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Octocog alfa, Plasma/ Albumin-Free Method

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Contents

Abstract

▲ Octocog alfa, plasma/albumin-free method (octocog alfa-PFM) is a recombinant, human, full length, coagulation factor VIII that has been produced without the addition of human- or animal-derived plasma proteins, thereby virtually eliminating the risk of transmission of blood-borne pathogens.

▲ Octocog alfa-PFM is structurally and functionally very similar to a previously marketed, albumin-containing formulation of the same recombinant factor VIII.

▲ The haemostatic efficacy of octocog alfa-PFM was rated excellent or good in the acute treatment of most breakthrough bleeding episodes in adolescents or adults with moderately severe or severe haemophilia A who were receiving prophylaxis with octocog alfa-PFM and who had been previously treated with factor VIII.

▲ Most bleeding episodes resolved after one or two infusions of octocog alfa-PFM. Efficacy was similar regardless of the cause or site of the bleeding episode.

▲ Similar excellent or good haemostatic efficacy was observed with octocog alfa-PFM in previously treated children aged <6 years with haemophilia A and during perioperative use in patients with haemophilia A undergoing surgical or invasive dental procedures.

▲ Octocog alfa-PFM was well tolerated during clinical development and in the 15-month post-marketing period. There were very few adverse events and serious events were rare. The risk for developing inhibitors (antibodies) to factor VIII was very low.

Features and properties of octocog alfa, plasma/albumin-free method (Advate®) in haemophilia A	
Indications	
Prevention and treatment of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency)	
Mechanism of action	
Antihaemorrhagic; coagulation factor VIII replacement	
Dosage and administration	
Recommended dosage	
acute bleeding episodes	Dosage (IU) = body weight (kg) × desired increase in plasma factor VIII (% or IU/dL) × 0.5 every 6–24 hours
prophylaxis (age ≥6y)	20–40 IU/kg every 2–3 days
prophylaxis (age <6y)	20–50 IU/kg 3–4 times weekly
Route of administration	Intravenous infusion
Pharmacokinetic profile (mean values after 50 IU/kg single infusion in adolescents and adults)	
Area under the plasma concentration-time curve (0–48h) [IU • h/dL]	1262–1544
Maximum plasma concentration (IU/dL)	111–129
Half-life (h)	11–12
Adjusted *in vivo* recovery (IU/dL rise per IU/kg administered)	2.2–2.6
Residence time (h)	18–23
Clearance (dL/kg • h)	0.03–0.04
Adverse events	
Most frequent	Headache, dizziness
Reported frequency of inhibitors to factor VIII in previously treated and untreated patients (post-marketing)	0.035 per million IU distributed

Haemophilia A, the most common form of haemophilia, is a bleeding disorder caused by a congenital deficiency of coagulation factor VIII.[1,2] Haemophilia A is characterised by a prolonged clotting time and occurs predominantly in males, since the gene for factor VIII resides on the X chromosome.[1] Factor VIII activity in plasma is reduced to 6–39% of normal levels in mild disease, 1–5% of normal in moderate disease and <1% of normal in severe disease.[1,3] Bleeding episodes, commonly occurring in joints and muscles, are usually associated with surgery or trauma in mild or moderate disease, but may also arise spontaneously in severe disease. The prevention and treatment of bleeding episodes in patients with haemophilia A normally involves factor VIII replacement therapy.[1,2,4]

The use of octocog alfa (recombinant human factor VIII), instead of plasma-derived factor VIII, has dramatically reduced the incidence of inadvertent transmission of viral infectious diseases such as hepatitis B and C, and HIV.[5] Nonetheless, there remains concern that other less well characterised infectious agents, such as the prion postulated to cause variant Creutzfeldt-Jakob disease, might still be transmitted via human- or animal-derived plasma proteins used in cell cultures or as stabilisers in the formulation of many octocog alfa preparations.[3,6]

Octocog alfa, plasma/albumin-free method (Octocog alfa-PFM) [Advate®][1] is a preparation of octocog alfa that is similar to an existing albumin-containing preparation of octocog alfa (octocog alfa-A) [Recombinate®] except that it has been produced without the addition of any exogenous human- or animal-derived proteins during the cell culture, purification or formulation processes.[3,7] A solvent/detergent viral inactivation step has also been added to the production process. The only other proteins in the final formulation are trace amounts of mouse immunoglobulin G, host Chinese hamster ovary cell proteins and recombinant von Willebrand factor.[3] Therefore, octocog alfa-PFM virtually eliminates the risk of transmission of blood-borne pathogens of any kind. This review focuses on the use of octocog alfa-PFM (Advate®) in the treatment and prophylaxis of patients with moderate or severe haemophilia A, including children aged <6 years (for whom the product's licence was recently extended in the EU[8]).

