# 1 PRODUCT NAME

**ADYNOVATE** 250 IU powder for injection with diluent
**ADYNOVATE** 500 IU powder for injection with diluent
**ADYNOVATE** 750 IU powder for injection with diluent
**ADYNOVATE** 1000 IU powder for injection with diluent
**ADYNOVATE** 1500 IU powder for injection with diluent
**ADYNOVATE** 2000 IU powder for injection with diluent
**ADYNOVATE** 3000 IU powder for injection with diluent

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rurioctocog alfa pegol

**ADYNOVATE** [rurioctocog alfa pegol, Recombinant Coagulation Factor VIII (rch), PEGylated] is supplied in single-use vials containing nominal potencies of 250, 500, 750, 1000, 1500, 2000 or 3000 International Units (IU) per vial for reconstitution with 5 mL or 2 mL sterile water for injections.

The 5 mL diluent of water for injections is available for **ADYNOVATE** 250, 500, 750, 1000, 1500, 2000, or 3000 IU.

The 2 mL diluent of water for injections is available for **ADYNOVATE** 250, 500, 750, 1000 or 1500 IU.

*Excipient(s) with known effect*

Each vial of **ADYNOVATE** contains 0.45 mmol (10 mg) sodium, see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

For the full list of excipients, see section 6.1.

*Biological origin of the active substance*

**ADYNOVATE** [rurioctocog alfa pegol, Recombinant Coagulation Factor VIII (rch), PEGylated] is a full-length form of human coagulation factor VIII (parent molecule: **ADVATE** [octocog alfa, Recombinant Human Factor VIII (rch)] with an extended half-life. **ADYNOVATE** is comprised of 2,332 amino acids [molecular weight (MW) 280kDa] covalently conjugated with a polyethylene glycol (PEG) reagent (MW 20kDa). The therapeutic activity of **ADYNOVATE** is derived from **ADVATE**, which is produced by recombinant DNA technology from a Chinese hamster ovary cell line. The **ADVATE** molecule is then covalently conjugated with the PEG reagent, which targets lysine residues. The PEG moiety is conjugated to the **ADVATE** molecule to increase the plasma half-life through the reduction of the LRP-1 receptor-mediated clearance of the factor VIII molecule.

# 3 PHARMACEUTICAL FORM

Powder for intravenous injection with diluent.

**ADYNOVATE** is formulated as a sterile, non-pyrogenic, white to off-white, lyophilised powder, for intravenous injection after reconstitution with water for injections.

For appearance after reconstitution, see sections 4.2 and 6.6.

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

**ADYNOVATE,** a long-acting antihaemophilic factor (recombinant), is indicated in haemophilia A (congenital factor VIII deficiency) patients for:

- Control and prevention of bleeding episodes
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Perioperative management (surgical prophylaxis).

**ADYNOVATE** is not indicated for the treatment of von Willebrand disease.

## 4.2 Dose and method of administration

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

*Treatment monitoring*

During the course of treatment, appropriate determination of factor VIII levels (by one-stage clotting or chromogenic assays) 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.

*Dosage*

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 is related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in International Units (relative to an International Standard for factor VIII in plasma).

One 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 1IU factor VIII per kg body weight raises the plasma factor VIII activity by 2IU/dL. The required dose is determined using the following formula:

**Required 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, the 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 for 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<br>Including tooth extraction. | 30 – 60 | Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved. |
| Major | 80 – 100 (pre- and postoperative) | Repeat injections every 8 to 24 hours (6 to 24 hours for patients under the age of 6) 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 per kg bodyweight of **ADYNOVATE** twice weekly in 3 to 4 day intervals. Dose and/or frequency should be adjusted to provide the necessary coverage to prevent bleeding. In some cases, doses up to 60IU per kg can be used.

*Paediatric population*

On demand treatment dosing in paediatric patients (0 to < 12 years of age) does not differ from adult patients. Higher doses or more frequent dosing may be required in some children.

For prophylactic therapy in patients under the age of 12, the recommended dose is 40 to 60IU per kg bodyweight of **ADYNOVATE** twice weekly in 3 to 4 day intervals. In some cases, doses up to 80IU per kg can be used.

*Method of administration*

**ADYNOVATE** should be administered via the intravenous route.

**ADYNOVATE** should be administered at room temperature not more than 3 hours after reconstitution.

Reconstituted products should be visually inspected for particulate matter and discolouration prior to administration. The solution should be clear to colourless. Do not administer if particulate matter or discolouration or cloudiness is found.

**ADYNOVATE** does not contain antimicrobial preservative. It is for single use in one patient only. Discard any residue.

The rate of administration should be determined to ensure the comfort of the patient up to a maximum of 10mL/min.

After reconstitution, the solution is clear, colourless, free from foreign particles and has a pH of 6.7 to 7.3. The osmolality is ≥ 380m Osmol/kg.

For instructions on reconstitution of **ADYNOVATE** powder for injection, before administration, see section 6.6.

