NEW ZEALAND DATA SHEET

1 PRODUCT NAME

ADVATE 250 IU powder for injection with diluent
ADVATE 500 IU powder for injection with diluent
ADVATE 1000 IU powder for injection with diluent
ADVATE 1500 IU powder for injection with diluent
ADVATE 2000 IU powder for injection with diluent
ADVATE 3000 IU powder for injection with diluent
ADVATE 4000 IU powder for injection with diluent

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Octacog alfa.

Laboratory code rAHF-PFM

ADVATE contains nominally 250, 500, 1000, 1500, 2000, 3000 or 4000 IU octocog alfa [recombinant coagulation factor VIII (rFVIII)]. The product contains approximately 40 to 960 IU per mL octocog alfa when reconstituted with either 5 mL or 2 mL sterile water for injections.

ADVATE is available in the following strengths with 5 mL diluent of water for injections:
250, 500, 1000, 1500, 2000, 3000 or 4000 IU.

ADVATE is available in the following strengths with 2 mL diluent of water for injections:
250, 500, 1000, 1500 IU.

Each ADVATE vial is labelled with the strength expressed in IU (International Units) per vial.

Biological origin of the active substance
Octocog alfa (rAHF-PFM / Recombinant Antihaemophilic Factor VIII Plasma/Albumin-Free Method) is produced from a genetically engineered Chinese Hamster Ovary (CHO) cell-line under conditions which are free from the use of animal derived protein.

Trehalose, a disaccharide of two glucose molecules linked by an α, α, glucopyranose of glycoside bond has been used as a stabiliser in the formulation, instead of human albumin. The active ingredient, octocog alfa, has been manufactured by a method that is free from the use of animal or human derived proteins. This manufacturing process provides a low risk of transmission of blood-borne viruses derived from exogenous human and animal origins.

The molecular integrity and biological activity of rAHF-PFM is indistinguishable from that of the first generation of rAHF. They differ on the culture media used during the manufacturing process and the cell lines. In the first generation of rAHF production, the cell lines are grown in a culture medium containing animal/human derived proteins, whereas in the rAHF-PFM production, the cell lines are adapted to grow without using animal/human components. The CHO cells transfected with factor VIII gene, express factor VIII within the cell as a glycosylated protein, rAHF-PFM, which is subsequently secreted into the culture medium. The isolation and purification of the rAHF-PFM from the culture medium is basically the same as in the first generation of rAHF, using a series of immunoaffinity chromatography column. In this process, the purification matrix packed into the column was produced by immobilisation of monoclonal antibodies directed to factor VIII to a carrier, which selectively binds the rAHF-PFM. It is followed by the elution of the bound rAHF-PFM from the matrix and subsequently the eluate is subjected to a series of ion-exchange column chromatography procedures to remove the buffer components.

The potency is determined using the one-stage clotting assay or by chromogenic method (EP), against an in-house standard that is referenced to the FDA/US Mega I Standard. The latter was calibrated against the third WHO standard. The specific activity is approximately 4,000 - 10,000 IU/mg protein.

Excipients with known effect
For the full list of excipients, see section 6.1.

After reconstitution, the product contains 0.45 mmol (10 mg) sodium per vial.

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

3 PHARMACEUTICAL FORM
Injection with diluent.

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

The water for injections diluent is a clear and colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
ADVATE is indicated for use in haemophilia A for prevention and control of haemorrhagic episodes. Patients with haemophilia A may be treated with ADVATE as perioperative management.

ADVATE is not indicated in von Willebrand's disease.

4.2 Dose and method of administration
Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

Although the dose can be estimated by the calculations below, it is highly recommended that, whenever possible, appropriate laboratory tests including serial factor VIII activity assays be performed.

Patients may vary in their pharmacokinetic (e.g., half-life, *in vivo* recovery) and clinical responses to ADVATE. The amount and frequency of administration should be adapted to the clinical effectiveness of the product in the individual case. Under certain circumstances (presence of a low responder inhibitor) doses larger than the calculated doses may be necessary.

Dosage
The dosage and duration of the substitution therapy depend on the severity of factor VIII deficiency, the location and the extent of the bleeding and on the patient's clinical condition. The dose of factor VIII administered is expressed in International Unit (IU), which is related to the WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IUs (relative to the 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. The calculation of the required dosage 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 dose is determined using the following formula and following table.

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

Control and prevention of bleeding episodes
A guide for dosing in the treatment of bleeding episodes is provided in the below table. The careful control of treatment dose is especially important in cases of life-threatening bleeding episodes.