1. Pharmacodynamic Profile

The pharmacodynamic properties of octocog alfa-PFM have not been determined in humans, only *in vitro* and in animals.[9] Octocog alfa-PFM is a recombinant, full length, human factor VIII molecule that is co-expressed with von Willebrand factor, factor VIII's natural stabiliser.[3] It has been developed to be as similar as possible to human plasma-derived factor VIII (including post-translational modifications) and is a modified form of the earlier-marketed octocog alfa-A that has proven efficacy in treating haemophilia A.[10] Therefore, the preclinical evaluation of octocog alfa-PFM was restricted to demonstrating comparability to octocog alfa-A.[3]

- Octocog alfa-PFM lyophilised powder was stable to a range of temperatures during storage, including 3 months at 40°C (84% residual activity), 12 months at 30°C (85%), 18 months at 25°C (82%) or 30 months at 5°C (92%).[11] A 2-week temperature excursion at 40°C did not compromise subsequent stability during storage at 5–30°C. Following reconstitution, an average of 92% of full activity was retained for 24 hours at room temperature.[11]
- *In vitro* studies demonstrated that octocog alfa-PFM was similar to octocog alfa-A with respect to primary, secondary and tertiary structure, the extent and time course of activation by thrombin, the level of post-translational tyrosine sulphation, glycosylation and sialic acid content, and the lack of protein aggregation.[3,10] The two preparations were also functionally similar with respect to binding to von Willebrand factor or factor IXa and in activated partial thromboplastin time and chromogenic substrate assays.[3,10]
- The haemostatic efficacies of intravenous octocog alfa-PFM and octocog alfa-A, each administered at a dose of 150 IU/kg, were shown to be

1 The use of trade names is for product identification purposes only and does not imply endorsement.

similar and superior (p-values not stated) to control vehicle in haemophilic (factor VIII-deficient) exon 16 knockout mice.[3,9,10] The cumulative blood loss over 20 minutes from a tail transection with either preparation was similar at 160–258μL compared with 363–393μL for control vehicle in one study and 499–609μL in another.[9]

- Likewise, plasma factor VIII activity was similar in mice treated with octocog alfa-PFM or octocog alfa-A and was significantly (p-values not stated) higher than in mice treated with control vehicle.[9]

2. Pharmacokinetic Profile

Pharmacokinetic analyses were performed in each of the four clinical studies completed to date as part of the clinical development programme for octocog alfa-PFM.[9,12-14] All patients had moderately severe or severe haemophilia A (baseline plasma factor VIII activity <2% of normal) and had been previously treated with factor VIII for ≥150 exposure days (or ≥50 exposure days in the paediatric study[13]). The primary analyses were conducted in the per-protocol groups, although intent-to-treat analyses were also performed.[9,12-14]