*Administration*

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

*Administration Steps*

1. Remove the blue cap from the BAXJECT II HI-FLOW/BAXJECT III device. Connect the syringe to the BAXJECT II HI-FLOW/BAXJECT III device. Use of a Luer-lock syringe is recommended. Do not inject air.
2. Turn the system upside down (**ADYNOVATE** vial now on top). Draw the factor concentrate into the syringe by pulling the plunger back slowly.
3. Disconnect the syringe; attach a suitable needle and inject intravenously. If a patient is to receive more than one vial of **ADYNOVATE**, the contents of multiple vials may be drawn into the same syringe.
   A separate BAXJECT II HI-FLOW device is required to reconstitute each vial of **ADYNOVATE** with the diluent.
4. Administer **ADYNOVATE** over a period of less than or equal to 5 minutes (maximum infusion rate 10 mL per min).

## 4.3 Contraindications

Known life-threatening hypersensitivity reaction, including anaphylaxis, to ADYNOVATE, to the parent molecule **ADVATE**, to mouse or hamster protein, or other constituents of **ADYNOVATE** (see excipients listed in section 6.1).

## 4.4 Special warnings and precautions for use

*Hypersensitivity*

Hypersensitivity reactions can occur following administration of **ADYNOVATE**. Allergic-type hypersensitivity reactions including anaphylaxis have been reported with recombinant antihaemophilic FVIII products, including ADYNOVATE and its parent molecule, ADVATE. Immediately discontinue administration and initiate treatment as clinically appropriate if hypersensitivity reactions occur.

*Inhibitor formation*

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

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

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.

*Cardiovascular events*

In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

*Catheter-related complications in treatment*

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

*Excipient related considerations*

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

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

*Paediatric use*

The listed precautions apply both to adults and children.

*Use in the elderly*

Clinical studies of **ADYNOVATE** did not include subjects aged 65 and over.

## 4.5 Interaction with other medicines 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

*Fertility*

The effects of **ADYNOVATE** on fertility have not been established.

*Pregnancy*

Pregnancy Category B2. The safety of **ADYNOVATE** for use in pregnant women has not been established. Animal reproduction studies with recombinant factor VIII, including **ADYNOVATE**, have not been conducted. Healthcare professionals should balance the potential risks and only prescribe **ADYNOVATE** if clearly needed.

*Lactation*

The safety of **ADYNOVATE** for use in lactating women has not been established. It is not known if **ADYNOVATE** or its metabolites are excreted in human milk. Healthcare professionals should

balance the potential risks and only prescribe **ADYNOVATE** to a breast feeding woman if clearly needed.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

*Summary of the safety profile*

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

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

*Tabulated list of adverse reactions*

The safety of **ADYNOVATE** has been evaluated in 6 completed multi-centre, prospective, open label clinical trials and 1 ongoing study in 365 previously treated and untreated patients with severe haemophilia A (FVIII < 1% of normal), who received at least one dose of **ADYNOVATE**. Table 2 lists the adverse drug reactions (ADRs) reported during clinical studies.

**Table 2: Adverse drug reactions (assessed by Sponsor) following treatment**

| MedDRA System Organ Class | Preferred MedDRA term | Number & rate by subject[a] (N = 365) n (%) | Frequency category[c] | Number & rate by infusion[b] (N = 74,487) n (%) | Frequency category[c] |
|---|---|---|---|---|---|
| **BLOOD AND LYMPHATIC DISORDERS** | Factor VIII inhibition | 1 (0.274) | Uncommon | 1 (0.001) | Very Rare |
| **GASTROINTESTINAL DISORDERS** | Diarrhoea | 25 (6.849) | Common | 31 (0.042) | Rare |
| | Nausea | 8 (2.192) | Common | 11 (0.015) | Rare |
| **EYE DISORDERS** | Ocular hyperaemia | 3 (0.822) | Uncommon | 3 (0.004) | Very Rare |
| **IMMUNE SYSTEM DISORDERS** | Hypersensitivity | 2 (0.548) | Uncommon | 2 (0.003) | Very Rare |
| **NERVOUS SYSTEM DISORDERS** | Headache | 41 (11.233) | Very Common | 67 (0.090) | Rare |
| | Dizziness | 7 (1.918) | Common | 7 (0.009) | Very Rare |
| **SKIN AND SUBCUTANEOUS TISSUE DISORDERS** | Rash | 10 (2.740) | Common | 11 (0.015) | Rare |
| | Urticaria | 7 (1.918) | Common | 7 (0.009) | Very Rare |
| | Rash Pruritic | 1 (2.740) | Uncommon | 1 (<0.01) | Very Rare |

| MedDRA System Organ Class | Preferred MedDRA term | Number & rate by subject[a] (N = 365) n (%) | Frequency category[c] | Number & rate by infusion[b] (N = 74,487) n (%) | Frequency category[c] |
|---|---|---|---|---|---|
| **VASCULAR DISORDERS** | Flushing | 1 (0.274) | Uncommon | 1 (0.01) | Very Rare |
| **INVESTIGATIONS** | Eosinophil count increased | 2 (0.548) | Uncommon | 4 (0.005) | Very Rare |
| **INVESTIATIONS INJURY, POISONING AND PROCEDURAL COMPLICATIONS** | Infusion related reaction | 2 (0.548) | Uncommon | 2 (0.003) | Very Rare |

[a] Rate by subject = total number of subjects experiencing the AE (related and unrelated) divided by total number of subjects (N) and multiplied by 100.
[b] Rate by infusions = total number of adverse events (related and unrelated) divided by total number of infusions (N) and multiplied by 100.
Frequencies presented were calculated using all adverse events, related and unrelated.
[c] Frequencies has been evaluated using the following criteria: 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).