Type of Bleeding Episodes	*Required Peak Post-infusion Factor VIII Activity in the Blood (% or IU/dL)*	*Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level*
Minor Early haemarthrosis, mild muscle bleeding, or mild oral bleeding episode	20 - 40	10-20 IU per kg[a] Repeat infusions every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for one to three days until the bleeding episode is resolved (as indicated by relief of pain) or healing is achieved.
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite haemarthrosis, and known trauma.	30 - 60	15-30 IU per kg[a] Repeat infusions every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for three days or more until bleeding episode is resolved (as indicated by relief of pain) or healing is achieved.
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal spaces or iliopsoas sheath, fractures, head trauma.	60 - 100	30-50 IU per kg[a] Repeat infusions every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until resolution of the bleeding episode has occurred.

[a] Dose (IU/kg) = Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).

Perioperative management
A guide for dosing in perioperative management is provided in the below table. The careful control of dose and duration of treatment is especially important in cases of major surgery.

Type of Surgery	*Required Peak Post-infusion Factor VIII Activity in the Blood (% or IU/dL)*	*Frequency of infusion*
Minor including tooth extraction	60 - 100	A single bolus infusion (30-50 IU/kg[a]) beginning within one hour of the operation. Optional additional dosing every 12 to 24 hours as needed to control bleeding. For dental procedures, adjunctive therapy may be considered.

Type of Surgery	*Required Peak Post-infusion Factor VIII Activity in the Blood (% or IU/dL)*	*Frequency of infusion*
Major Examples include intracranial, intra-abdominal, or intrathoracic surgery, joint replacement surgery	80 - 120 (pre- and post-operative)	Pre-operative bolus infusion: 40-60 IU/kg[a] Verify 100% activity has been achieved prior to surgery. Maintenance bolus infusion (40-60 IU/kg[a]) repeat infusions every 8 to 24 hours (6 to 24 hours for patients under the age of 6), depending on the desired level of factor VIII and state of wound healing.

[a] Dose (IU/kg) = Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).

In cases of the haemorrhagic events as shown in the above table, the factor VIII activity should not fall below the given plasma activity level (in % normal or IU/dL) in the corresponding period. The above table can be used to guide dosing in bleeding episodes and surgery.

Careful control of replacement therapy is especially important in cases of major surgery or life-threatening haemorrhages. During the course of treatment, appropriate determination of plasma factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of plasma factor VIII activity assay is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

Prophylaxis

For prevention of bleeding episodes, doses between 20 to 40 IU of factor VIII per kg body weight every other day (3 to 4 times weekly) may be utilised. In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary. There are data on 13 paediatric patients collected on the use of ADVATE.

Patients with inhibitors

Patients should be evaluated for the development of factor VIII inhibitors, if the expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose. 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 patients with haemophilia A (see section 4.4/Antibodies against Mouse or Hamster (CHO) Proteins).

Laboratory tests

Although dosage can be estimated by the calculations as described above, it is strongly recommended that, whenever possible, appropriate laboratory tests including serial AHF assays be performed on the patient's plasma at suitable intervals to ensure that adequate AHF levels have been reached and maintained.

If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of ADVATE should be administered to achieve a satisfactory clinical response.

If the patient's plasma factor VIII fails to reach the expected levels or if bleeding is not controlled after adequate dosage, the presence of inhibitor should be suspected. By performing appropriate laboratory investigations, the presence of an inhibitor can be demonstrated and quantified in terms of IU factor VIII neutralised by each mL of plasma. If the inhibitor is present at a level of less than 10 BU/mL, administration of additional factor VIII may neutralise the inhibitor. Thereafter, the administration of additional factor VIII should elicit the predicted response. The control of factor VIII and inhibitor levels by laboratory assays is necessary in this situation. Inhibitor titres above 10 BU/mL may make haemostatic control with factor VIII either impossible or impractical because of the large dose required. In addition, the inhibitor titre may rise following AHF infusion because of an anamnestic response to factor VIII.

Method of administration
Intravenous administration.

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

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

Reconstituted products should be inspected for particulate matter and discoloration prior to administration. The solution should be clear to colourless and free from foreign particles. Do not administer if particulate matter or discolouration or cloudiness is found, contact Takeda Customer Service.

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

Administration by bolus infusion
A dose of ADVATE should be administered over a period of ≤ 5 minutes (maximum infusion rate 10 mL/min). The pulse rate should be determined before and during administration of ADVATE. Should a significant increase in pulse rate occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

Administration by continuous infusion
The 1500, 1000 and 500 IU/vial nominal potency of ADVATE are suitable for use in a continuous infusion mode of administration. Continuous infusion of ADVATE must employ either a syringe pump running at a rate of greater than or equal to 0.4 mL/hour, or a CADD-1 type infusion pump running at a rate of 1.5 mL/hour. In vitro studies employing a syringe pump or CADD-1 pump have demonstrated > 80% of the hour 0 potency of ADVATE for up to 48 hours of continuous infusion. For sterility assurance purposes, a fresh supply of reconstituted ADVATE for continuous infusion (prepared under laminar air flow conditions) should be replaced at bedside no less frequently than every 12 hours. The post-reconstitution photostability of ADVATE is acceptable under the conditions of visible and ultra-violet light exposure in a clinical setting. It is highly recommended that factor VIII levels be checked within 3 to 6 hours after the initiation of continuous infusion in order to document that the desired factor VIII levels are being maintained.

