVI 250 IU / 2 ml powder and solvent for solution for injection
ADYNOVI 500 IU / 2 ml powder and solvent for solution for injection
ADYNOVI 1 000 IU / 2 ml powder and solvent for solution for injection

rurioctocog alfa pegol (pegylated recombinant human coagulation factor VIII)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADYNOVI is and what it is used for

ADYNOVI contains the active substance rurioctocog alfa pegol, pegylated human coagulation factor VIII. The human coagulation factor VIII has been modified to prolong its duration of action. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn lack of factor VIII), it is missing or not working properly.

ADYNOVI is used for the treatment and prevention of bleeding in patients from 12 years of age with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII).

2. What you need to know before you use ADYNOVI

Do not use ADYNOVI

- if you are allergic to rurioctocog alfa pegol, octocog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

It is important to keep a record of the batch number of your ADYNOVI. So, every time you get a new package of ADYNOVI, note down the date and the batch number (which is on the packaging after *{abbreviation used for batch number}*) and keep this information in a safe place.

Talk to your doctor before using ADYNOVI.

There is a rare risk that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ADYNOVI. You should be aware of the early signs of allergic reactions such as rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, general feeling of being unwell, and dizziness. These could be early symptoms of anaphylactic shock; additional symptoms may include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.

If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

If you suffer from cardiac disease, please inform your doctor, as there is an increased risk of blood clotting (coagulation) complications.

Patients developing factor VIII inhibitors
The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child´s bleeding is not being controlled with ADYNOVI, tell your doctor immediately.

Catheter-related complications
If you require a central venous access device (CVAD), risk of CVAD-related complications including local infections, presence of bacteria in the blood and catheter site thrombosis should be considered.

Children and adolescents

ADYNOVI can be used only in adolescents and adults (12 years and above). The listed warnings and precautions also apply to adolescents.

Other medicines and ADYNOVI

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Haemophilia A occurs only rarely in women. Therefore no experience regarding the use of ADYNOVI during pregnancy and breast-feeding is available.

Driving and using machines

ADYNOVI has no or negligible influence on the ability to drive or use machines.

ADYNOVI contains sodium

ADYNOVI contains up to 12.42 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.62% of the recommended maximum daily dietary intake of sodium for an adult. Depending on your body weight and your dose of ADYNOVI, you could receive multiple vials. This should be taken into consideration if you are on a low salt diet.

3. How to use ADYNOVI

Treatment with ADYNOVI will be started and supervised by a doctor who is experienced in the care of patients with haemophilia A.

Your doctor will calculate your dose of ADYNOVI depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. The frequency of administration will depend on how well ADYNOVI is working for you. Usually, the replacement therapy with ADYNOVI is a life-long treatment.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Prevention of bleeding
The usual dose of ADYNOVI is 40 to 50 IU per kg body weight, administered 2 times per week.

Treatment of bleeding
The dose of ADYNOVI is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.
If you think that the effect of ADYNOVI is insufficient, talk to your doctor.
Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Use in children and adolescents

ADYNOVI can be used only in adolescents and adults (12 years and above). The dose in adolescents is also calculated to body weight and is the same dose as for adults.

How ADYNOVI is given

ADYNOVI is usually injected into a vein (intravenously) by your doctor or nurse. You or someone else might also administer ADYNOVI as an injection, but only after receiving adequate training. Detailed instructions for self-administration are given at the end of this package leaflet.

If you use more ADYNOVI than you should

Always use ADYNOVI exactly as your doctor has told you. You should check with your doctor if you are not sure. If you inject more ADYNOVI than recommended, tell your doctor as soon as possible.

If you forget to use ADYNOVI

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using ADYNOVI

Do not stop using ADYNOVI without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If **severe, sudden allergic reactions** (anaphylactic) occur, the injection **must be stopped immediately**. You must **contact your doctor immediately** if you have any of the following early symptoms of allergic reactions:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment.

For patients who have received previous treatment with Factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens your medicine may stop working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Headache

Common side effects (may affect up to 1 in 10 people)
Nausea
Diarrhoea
Rash
Dizziness
Hives

Uncommon side effects (may affect up to 1 in 100 people)
Flushing, allergic reaction (hypersensitivity)
Factor VIII inhibitors (for patients who have received previous treatment with Factor VIII (more than 150 days of treatment))
Increase in some type of white blood cells
Infusion reaction
Redness of the eye
Adverse drug reaction of the skin

Side effects with unknown frequency (frequency cannot be estimated from the available data)
Potentially life-threatening reactions (anaphylaxis)

Additional side effects in children

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

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADYNOVI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the blister in the outer carton in order to protect from light.