- Octocog alfa-PFM was shown to be pharmacokinetically very similar to octocog alfa-A as measured by area under the concentration-time curve (AUC) and *in vivo* recovery, in a single-dose, randomised, crossover comparison in patients (n = 30), aged 10–65 years, administered 50 IU/kg of each agent by intravenous infusion as part of the pivotal clinical study.[12] The mean values with octocog alfa-PFM and octocog alfa-A for AUC from time zero to 48 hours (AUC_{48}) were 1534 and 1530 IU • h/dL and for *in vivo* recovery were 2.4 and 2.6 IU/dL rise per IU/kg administered.[9,12]
- Analyses conducted prior to (n = 30) and after prophylactic therapy for ≥75 days (n = 37) in different phases of the pivotal trial or its continuation (n = 13) indicated that a single 50 IU/kg infusion of octocog alfa-PFM produced mean values for AUC_{48} of 1262–1544 IU • h/dL, maximum plasma concentrations of 111–129 IU/dL, half-lives of 10.89–11.98 hours, residence times of 18.14–22.83 hours, distribution volumes of 0.60–0.68 dL/kg, adjusted *in vivo* recoveries of 2.20–2.55 IU/dL rise per IU/kg infused and clearances of 0.03–0.04 dL/kg • h.[9,12]
- In children aged <6 years (n = 48) administered a single intravenous infusion of octocog alfa-PFM 50 IU/kg, the mean half-life of octocog alfa-PFM was shorter (9.8 vs 12.0 hours) and the mean adjusted recovery was lower (1.9 vs 2.4 IU/dL per IU/kg) than previously measured in older children and adults.[12,13] The mean AUC_{48} (1230 vs 1534 IU • h/dL), maximum plasma concentration (95 vs 120 IU/dL) and residence time (12.5 vs 15.7 hours) were also lower and the volume of distribution (0.51 vs 0.47 dL/kg) and clearance (0.04 vs 0.03 dL/kg • h) were higher in children aged <6 years compared with adolescents and adults.[12,13]
- Clearance rates in patients aged ≥5 years undergoing surgical or invasive dental procedures and receiving continuous infusion of octocog alfa-PFM (4–5 IU/kg/h) for ≥72 hours were generally less than 0.05–0.08 dL/kg • h and most often did not exceed 0.05 dL/kg • h (compared with 0.03–0.04 dL/kg • h after single-dose infusion[9]).[14]

3. Therapeutic Efficacy

The haemostatic efficacy of octocog alfa-PFM in patients with moderately severe or severe haemophilia A (baseline plasma factor VIII activity ≤2% of normal), who had previously been treated with factor VIII, has been assessed in four prospective, open-label, noncomparative clinical trials for which data are available to date. Only the pivotal trial has been published in full.[12] Interim data from an ongoing long-term continuation of the pivotal study are available in the European Medicines Agency's scientific discussion of the approval submission for octocog alfa-PFM.[9] Results from a paediatric study in children aged <6 years (interim analysis)[13] and a study in patients undergoing surgical or invasive dental procedures (interim analysis)[14] are available in posters presented at a recent scientific congress.

Treatments were prophylactic over ≥75 days (pivotal study), ≥50 days (continuation and paediatric studies) or ≥72 hours (surgery study), although

the continuation and paediatric studies also included an on-demand treatment arm.[9,12-14] The standard prophylactic dosage was 25–40 IU/kg (pivotal and continuation studies)[9,12] or 25–50 IU/kg (paediatric study)[13] by intravenous infusion three to four times per week, although some studies included a physician-modified prophylaxis arm.[9,13] In the surgery study, the dosage was adjusted to produce plasma factor VIII target levels of 60–100% of normal activity for dental procedures and 80–120% of normal for surgical procedures.[14]

The primary endpoints were usually the number of infusions of octocog alfa-PFM required to achieve adequate haemostasis for each new bleeding episode,[9,12,13] the overall rating of the haemostatic response by the patient (outpatient therapy) or the physician (inpatient therapy) on a 4-point scale (excellent, good, fair and none) following each bleeding episode[9,12,13] or the number and frequency of new bleeding episodes.[13]

General Efficacy In Adolescents and Adults

- In the pivotal trial, in which patients aged 10–65 years (n = 107) received prophylaxis for ≥75 days, treatment with octocog alfa-PFM was rated as excellent or good in 86% of the 510 new bleeding episodes and fair in 12% (figure 1).[12] The majority of episodes were managed with one (81%) or two (12%) infusions; only 4% of episodes required four or more infusions (figure 1). The median dose used in the acute treatment of a bleeding episode was 34.5 IU/kg. The efficacy was similar regardless of the cause or the site of the bleeding episode.[12]
- Thirty percent of patients receiving prophylaxis did not experience any bleeding episodes.[12] For the 70% of patients who did experience breakthrough bleeding, the mean incidence was 6.3 bleeding episodes per patient per year; 32% of episodes were spontaneous bleeds and 45% were related to trauma (23% unknown).[12] The total incidence was higher in younger patients, aged 10–18 years, than in older patients (7.3 vs 5.3 episodes per patient per year), mainly as a result of an approximately 2-fold higher incidence of trauma-related bleeding episodes in younger patients. The incidence of new bleeding episodes was also lower in medication-adherent than in nonadherent patients (4.4 vs 9.9 episodes/year; $p < 0.03$).[12]
- In the continuation study (following successful completion of the pivotal study), 13 of 27 patients receiving prophylaxis with octocog alfa-PFM for a