Rates of infusion should be modified based on the levels of plasma factor VIII activity measured at least once per day thereafter and based on the desired level of factor VIII.

4.3 Contraindications

Known hypersensitivity to any component or to mouse or hamster proteins.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE and have been manifested by dizziness, paraesthesia, rash, flushing, face swelling, urticaria, and pruritus.

Patients should be informed of the signs of hypersensitivity reactions (including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis). If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physicians. In the case of anaphylactic shock, the current medical standards for shock treatment should be implemented.

Inhibitor formation

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. In particular when the subject has not been treated with antihaemophilic factor VIII previously, the chance of antibodies formation is high. These inhibitors are usually IgG immunoglobulins directed against factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified Bethesda assay.

The risk of developing inhibitors is correlated to the extent of exposure to the factor VIII, the risk is being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patients treated with ADVATE should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have predominantly been reported in previously untreated patients.

The risk for inhibitor development depends on other genetic and environmental factors relating to the characteristics of the patient, e.g. type of the factor VIII gene mutation, family history, ethnicity, which are believed to represent the most significant risk factors for inhibitor formation.

Among 136 treated subjects greater or equal to 10 years of age, all of whom had > 150 exposure days to factor VIII at study entry, 102 had at least 75 exposure days to ADVATE. None of these subjects developed an inhibitor. One subject who had < 50 exposure days to ADVATE while on the study developed an inhibitor. This subject manifested a low titre inhibitor (2.0 BU by the Bethesda assay) after 26 exposure days with ADVATE.

Antibodies against mouse or hamster (CHO) proteins

ADVATE contains trace amounts of mouse immunoglobulin G (MuIgG); maximum level of 0.1 ng/IU and hamster (CHO) proteins (maximum levels of 1.5 ng/IU). As such, there exists a remote possibility that patients treated with this product may develop hypersensitivity to these non-human derived proteins.

In the Phase 2/3 pivotal study of ADVATE, serum samples were tested by enzyme immunoassays at base line and after every 15 ± 2 days for the presence of antibodies to CHO proteins and MuIgG. Four study subjects showed a statistically significant increasing trend in the levels of anti-CHO (n = 1) or anti-MuIgG (n = 3) antibody levels over the course of the study. A fifth study subject showed a marked increase in anti-MuIgG antibodies coincident with the 60 and 75 day interval study visits. None of these subjects exhibited adverse experiences (AEs) or other study findings consistent with an allergic or hypersensitivity response.

4.5 Interaction with other medicines and other forms of interaction

No interactions of ADVATE with other medicinal products are currently known, based upon the absence of data from clinical trials, current medical/scientific literature, and post marketing safety reports.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Animal studies examining the effects of ADVATE on fertility have not been conducted.

Use in pregnancy (Category B2)

Factor VIII deficiency is an X-chromosome linked (male) congenital disease. The safety of ADVATE for use in pregnant women has not been established. Physicians should balance the potential risks and only prescribe if clearly needed. Animal reproduction studies with recombinant factor VIII, including ADVATE, have not been conducted.

Use in lactation

It is not known if ADVATE or its metabolites are excreted in human milk. The safety of ADVATE for use in lactating women has not been established. Breastfeeding is not recommended in women being treated with ADVATE. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing ADVATE.

4.7 Effects on ability to drive and use machines

There is no information on the effects of ADVATE on the ability to drive or operate an automobile or other heavy machinery.

4.8 Undesirable effects

Summary of the safety profile

Although hypersensitivity or allergic reactions were not observed in any subjects participating in the clinical trials with ADVATE, such reactions have been reported in the post-marketing setting. Patients should be informed of the early signs of hypersensitivity reactions, which may include nausea, vomiting, rash, urticaria, dizziness, shortness of breath, hypotension and syncope. Patients should be advised to contact their physician if these symptoms occur.

Tabulated summary of adverse reactions

Clinical Studies with ADVATE enrolled 450 unique subjects. The safety analysis set included 418 subjects with at least one exposure to ADVATE from 12 clinical studies: 069901, 060102, BLB-200-01, 060101, 060401, 069902, 060201,060103, 060403, 060702, 060601, and 060801.

A total of 93 adverse reactions (ADR) were reported in 45 of the 418 unique treated subjects. The most common adverse reaction included factor VIII inhibition, pyrexia, and headache. Of these, 17 ADRs for factor VIII inhibition were considered serious. Factor VIII inhibition was the most frequent ADR that was reported in 4.1% of treated subjects (n=17). Of the 93 ADRs, none were reported in neonates (0 to < 1 month of age), 30 ADRs were reported in 20/60 infants (1 month to <2 years of age), 7 ADRs were reported in 3/68 children (2 to <12 years of age), 10 ADRs were reported in 5/38 adolescents (12 to <16 years of age), and 46 ADRs were reported in 17/147 adults (16 years of age and older).