During the shelf life the powder vial may be kept at room temperature (up to 30 °C) for a single period not exceeding 3 months. In this case, this medicine expires at the end of this 3-month period or the expiry date printed on the product vial, whichever is earlier. Please record the end of the 3-month storage at room temperature on the outer carton. The product may not be returned to refrigerated storage after storage at room temperature. Do not refrigerate the solution after preparation.

Use the product within 3 hours once the powder is completely dissolved.

The product is for single use only. Discard any unused solution appropriately.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADYNOVI contains

- The active substance is rurioctocog alfa pegol (pegylated human coagulation factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, or 1 000 IU rurioctocog alfa pegol.
- The solvent vial contains 2 ml of water for injections.
- The other ingredients are mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris(hydroxymethyl)aminomethane and polysorbate 80. See section 2 “ADYNOVI contains sodium”.

What ADYNOVI looks like and contents of the pack

ADYNOVI is provided as a powder and solvent for solution for injection (powder for solution for injection). The powder is a white to off-white crumbly powder. The solvent is a clear, colourless solution. After reconstitution, the solution is clear, colourless and free from foreign particles.

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Manufacturer

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This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

Instructions for preparation and administration

ADYNOVI must not be mixed with other medicinal products or solvents.

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

Instructions for reconstitution

- Do not use after the expiry date stated on the labels and carton.
- Do not use if the lid is not completely sealed on the blister
- Do not refrigerate the solution after preparation.

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 ADYNOVI 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 foreign particles.

Figure 1

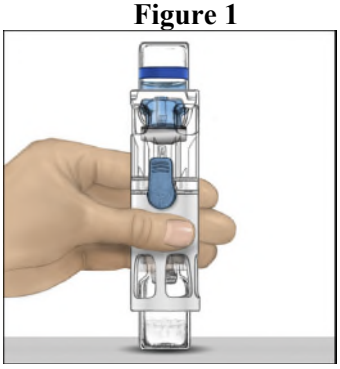
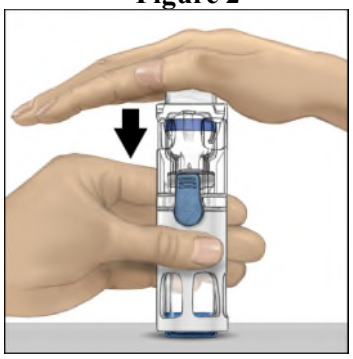


Figure 2



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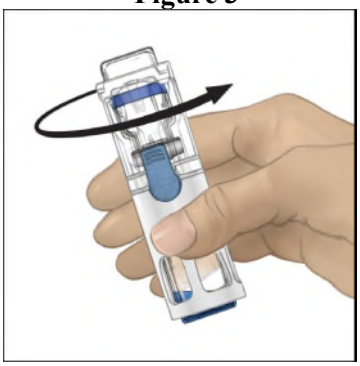


Figure 4

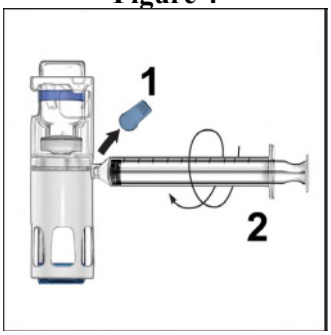
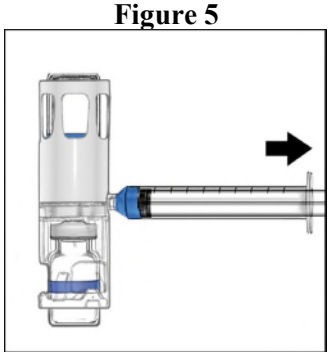


Figure 5



Instructions for injection

Antiseptic technique (clean and low-germ conditions) is required during administration.

Important note:

- Inspect the prepared solution for particulate matter and discolouration prior to administration (the solution should be clear, colourless and free from particles).
  Do not use if the solution is not fully clear or not completely dissolved.

1. Remove the blue cap from BAXJECT III (Figure 4). **Do not draw air into the syringe**.
   Connect the syringe to BAXJECT III. 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 5).
3. Disconnect the syringe; attach a butterfly needle to the syringe and inject the reconstituted solution into a vein. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute. (See section 4 "Possible side effects").
4. Discard any unused solution appropriately.

The following information is intended for healthcare professionals only:

On demand treatment
In 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 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 ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Paediatric population
On demand treatment dosing in paediatric patients (12 to 18 years of age) is the same as for adult patients. Prophylactic treatment for patients from 12 to <18 years is the same as for adult patients. The long-term safety of ADYNOVI in children below 12 years has not yet been established. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.