*Description of selected adverse reactions*

Immunogenicity: Clinical trial subjects were monitored for neutralising (inhibitory) antibodies to FVIII. None of the subjects who participated in one or more of 6 completed clinical trials in previously treated patients (PTPs) developed persistent neutralising (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 personalised prophylaxis targeting a FVIII level of 8-12%.

Immunogenicity was also evaluated by measuring the development of binding IgG and IgM antibodies against factor VIII, PEGylated (PEG)-factor VIII, PEG and Chinese hamster ovary (CHO) protein using validated ELISA assays. No subject developed persistent treatment-emergent binding antibodies against FVIII, PEG-FVIII or PEG. Binding antibodies that were detected prior to exposure to **ADYNOVATE**, that transiently developed during the trials or were still detectable at study completion or data cut-off could not be correlated to any impaired treatment efficacy. There was no causal relationship between observed adverse events and binding antibodies except in one subject, a PUP where a causal relationship can neither be confirmed nor ruled out based on available data. No subject had pre-existing or treatment-emergent antibodies to CHO protein.

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

The detection of antibodies that are reactive to factor FVIII is highly dependent on many factors, including: the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to rurioctocog alfa pegol with the incidence of antibodies to other products may be misleading.

Hypersensitivity: Hypersensitivity reactions are possible with **ADYNOVATE** (see Table 2). Allergic-type hypersensitivity reactions, including anaphylaxis, are rare complications of treatment with recombinant factor VIII, including the parent molecule, **ADVATE**.

*Paediatric population*

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

*Class reactions*

Adverse reactions include: Anaphylactic reaction, Hypersensitivity, Factor VIII inhibition.

*Post-marketing Adverse Reactions*

Following is a list of ADRs which have been observed in post-marketing:

Immune System Reactions: Anaphylactic reaction

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions **https://nzphvc.otago.ac.nz/reporting/**

### 4.9 Overdose

There has been no reported clinical adverse experience that could be associated with overdosage.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:* Blood and blood forming organs, antihemorrhagics, vitamin K and other hemostasis, blood coagulation factors, coagulation factor VIII.

*ATC Code:* B02BD02.

*Mechanism of action*

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

*Clinical trials*

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

Subjects received either prophylactic treatment (n = 120) with **ADYNOVATE** at a dose of 40 - 50IU per kg twice weekly or on-demand treatment (n = 17) with **ADYNOVATE** at a dose of 10 - 60IU per kg for a 6-month period. The mean (SD) dose per prophylaxis infusion was 44.4(3.9)IU per kg with a median dosing interval of 3.6 days. There were 91 out of 98 (93%) subjects previously treated

prophylactically prior to enrolment, who experienced a reduction in dosing frequency during routine prophylaxis in the study, with a median reduction of 33.7% (approximately one more day between doses). One hundred eighteen of 120 (98%) prophylaxis subjects remained on the starting recommended regimen without dose adjustment, and 2 subjects increased their dose to 60IU/kg during prophylaxis due to bleeding in target joints.

On-demand treatment and control of bleeding episodes

A total of 518 bleeding episodes were treated with **ADYNOVATE** in the per-protocol population, i.e. dosed according to the protocol specific dosing requirements. Of these, 361 bleeding episodes (n = 17 subjects) occurred in the on-demand arm & 157 (n = 61 subjects) occurred in the prophylaxis arm. The median total dose to treat all bleeding episodes in the per-protocol population was 30.9 (Q1: 21.6; Q3: 45.3)IU per kg. The median dose per infusion to treat all bleeding episodes in the per-protocol population was 29 (Q1: 20.0; Q3: 39.2)IU per kg. The median dose per infusion to treat a minor, moderate, or severe/major bleeding episode in the per-protocol population was 25.5 (Q1: 16.9; Q3: 37.6)IU/kg, 30.9 (Q1: 23.0; Q3: 43.1)IU/kg, or 36.4 (Q1: 29.0; Q3: 44.5)IU/kg, respectively.

A total of 591 bleeding episodes were treated with **ADYNOVATE** in the treated population, which was identical to the safety analysis set of subjects assigned to routine prophylaxis or on-demand treatment with **ADYNOVATE** and who received at least one dose of the product. Of these, 361 bleeding episodes (n = 17 subjects) occurred in the on-demand arm and 230 bleeding episodes (n = 75 subjects) occurred in the routine prophylaxis arm. Efficacy in control of bleeding episodes is summarised in Table 3.