ADVATE Clinical Study Adverse Reactions[a]

Class (SOC)	*Preferred MedDRA Term (Version 23)*	*Number of Unique Subjects N=418*	*ADR Rate (% of subjects)*[b]	*Frequency Category*
Infections and infestations	Influenza	1	0.24	Uncommon
	Laryngitis	1	0.24	Uncommon
Blood and lymphatic system disorders	Factor VIII inhibition[c]	1 (PTP[d])	0.28	Uncommon
		16 (PUPs[d])	29.09	Very common
	Lymphangitis	1	0.24	Uncommon
Nervous system disorders	Headache	7	1.67	Common
	Dizziness	4	0.96	Uncommon
	Dysgeusia	1	0.24	Uncommon
	Memory impairment	1	0.24	Uncommon
	Migraine	1	0.24	Uncommon
	Syncope	1	0.24	Uncommon
	Tremor	1	0.24	Uncommon
Eye disorders	Eye inflammation	1	0.24	Uncommon
Cardiac disorders	Palpitations	1	0.24	Uncommon
Vascular disorders	Hematoma	1	0.24	Uncommon
	Hot flush	2	0.48	Uncommon
	Pallor	1	0.24	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnea	2	0.48	Uncommon
Gastrointestinal disorders	Abdominal pain upper	2	0.48	Uncommon
	Diarrhea	2	0.48	Uncommon
	Nausea	1	0.24	Uncommon
	Vomiting	1	0.24	Uncommon
Skin and subcutaneous tissue disorders	Hyperhidrosis	2	0.48	Uncommon
	Pruritus	2	0.48	Uncommon
	Rash	4	0.96	Uncommon
	Urticaria	1	0.24	Uncommon
General disorders and administration site conditions	Pyrexia	6	1.44	Common
	Chest discomfort	1	0.24	Uncommon
	Chest pain	1	0.24	Uncommon
	Chills	1	0.24	Uncommon
	Feeling abnormal	1	0.24	Uncommon
	Peripheral edema	1	0.24	Uncommon
	Vessel puncture site hematoma	1	0.24	Uncommon
Investigations	Coagulation factor VIII level decreased	1	0.24	Uncommon
	Hematocrit decreased	1	0.24	Uncommon
	Laboratory test abnormal	1	0.24	Uncommon
	Monocyte count increased	1	0.24	Uncommon
Injury, poisoning and procedural complications	Post procedural complication	1	0.24	Uncommon
	Post procedural hemorrhage	1	0.24	Uncommon
	Procedural site reaction	1	0.24	Uncommon

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

[a] ADRs are defined as all ADRs related to investigational product: 93.

[b] Percent is based on total number of subjects who received ADVATE: 418.

[c] In study 060103 (PUP), 16 subjects reported an ADR for inhibitor development. In study 060201, one subject reported an ADR for inhibitor development that was not confirmed. In study 069901, one subject had an inhibitor that was not reported as an ADR. In total, there were 17 confirmed inhibitors reported in 17 subjects.

[d] Of the 418 unique subjects, 363 are PTPs and 55 are PUPs.

Adverse reactions from spontaneous reporting
In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These adverse reactions are listed by preferred MedDRA term in order of severity:

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction, Hypersensitivity.

GENERAL AND ADMINISTRATION SITE CONDITIONS: Injection site reaction, Fatigue, Malaise.

Description of selected adverse reactions

Immunogenicity
A total of 276 patients, diagnosed with severe to moderately severe haemophilia A (factor VIII ≤2%), entered studies that required a minimum of 150 exposure days in adults and older children and 50 exposure days in children < 6 years of age to factor VIII concentrates prior to participation. Among these patients, one displayed evidence of a factor VIII inhibitor. This subject manifested a low titre inhibitor (2.0 BU by the Bethesda assay) after 26 exposure days. Follow-up inhibitor tests in this subject after withdrawal from the study were negative. Across all studies, median exposure to ADVATE was 97.0 exposure days per subject (range 1 to 709) for previously treated patients. The overall incidence and 95% CI of any factor VIII inhibitor development (low or high) was 0.36% (1 of 276), the 95% CIs: 0.009 to 2.002% based on 276 previously treated patients. The incident results for low titre and overall titre (low and high) were the same. The high titre incidence and 95% CI of factor VIII inhibitor development was 0.00% (0 of 276), the 95% CIs: 0.000 to 1.328%.

In addition, 16 out of 55 previously untreated patients developed factor VIII inhibitors: 7 subjects developed high-titre inhibitors and 9 subjects developed low-titre inhibitors, 1 of which was also classified as a transient inhibitor.