**Table 3: Summary of efficacy in control of bleeding (Treated Population)**

| **Bleeding Episode Aetiology** | | **All** | **Joint** | **Non-joint** |
|---|---|---|---|---|
| Number of bleeds treated | | 591 | 455 | 136 |
| Number of infusions to treat bleeding episodes | 1 infusions: | 85.4% | 85.9% | 83.8% |
| | 2 infusions: | 10.8% | 10.8% | 11.0% |
| | Total (1 or 2 infusions) | 96.2% | 96.7% | 94.8% |
| Rate of success to treat bleeding episodes* | Excellent or good | 95.3% | 95.8% | 93.4% |
| *Excellent defined as full relief of pain and objective signs of bleeding cessation; Good defined as definite pain relief and/or improvement in signs of bleeding; Fair defined as probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution; None defined as no improvement or condition worsened. | | | | |

Routine prophylaxis

A total of 120 subjects (treated population) received a twice a week regimen in the prophylaxis arm, and an additional 17 subjects were treated episodically in the on- demand arm. In the treated population, the median [mean] annualised bleed rate (ABR) in the on-demand treatment arm was 41.5 [40.8] compared to 1.9 [4.7] while on a twice a week prophylaxis regimen (Table 4). In the per-protocol population, the median [mean] annualised bleed rate (ABR) in the on-demand treatment arm was 41.5 [40.8] compared to 1.9 [3.7] while on a twice a week prophylaxis regimen. Using a negative binomial model to estimate the ABR, there was a significant reduction in the ABR ($p < 0.0001$) for subjects in the prophylaxis arm compared to the on-demand arm.

**Table 4: Annualised bleed rate by treatment for ≥ 12 years of age (Treated Population)**

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

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

Routine prophylaxis study in paediatric subjects (<12 years of age)

The safety and efficacy of **ADYNOVATE** was evaluated in a total of 73 paediatric PTPs with severe haemophilia A, of which 66 subjects were dosed (32 subjects aged < 6 years and 34 subjects aged 6 to < 12 years) in a separate paediatric study. The prophylactic regimen was 40 to 60IU/kg of **ADYNOVATE** twice a week. The median [mean] overall ABR was 2.0 [3.61] for the 66 subjects in the treated population and the median [mean] ABRs for spontaneous and joint bleeding episodes were both 0 [1.18 and 1.12, respectively]. Of the 66 subjects treated prophylactically, 25 (38%) experienced no bleeding episodes, 44 (67%) experienced no spontaneous bleeding episodes, and 48 (73%) experienced no joint bleeding episodes.

Of the 70 bleeding episodes observed during the 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 or good in 63 out of 70 (90%) bleeding episodes. The definitions of excellent or good in the paediatric study were unchanged as compared to the previously conducted prophylaxis study in adolescent and adult subjects.

Long-term prophylaxis treatment in paediatric and adult subjects

The long-term safety and efficacy of **Adynovate** 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 **Adynovate** studies or were naive to **Adynovate**. 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 personalised (pharmacokinetically-tailored) prophylactic regimen received doses up to 80 IU/kg per infusion that targeted FVIII trough levels of ≥ 3% at least twice weekly. Subjects aged ≥ 12 years on a twice-weekly regimen who had zero spontaneous bleeds during a consecutive 6-month period could switch to fixed-dose prophylaxis every 5 days. If these subjects continued to have zero spontaneous bleeds for an additional 6 months, they were eligible for dosing every 7 days. Overall, exposure was long-term at a mean (SD) of 195.4 (101.57) prophylactic exposure days (EDs) per subject. ABR per prophylactic regimen, bleeding site and etiology are presented in Table 5.

**Table 5: Annualised bleed rate (ABR) by prophylactic regimen (ITT population)**

| **Bleeding site eiology** | 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] |
| Non-joint | 1.0 [0.77 - 1.21] | 1.0 [0.60 - 1.55] | 0.8 [0.41 - 1.51] | 1.2 [0.65 - 2.10] |
| 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] |
| Traumatic | 1.0 [0.83 - 1.28] | 0.7 [0.45 - 0.99] | 0.9 [0.41 - 1.91] | 1.6 [1.03 - 2.50] |
| Point estimates and 95% confidence intervals obtained from a generalised linear model fitting a negative binomial distribution with logarithmic link function.<br>Subjects receiving doses in multiple regimens are included in summaries for multiple regimens.<br>N = Number of subjects included in the analysis<br>[a]Targeting FVIII activity trough levels of ≥ 3% of normal | | | | |

Long-term haemostatic efficacy was evaluated in 910 bleeding episodes treated with **Adynovate** 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. Overall, during long-term exposure at a mean (SD) of 195.4 (101.57) prophylactic EDs per subject (median 208.5 EDs), 16.7% (36/216) of subjects had no bleeding episodes during this extended period.

Haemostatic efficacy of long-term treatment was reflected in Patient Reported Outcomes (PROs). Among the study population ≥18 years who completed the Haemo-SYM questionnaire at baseline and study completion, 60.4% (55/91) reported an improvement in the total Haemo-SYM score (p-value = 0.0023).

Personalised prophylaxis PROPEL clinical trial in adolescents and adult subjects

The safety and efficacy of **Adynovate** was evaluated in a prospective, randomised, open-label multicenter study in 121 (115 randomised) adolescents (12-18 years old) and adult PTPs with severe haemophilia A for a 12 months treatment period. The study compared 2 PK-guided prophylactic dosing regimens of **Adynovate** 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.

Although the primary endpoint was not reached, the proportion of subjects in the ITT patient population who had a total ABR of 0 during the second 6-month period was higher in the 8 - 12% trough level arm (62%; 95% CI=49% to 75%) than in the 1-3% trough level arm (42%; 95% CI=29% to 55%) with a p-value of 0.0545. In the per-protocol population of subjects who completed the second 6-month of prophylactic treatment and had no major deviations from the protocol affecting the study results, the difference between the proportions of subjects with a total ABR of 0 was significant, favouring the 8-12% trough arm with a point estimate (95% CI) of 2.423 (0.463; 4.383) and a p-value of 0.0154. The proportions of randomised subjects with total ABRs, spontaneous ABRs

and spontaneous annualised joint bleeding rates (AJBRs) of 0 during the second 6-month study period are presented in Table 6.

**Table 6: Annualised bleed rate (ABR) of 0, Second 6-month Study Period**

| | **Proportion of subjects without bleeding 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 = Annualised bleeding rate, AJBR = Annualised joint bleeding rate<br>Annualised bleeding rate determined by dividing the number of bleeds by observation period in years. | | |
| | **Proportion of subjects without bleeding 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 = Annualised bleeding rate, AJBR = Annualised joint bleeding rate<br>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.<br>Annualised bleeding rate determined by dividing the number of bleeds by observation period in years. | | |

Total ABRs, spontaneous ABRs and spontaneous AJBRs during the second 6-month study period are presented in Table 7.

**Table 7: Annualised 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 = Annualised bleeding rate, AJBR = Annualised joint bleeding rate<br>Annualised 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 | 2.8 (3.0) | 0.0 | 1.2 (2.4) |
| **Spontaneous ABR** | 0.0 | 1.7 (2.5) | 0.0 | 0.6 (1.5) |
| **Spontaneous AJBR** | 0.0 | 1.2 (2.0) | 0.0 | 0.4 (1.4) |
| ABR = Annualised bleeding rate, AJBR = Annualised joint bleeding rate<br>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.<br>Annualised 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 **Adynovate**; 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.

Haemostatic efficacy in the prevention and treatment of bleeds was reflected in the patient-reported outcomes with improvements between baseline and study completion in the Short Form-36 Physical Component Score administered to subjects ≥14 years of age, and in the Haemo-SYM bleed and pain severity scores administered to subjects ≥18 years of age.

Perioperative management study

A total of 26 procedures, 21 major and 5 minor were performed in 21 unique subjects between 16 and 61 years of age. The 21 major surgeries comprised 14 orthopaedic (3 knee replacements, 1 hip replacement, 1 hip replacement revision, 3 arthroscopic synovectomies, 1 elbow cyst extirpation, 1 needle removal from the elbow, 3 alloplastic knee surgeries and 1 Achilles tendon reconstruction) and 7 non-orthopaedic procedures (5 dental, 1 cardiovascular and 1 abdominal). The 5 minor surgeries comprised 2 dermatological, 1 orthopaedic and 1 dental procedure, and 1 radio synovectomy. The preoperative loading dose ranged from 36 IU/kg to 99 IU/kg (median: 60 IU/kg) and the total postoperative dose ranged from 23 IU/kg to 769 IU/kg (median: 183 IU/kg). The median total dose for major orthopaedic surgeries was 629 IU/kg (range: 464-1457 IU/kg, the median total dose for major non-orthopaedic surgeries was 489 IU/kg (range: 296-738 IU/kg) and the median total dose for minor surgeries was 120 IU/kg (range: 104-151 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 24 (21 major, 3 minor) procedures with available assessments.

## 5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of **ADYNOVATE** were evaluated in a crossover study with **ADVATE** in 26 subjects (18 adults and 8 adolescents) and in 22 subjects (16 adults and 6 adolescents) after 6 months of treatment with **ADYNOVATE**. A single dose of 45 ± 5IU/kg was utilised for both products. In the paediatric study, a single dose of 60 ± 5IU/kg was utilised for both **ADVATE** and **ADYNOVATE** to evaluate PK in 31 paediatrics subjects (< 6 years and 6 to < 12 years of age). Plasma factor VIII activity was measured by the one-stage clotting assay & chromogenic assay as shown in Tables 8-11.

**ADYNOVATE** has an extended half-life of 1.4 to 1.5-fold compared to recombinant full-length human coagulation factor VIII (**ADVATE**) in the adolescent and adult population, as determined based on one-stage clotting and chromogenic assays, respectively. The half-life extension in the paediatric population was 1.3 to 1.5 fold using both the one stage clotting and chromogenic assays. An increase in AUC and a decrease in clearance as compared to the parent molecule, **ADVATE**, 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.