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 phone number: 0800 764 766 [0800 POISON] in New Zealand.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Blood Coagulation Factor VIII
ATC Code: B02BD02.

The chemical structure of rAHF-PFM is that of a dimeric glycoprotein, which has been shown to have a similar amino acid sequence with that of the human plasma derived factor VIII. Amino acid analysis of the purified glycosylated protein demonstrated that it constitutes 2332 amino acids with a molecular mass of approximately 280kDa. Thus, the rAHF-PFM is a full length factor VIII.

Mechanism of action
Under normal physiological conditions, factor VIII is essential for blood clotting and haemostasis. The activated factor VIII (factor VIIIa) acts as a cofactor for activating factor IX to IXa cascading to activate factor X to Xa. By the actions of the activated factors Va and Xa, circulating pro-thrombin is converted

into thrombin. Subsequently, thrombin converts fibrinogen to fibrin monomer cascading to formation of linear fibrin polymer. By the action of factor XIII the fibrin monomer is cross-linked to form fibrin clots leading to the arrest of bleeding episodes.

In patients with haemophilia A (classical haemophilia), a sex-linked hereditary disorder of blood coagulation, the level of circulating factor VIII is decreased, leading to profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. The use of plasma-derived or recombinant derived factor VIII has been shown successfully to correct this deficiency. Thus, plasma derived and recombinant derived factor VIII have the same pharmacological actions.

Clinical efficacy and safety

In the phase 2/3 pivotal study, the safety, hemostatic efficacy, pharmacokinetics and immunogenicity of ADVATE were evaluated in a double-blinded, randomized, cross-over, open label study in 111 subjects aged 10 years and older. The trial was conducted in previously treated subjects (PTPs with ≥ 150 exposure days) diagnosed with moderate to severe hemophilia A (factor VIII level ≤ 2% of normal) who were ≥10 years of age (20 were 10 to <13, 22 were 13 to <16, and 69 were 16 years and older). Subjects with a history of, or a detectable factor VIII inhibitor were excluded.

Subjects self-administered ADVATE for routine prophylaxis (≥ 25 IU/kg body weight 3-4 times per week) and for the on-demand treatment of bleeding episodes. A global assessment of efficacy was rendered either by the subject (for home treatment) or study site investigator (for treatment under medical supervision) using an ordinal scale of excellent, good, fair, or none, based on the quality of haemostasis achieved with ADVATE for the treatment of each new episode.

A total of 510 bleeding episodes were reported, with a mean (± SD) of 6.1 ± 8.2 bleeding episodes per subject. Of the 510 new bleeding episodes treated with ADVATE, 439 (86%) were rated excellent or good in their response to treatment, 61 (12%) were rated fair, 1 (0.2%) was rated as having no response, and for 9 (2%), the response to the treatment was unknown. A total of 411 (81%) new bleeding episodes were managed with a single infusion, 62 (12%) required 2 infusions, 15 (3%) required 3 infusions, and 22 (4%) received 4 or more infusions of ADVATE for satisfactory resolution. A total of 162 (32%) new bleeding episodes occurred spontaneously, 228 (45%) were the result of antecedent trauma, and for 120 (24%) bleeding episodes the etiology was unknown.

The rate of new bleeding episodes during the protocol-mandated minimum of 75 exposure day prophylactic regimen was calculated as a function of the bleeding episodes for 107 evaluable subjects (n = 274) new bleeding episodes. These rates are presented in the following table. The overall rate of new bleeding episodes in the prophylaxis study was 0.52 ± 0.71.

Rate of New Bleeding Episodes During Prophylaxis	
Bleeding Episode Etiology	*Mean (± SD) New Bleeding Episodes/Subjects/Month*
Spontaneous	0.34 ± 0.49
Post Traumatic	0.39 ± 0.46
*Unknown**	0.33 ± 0.34
Overall	0.52 ± 0.71

*Etiology was indeterminate

In a *post-hoc* analysis, the overall rate of bleeding was correlated with the degree of compliance with the prescribed prophylactic regimen. Subjects who infused less than 25 IU ADVATE per kg per dose for more than 20% of prophylactic infusions or administered less than 3 infusions per week for more than 20% of study weeks (n = 37) experienced a 2.3-fold higher rate of bleeding in comparison with

subjects who complied with prescribed prophylactic regimen at least 80% of the time and at ≥ 80% of the prescribed dose (n = 70).

Additional (open-label) safety and efficacy data were collected on 82 subjects who continued with treatment following participation in the original safety and efficacy study. Bleeding episodes were treated with ADVATE and the outcome of treatment was rated as excellent, good, fair, or none, based on the quality of hemostasis achieved. Final analysis of efficacy was conducted for 81 subjects who self-administered ADVATE on a routine prophylactic regimen for a minimum period of 75 exposure days.