**Table 8. Pharmacokinetic parameters in adults using the one-stage clotting assay (arithmetic mean ± SD)**

| **PK Parameters** | **ADVATE N = 18** | **ADYNOVATE N = 18** |
|---|---|---|
| **Design** | **Individual PK with full sampling[a]** | |
| Terminal half-life [h] | 10.83 ± 2.08 | 14.69 ± 3.79 |
| MRT [h] | 13.41 ± 3.00 | 20.27 ± 5.23 |
| $C_L$ [mL/(kg·h)] | 3.88 ± 1.24 | 2.27 ± 0.84 |
| Incremental Recovery [(IU/dK)/(IU/kg)] | 2.57 ± 0.43 | 2.66 ± 0.68 |
| $AUC_{0\text{-}Inf}$ [IU·h/dL] | 1286 ± 390 | 2264 ± 729 |
| $V_{SS}$ [dL/kg] | 0.50 ± 0.11 | 0.43 ± 0.11 |
| $C_{max}$ [IU/dL] | 117 ± 20 | 122 ± 29 |
| $T_{max}$ [h] | 0.33 ± 0.19 | 0.46 ± 0.29 |

Abbreviations: CI: confidence interval; $C_{max}$: maximum observed activity; AUC: area under the curve; MRT: mean residence time; $C_L$: clearance; $V_{ss}$: body weight adjusted volume of distribution at steady-state, $T_{max}$: time to reach the maximum concentration. [a] Individual PK with 12 post-infusion samples.

**Table 9. Pharmacokinetic parameters in adults using the chromogenic assay (arithmetic mean ± SD)**

| PK Parameters | ADVATE N = 18 | ADYNOVATE N = 18 |
|---|---|---|
| **Design** | **Individual PK with full sampling[a]** | |
| Terminal half-life [h] | 10.43 ± 3.41 | 15.01 ± 3.90 |
| MRT [h] | 13.00 ± 3.87 | 19.70 ± 5.05 |
| $C_L$ [mL/(kg·h)] | 3.95 ± 1.37 | 1.97 ± 0.70 |
| Incremental Recovery [(IU/dK)/(IU/kg)] | 2.74 ± 0.39 | 3.16 ± 0.68 |
| $AUC_{0\text{-}Inf}$ [IU·h/dL] | 1281 ± 424 | 2589 ± 849 |
| $V_{SS}$ [dL/kg] | 0.48 ± 0.14 | 0.37 ± 0.08 |
| $C_{max}$ [IU/dL] | 125 ± 17 | 145 ± 29 |
| $T_{max}$ [h] | 0.26 ± 0.12 | 0.32 ± 0.16 |

Abbreviations: CI: confidence interval; $C_{max}$: maximum observed activity; AUC: area under the curve; MRT: mean residence time; $C_L$: clearance; $V_{ss}$: body weight adjusted volume of distribution at steady-state, $T_{max}$: time to reach the maximum concentration. [a] Individual PK with 12 post-infusion samples.

*Paediatric pharmacokinetics*

Pharmacokinetic parameters calculated from 39 subjects less than 18 years of age (intent-to-treat analysis) are available for 14 children (1 to less than 5 years), 17 older children (6 to less than 12 years) and 8 adolescent subjects (12 to < 18 years of age), as shown in Table 10. The mean clearance (based on body weight) of **ADYNOVATE** was higher and the mean half-life was lower in children less than 12 years of age than adults. A higher dose may be required in children less than 12 years of age.

**Table 10. Summary of pharmacokinetic parameters of ADYNOVATE for paediatrics using the one-stage clotting assay**

| Parameter (mean ± standard deviation) | Paediatric Study | | Pivotal Study in adolescents & adults |
|---|---|---|---|
| | < 6 years (n = 14) | 6 to < 12 years (n = 17) | 12 to < 18 years (n = 8) |
| **Design** | **Population PK with sparse sampling[a]** | | **Individual PK with full sampling[b]** |
| Terminal half-life [h] | 11.8 ± 2.43 | 12.4 ± 1.67 | 13.43 ± 4.05 |
| MRT [h] | 17.0 ± 3.50 | 17.8 ± 2.42 | 17.96 ± 5.49 |
| $C_L$ [mL/(kg·h)] | 3.53 ± 1.29 | 3.11 ± 0.76 | 3.87 ± 3.31 (2.73 ± 0.93) [d] |
| Incremental Recovery [(IU/dK)/(IU/kg)] | 1.89 ± 0.49 | 1.95 ± 0.47) | 2.12 ± 0.60 |
| $AUC_{0\text{-}Inf}$ [IU·h/dL] | 1947 ± 757 | 2012 ± 495 | 1642 ± 752 |
| $V_{SS}$ [dL/kg] | 0.56 ± 0.12 | 0.54 ± 0.09 | 0.56 ± 0.18 |
| $C_{max}$ [IU/dL] | 115 ± 30 | 115 ± 33 | 95 ± 25 |
| $T_{max}$ [h] | -[c] | -[c] | 0.26 ± 0.10 |

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

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

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

[c] $T_{max}$ could not be calculated for subjects in the paediatric study as only one sample was drawn (15-30 minutes post-infusion) within the first 3 hours of the infusion.

[d] Estimated mean and SD calculated not including one subject whose clearance estimate was 11.8mL/(kg·h). Median including all subjects is 2.78 mL/(kg·h).

**Table 11. Summary of pharmacokinetic parameters of ADYNOVATE for paediatrics using the chromogenic assay**

| **Parameter (mean ± standard deviation)** | **Paediatric Study** | | **Pivotal Study in adolescents & adults** |
|---|---|---|---|
| | **< 6 years (n = 14)[a]** | **6 to < 12 years (n = 17)[a]** | **12 to < 18 years (n = 8)[b]** |
| **Design** | **Population PK with sparse sampling[a]** | | **Individual PK with full sampling[b]** |
| Terminal half-life [h] | 12.99 ± 8.75 | 11.93 ± 2.58 | 13.80 ± 4.01 |
| MRT [h] | 18.74 ± 12.60 | 17.24 ± 3.72 | 17.73 ± 5.44 |
| $C_L$ [mL/(kg·h)] | 3.49 ± 1.21 | 2.80 ± 0.67 | 2.58 ± 0.84 |
| Incremental Recovery [(IU/dK)/(IU/kg)] | NA[c] (1.90 ± 0.27) | NA[c] (2.19 ± 0.40) | 2.34 ± 0.62 |
| $AUC_{0\text{-}Inf}$ [IU·h/dL] | 2190 ± 1593 | 2259 ± 514 | 1900 ± 841 |
| $V_{SS}$ [dL/kg] | 0.54 ± 0.03 | 0.46 ± 0.04 | 0.54 ± 0.22 |
| $C_{max}$ [IU/dL] | NA[c] (117 ± 16) | NA[c] (130 ± 24) | 117 ± 28 |
| $T_{max}$ [h] | -[e] | -[e] | 0.26 ± 0.14 |

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

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

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

[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.

[e] $T_{max}$ could not be calculated for subjects in the paediatric study as only one sample was drawn (15-30 minutes post-infusion) within the first 3 hours of the infusion

The PK data demonstrates that **ADYNOVATE** has an extended circulating half-life.

### 5.3 Preclinical safety data

*Genotoxicity*

No studies on Genotoxicity have been performed with **ADYNOVATE**.

*Carcinogenicity*

No studies on carcinogenicity have been performed with **ADYNOVATE**.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Calcium chloride dihydrate
Glutathione
Histidine
Mannitol
Polysorbate 80
Sodium chloride
Trehalose dihydrate
Trometamol
Water for injections (diluent)

The amounts of the inactive ingredients are constant in all strengths.

### 6.2 Incompatibilities
Not stated.

### 6.3 Shelf life
2 years.

### 6.4 Special precautions for storage
Store **ADYNOVATE** in powder form at 2°C to 8°C. Do not freeze.

**ADYNOVATE** may be stored at room temperature not to exceed 30°C for a period of up to 3 months not to exceed the expiration date. If stored at room temperature, write the date on the carton when **ADYNOVATE** is removed from refrigeration.

After storage at room temperature, do not return the product to the refrigerator.

Do not use beyond expiration date printed on the carton or vial.

Store vials in their original box and protect them from extreme exposure to light.

After reconstitution, do not refrigerate the solution. Use the reconstituted solution immediately or within 3 hours after reconstitution. Discard any remaining solution.

### 6.5 Nature and contents of container
Each pack contains a powder vial and a vial containing 2mL or 5mL diluent (both type I glass closed with chlorobutyl rubber stoppers). The product is supplied in either one of the following configurations:

- **ADYNOVATE** with BAXJECT II HI-FLOW device: Each pack contains a powder vial, a vial containing diluent and a device for reconstitution (BAXJECT II HI-FLOW).
- **ADYNOVATE** in BAXJECT III system: Each pack contains a ready to use BAXJECT III system in a sealed blister (the powder vial and the vial containing diluent are preassembled with the system for reconstitution).

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

After reconstitution, the solution is clear, colourless, free from foreign particles and has a pH of 6.7 to 7.3. The osmolality is ≥ 380m Osmol/kg.

*Preparation and reconstitution*

Use aseptic technique.

*Using the BAXJECT II HI-FLOW Device*

For reconstitution use only the sterilised water for injections and the reconstitution device provided in the pack.

1. Use aseptic technique (clean and germ free) and a flat work surface during the reconstitution procedure.
2. Allow the vials of **ADYNOVATE** and diluent to reach room temperature before use.
3. Remove plastic caps from the **ADYNOVATE** and diluent vials.
4. Cleanse 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 diluent 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 diluent vial is on top. Quickly insert the purple plastic spike fully into the **ADYNOVATE** vial stopper by pushing straight down (Figure D). The vacuum will draw the diluent into the **ADYNOVATE** vial.
9. Swirl gently until **ADYNOVATE** is completely dissolved. Do not refrigerate after reconstitution.