A total of 837 bleeding episodes occurred in 70 of the 81 subjects. The other 11 subjects experienced no bleeding episodes. The response to treatment with ADVATE was rated as excellent or good for 80.4% of all bleeding episodes. Most (88%) bleeding episodes required only 1 or 2 infusions to obtain hemostasis. Among the 837 bleeding episodes, 2 (0.3%) did not require treatment (0 infusions), 521 (62.2%) required 1 infusion, 216 (25.8%) required 2 infusions, 23 (2.7%) required 3 infusions, and 75 (9.0%) required 4 or more infusions. By etiology, 45.3% of these bleeding events were secondary to trauma and 27.7% occurred spontaneously; the other 27% had an undetermined etiology.

Perioperative management study

The safety and efficacy of ADVATE for perioperative management was investigated in 59 subjects with severe or moderately severe hemophilia A (factor VIII ≤ 2%). They were between the ages of 7 to 65 years of age (3 were 7 to <13, 6 were 13 to < 16, and 50 were ≥ 16). One subject elected not to undergo the planned surgery. Thus, 58 subjects underwent 65 surgical procedures, among which, 6 subjects underwent more than 1 procedure each. One subject withdrew during the post-operative period; thus, 57 subjects completed the study. Of the 65 procedures, 22 in 22 subjects were classified as major, 35 in 28 subjects were classified as minor, and 8 in 8 subjects were dental.

Prior to surgery, subjects received a pre-operative loading dose aimed at increasing the plasma factor VIII level to 60% to 100% of normal for dental procedures or 80% to 120% of normal for all other surgical procedures. During the surgery, subjects received replacement therapy by either bolus (47 procedures) or continuous infusion (18 procedures). For continuous infusion, the initial rate was 4 IU/kg/hr for subjects >12 years of age and 5 IU/kg/hr for subjects 5 to 12 years of age. After discharge, subjects continued to receive ADVATE for control of hemostasis as prescribed by the investigator for up to 6 weeks for major orthopedic procedures and up to 2 weeks for all other procedures.

Intraoperative efficacy was rated as excellent or good (excellent intraoperative blood loss was less than expected for the type of procedure performed; good intraoperative blood loss was as expected for the type of procedure performed.) for 61 (93.9%) of the 65 procedures; the rating was not done for 3 procedures and unknown for 1 procedure. Post-operative efficacy was rated as excellent or good for 62 (95.4%) of the 65 procedures; the rating was unknown for 2 procedures and not done for 1 procedure. Of the 24 procedures requiring surgical drains, efficacy assessments at the time of drain removal were rated as excellent or good for 20 (83.3%) procedures and fair (fair intraoperative blood loss was more than expected for the type of procedure performed) for 2 (8.3%) procedures; the rating was unknown for 1 procedure and not done for 1 procedure. Both procedures requiring surgical drains with fair ratings were major orthopedic surgeries.

Routine prophylaxis study

In a multicentre, open-label, prospective, randomised, controlled post-marketing clinical study (060201) of ADVATE, two long-term prophylaxis treatment schemes have been compared in 53 PTPs: an individualised pharmacokinetic guided dosing regimen (within a range of 20 to 80 IU of factor VIII

per kg body weight at intervals of 72 ± 6 hours, n=23) with a standard prophylactic dosing regimen (20 to 40 IU/kg every 48 ± 6 hours, n=30). The pharmacokinetic guided dosing regimen (according to a specific formula) was targeted to maintain factor VIII trough levels ≥ 1% at the inter-dosing interval of 72 hours. The data from this study demonstrate that the two prophylactic dosing regimens are comparable in terms of reduction of bleeding rate.

Immune tolerance induction

Data on Immune Tolerance Induction (ITI) in patients with inhibitors have been collected in a total of 85 subjects. 11 paediatric PUPs (PUP study 060103), 30 paediatric subjects from retrospective chart review (study 060703) and 44 paediatric and adult subjects of whom 36 completed ITI therapy (PASS-INT-004) have been documented with ITI treatment. In patients where immune tolerance was achieved, the bleedings were prevented or controlled with ADVATE and the patients continued with ADVATE prophylactic treatment as maintenance therapy.

Smaller diluent vial (2 mL water for injections) for potencies up to 1500 IU inclusive

An open label, randomised, crossover clinical study was conducted in 35 evaluable subjects diagnosed with severe haemophilia A (factor VIII ≤ 1% of normal) to investigate the PK parameters and safety of a single dose of ADVATE (50 IU/kg ± 100 IU) reconstituted in two different volumes of sterilised water for injections (2 mL or 5 mL). Subjects were randomised (1:1) to receive an infusion with ADVATE reconstituted in 2 mL followed by an infusion with ADVATE reconstituted in 5 mL water for injections or vice versa.

Results of this clinical study are summarized in the following table.