**Figure A**

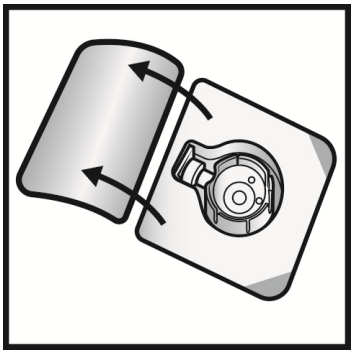


**Figure B**

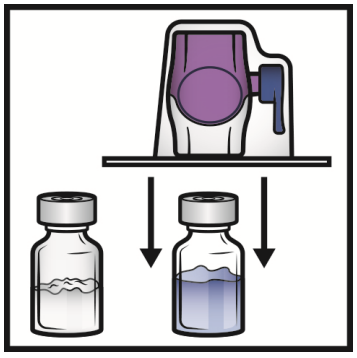


**Figure C**

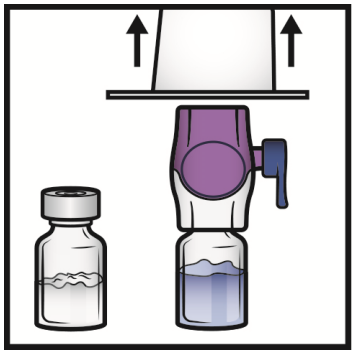


**Figure D**

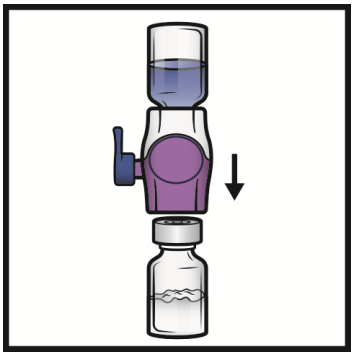


**Figure E**

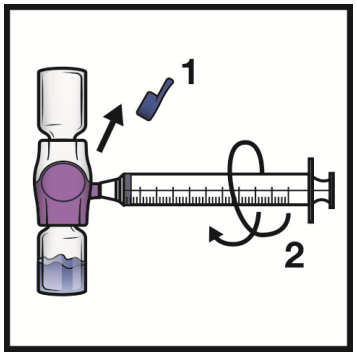
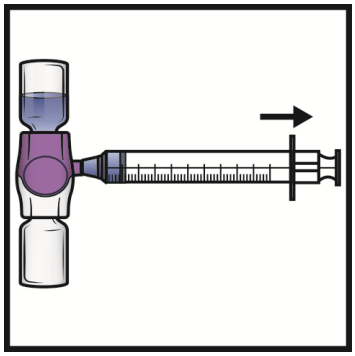



**Figure F**



*Using 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 diluent vials preassembled with the system for reconstitution) from the refrigerator and let it reach room temperature
2. Wash your hands thoroughly using soap and warm water.
3. Open the **ADYNOVATE** package by peeling away the lid. Remove the BAXJECT III system from the blister.
4. Place **ADYNOVATE** on a flat surface with the diluent vial on top (Fig. 1). The diluent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.
5. With one hand holding **ADYNOVATE** in the BAXJECT III system, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the **ADYNOVATE** vial (Fig. 2). Do not tilt the system until the transfer is complete.

6. Verify that the diluent transfer is complete. Swirl gently until all material is dissolved. Be sure that the **ADYNOVATE** 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.

**Fig. 1**

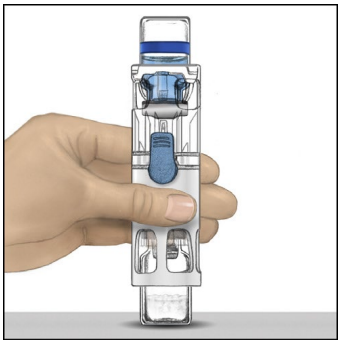


**Fig. 2**

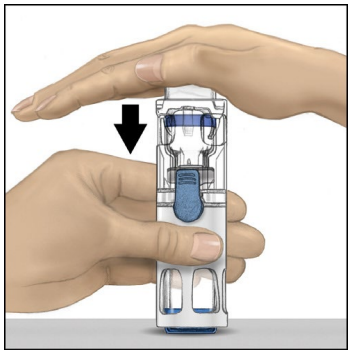
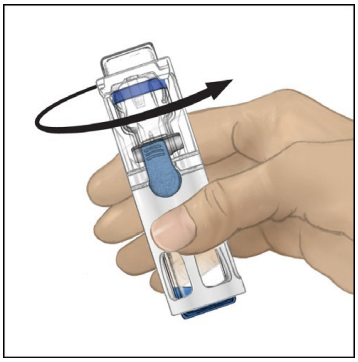


**Fig. 3**



## 7 MEDICINE SCHEDULE

General Sale Medicine.

## 8 SPONSOR

ADYNOVATE is distributed in New Zealand by:
Takeda New Zealand Limited
Level 10, 21 Queen Street
Auckland 1010
New Zealand

Phone 0508 169 077
www.takeda.com/en-au

## 9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

ADYNOVATE 250 IU, 500 IU, 1000 IU, 2000 IU: 20 December 2018
ADYNOVATE 750 IU, 1500 IU, 3000 IU: 5 August 2021

## 10 DATE OF REVISION OF THE TEXT

23 January 2023

## SUMMARY TABLE OF CHANGES

| *Section changed* | *Summary of new information* |
|---|---|
| 4.2 | Updated existing contraindications to reflect that anaphylactic reactions have been observed with ADYNOVATE |
| 4.3 | Updated existing warning on hypersensitivity to reflect that anaphylactic reactions have been observed with ADYNOVATE and its parent molecule ADVATE |
| 4.8 | Amended the existing ADR term “Drug Eruption” in Table 2 to “Rash Pruritic”<br>Updated to reflect that anaphylactic reaction has been observed as an ADR in post-marketing |
| 4.8, 5.1 | Minor editorial changes |

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