PK Parameters for Adolescent/Adult Cohort (Study 060702: PP Dataset)				
Parameter	*2mL infusion*		*5mL infusion*	
	Mean (geometric mean) value for 2mL infusion	*SD (2mL)*	*Mean (geometric mean) value for 5mL infusion*	*SD (5mL)*
$AUC_{(0-48h)}$ (IU·h/dL)	1298.67	380.60	1363.56	487.57
C_{max} (IU/dL)	104.42	19.35	107.89	17.95
Adjusted in vivo *IR*[1] *(IU/dL : IU/kg)*	1.93	0.35	2.00	0.36
Half-life (h)	12.54	3.80	12.50	2.89
CL (mL/(kg/h))	3.85	0.95	3.81	1.20
MRT (h)	14.79	5.24	14.34	4.27
V_{ss} (dL/kg)	0.54	0.13	0.51	0.13

Abbreviations: PP = per-protocol, SD = standard deviation

[1] Mean adjusted *in vivo* incremental recovery (IR) values were computed using C_{max}.

5.2 Pharmacokinetic properties

A randomised, crossover pharmacokinetic comparison of ADVATE (rAHF-PFM) and RECOMBINATE (rAHF) was conducted in the context of a pivotal Phase 2/3 study. Pharmacokinetic parameters area under the plasma curve versus time (AUC), C_{max}, mean residence time (MRT) and volume of distribution in steady state [V_{ss}] were calculated from factor VIII activity measurements in blood samples obtained immediately before and at standardized time intervals up to 48 hours following each infusion. The results are shown in the following table.

Pharmacokinetic Parameters for ADVATE (rAHF-PFM) and RECOMBINATE (rAHF)				
Parameters	*RECOMBINATE (rAHF)*		*ADVATE (rAHF-PFM)*	
	N	*Mean ± sd*	*N*	*Mean ± sd*
$AUC_{(0-48h)}$ (IU·h/dL)	30	1530 ± 380	30	1534 ± 436
In vivo *recovery (IU/dL/kg)*	30	2.59 ± 0.52	30	2.41 ± 0.50
Half-life ($t_{½}$)	30	11.24 ± 2.53	30	11.98 ± 4.28
C_{max} (IU/dL)	30	129 ± 27	30	120 ± 26
MRT (h)	30	14.52 ± 3.81	30	15.68 ± 6.21
V_{ss} (dL/kg)	30	0.46 ± 0.10	30	0.47 ± 0.10
CL (dL/kg/hr)	30	0.03 ± 0.01	30	0.03 ± 0.01

For the pharmacokinetic parameters $AUC_{(0-48h)}$ and the *in vivo* recovery, the 90% confidence intervals for the ratios of the mean values for the test and control articles were within the pre-established bioequivalence limits of 0.80 and 1.25 for the per-protocol (n = 30) study population. This was also true in the intent-to-treat study (n = 50) population for the total AUC and *in vivo* recovery. In addition, *in vivo* recovery at the onset of treatment and after 75 exposure days was compared for 62 subjects. Results indicated no significant change in the *in vivo* recovery at the onset of treatment and after 75 exposure days.

Distribution
When infused into a hemophilia patient, ADVATE binds to endogenous von Willebrand factor in the patient's circulation. The factor VIII/von Willebrand factor complex is distributed primarily in the intravascular space.

Metabolism
Not applicable

Elimination
Factor VIII clearance is mediated by vascular receptors, including low-density lipoprotein receptor-related protein and heparin sulphate proteoglycans, by mechanisms that have not been fully elucidated.

5.3 Preclinical safety data
Mutagenicity studies and long-term studies in animals to evaluate carcinogenic potential of ADVATE have not been performed. Animal studies examining the effects of ADVATE on fertility have not been conducted.

Its mechanism of action and nature do not suggest that ADVATE interacts directly with the DNA or any other chromosomal material and hence ADVATE is not considered to have any genotoxic potential.

ADVATE is a recombinant protein and is not considered to be mutagenic nor clastogenic, or have any carcinogenic potential based on the pharmacological mode of action.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Trehalose dihydrate
Histidine
Trometamol
Sodium chloride
Calcium chloride dihydrate

Glutathione
Polysorbate 80
Mannitol
Water for injections (diluent)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Two years.

The product is stable for the duration of the specified shelf life when stored in the specified temperature storage condition. Do not use beyond the expiration date printed on the label.

ADVATE should be administered at room temperature not more than 3 hours after reconstitution. For single use only.

6.4 Special precautions for storage
ADVATE should be stored at 2°C - 8°C for the duration of its shelf life. Do not freeze.

In the case of a need for ambulatory use, ADVATE may be kept at or below 25°C (room temperature) for a single period of up to 6 months and then discarded.

After ADVATE has been stored at room temperature, it should not be re-refrigerated.

Protect from light.

Product is for single use in one patient only. Discard any residue.

6.5 Nature and contents of container
ADVATE is available as a lyophilised powder in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 3000 or 4000 IU per vial and a diluent vial containing either 5 mL or 2 mL water for injections for reconstitution. See also section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION for details on the available potencies for each diluent volume.

Each pack of ADVATE contains a powder vial, a diluent vial and a needless transfer device for reconstitution.

Both the powder and the diluent are filled in a neutral Type 1 borosilicate glass vial with a nominal capacity of 6 mL. The vial is closed with a butyl rubber stopper with an inert coating, and sealed with aluminium overseal and tamper proof snap off plastic cap.

Not all presentations may be marketed.

Needleless transfer device (BAXJECT II)
The accompanied reconstitution device is a needleless transfer device designed for transferring and mixing medicines contained in two vials (product and diluent). Each needleless transfer device has a two-vial holder, a two-sided siliconised piercing plastic spike for penetration into the rubber stoppers of the two vials, a stopcock with an embedded/filter, and a female port designed for connection to a syringe (see section 4.2 for illustrations).

6.6 Special precautions for disposal and other handling

Discard any unused portion of the product appropriately.

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

Instructions for use and handling

Use aseptic technique.

Plastic syringes must be used with this product, since proteins such as ADVATE tend to stick to the surface of glass syringes.

Reconstitution using the BAXJECT II device

1. Bring the ADVATE (dry factor concentrate) and Sterile Water for injections (diluent) to room temperature (25°C).
2. Remove caps from the factor concentrate and diluent vials.
3. Cleanse stoppers with a germicidal solution, and allow to dry prior to use. Place the vials on a flat surface.
4. Open the BAXJECT II device package by peeling away the lid, without touching the inside (Figure A). Do not remove the device from the package.
5. Turn the package over. Press straight down to fully insert the clear plastic spike through the diluents vial stopper (Figure B).
6. Grip the BAXJECT II package at its edge and pull the package off the device (Figure C). Do not remove the blue cap from the BAXJECT II device. Do not touch the exposed white plastic spike.
7. Turn the system over, so that the diluent vial is on top. Quickly insert the white plastic spike fully into the ADVATE vial stopper by pushing straight down (Figure D). The vacuum will draw the diluent into the ADVATE vial.
8. Swirl gently until ADVATE is completely dissolved.

NOTE: do not refrigerate after reconstitution.

9. Remove the blue cap from the BAXJECT II device. Connect the syringe to the BAXJECT II device (Figure E). DO NOT INJECT AIR.
10. Turn the system upside down (factor concentrate vial now on top). Draw the factor concentrate into the syringe by pulling the plunger back slowly (Figure F).
11. Disconnect the syringe; attach a suitable needle and inject intravenously as instructed under Administration by Bolus Infusion.
12. If a patient is to receive more than one vial of ADVATE, the contents of multiple vials may be drawn into the same syringe. Please note that the BAXJECT II reconstitution device is intended for use with a single vial of ADVATE and Sterile Water for Injections only, therefore reconstituting and withdrawing a second vial into the syringe requires a second BAXJECT II reconstitution device.

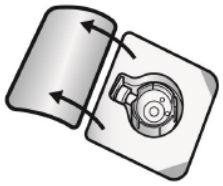
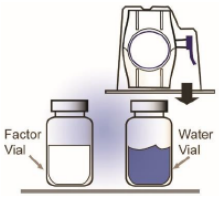
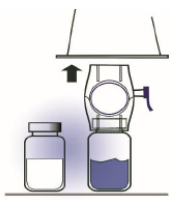
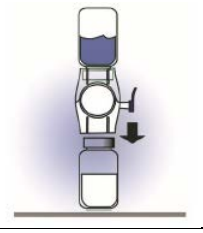
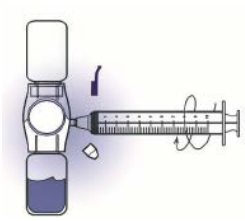
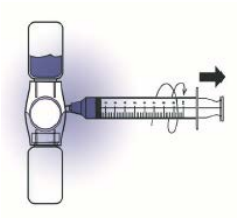
Figure A	Figure B	Figure C
		

Figure D	Figure E	Figure F
		

7 MEDICINE SCHEDULE

General Sale Medicine.

8 SPONSOR

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

Telephone: 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:
ADVATE 250IU, 25/01/2007
ADVATE 500IU, 25/01/2007
ADVATE 1000IU, 25/01/2007
ADVATE 1500IU, 25/01/2007
ADVATE 2000IU, 21/04/2009
ADVATE 3000IU, 16/04/2009
ADVATE 4000IU, 09/07/2015.

10 DATE OF REVISION OF THE TEXT

13 October 2020

SUMMARY TABLE OF CHANGES

Section changed	*Summary of new information*
4.2, 8	Change of Sponsor details

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.