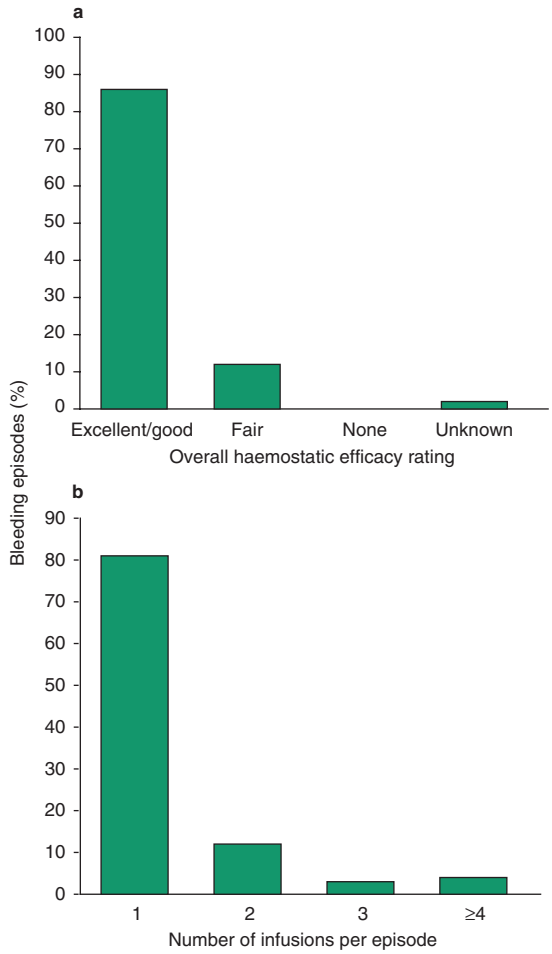

Fig. 1. Haemostatic efficacy of octocog alfa, plasma/albumin-free method (octocog alfa-PFM) in patients, aged 10–65 years, with moderately severe or severe haemophilia A and previously treated with factor VIII.[12] Patients (n = 107) received prophylactic octocog alfa-PFM 25–40 IU/kg by intravenous infusion three to four times per week for ≥75 days and 75 patients experienced 510 new breakthrough bleeding episodes requiring treatment. (**a**) Overall haemostatic efficacy rating by the patient (outpatient therapy) or physician (inpatient therapy) for the treatment of each new bleeding episode on a 4-point scale (excellent, good, fair or none). (**b**) Number of infusions of octocog alfa-PFM required to achieve adequate haemostasis for each new bleeding episode.

mean of 55 days experienced 51 new bleeding episodes (14 spontaneous, 27 trauma-related and 10 unknown).[9] Twenty-three patients received the standard prophylactic regimen and four received a physician-modified prophylactic regimen. The haemostatic efficacy of octocog alfa-PFM was rated excellent or good in 63% of episodes and fair in 33% of episodes. One infusion of octocog alfa-PFM was sufficient to manage bleeding in 86% of episodes and only 6% of episodes required ≥4 infusions.[9]

In Children Aged <6 Years

- In previously treated children, aged <6 years, with haemophilia A (n = 40) who received prophylaxis with octocog alfa-PFM for ≥50 days, 30 children experienced 234 new breakthrough bleeding episodes.[13] The median number of new episodes per year with standard prophylaxis, intermittent/modified prophylaxis and on-demand therapy were 2.85, 2.31 and 20.07, respectively.[13]
- The haemostatic efficacy of octocog alfa-PFM was rated excellent or good in 92% of the 210 new bleeding episodes that were treated (figure 2).[13] Similarly, 92% of treated bleeding episodes were controlled with 1 or 2 infusions. The median dose required to treat bleeding episodes was 43.9 IU/kg (range 17–310 IU/kg).[13]

In Surgical and Invasive Procedures

- In an interim assessment of the haemostatic efficacy of perioperative octocog alfa-PFM administered as repeat bolus infusions (27 procedures) or continuous infusion (4–5 IU/kg/h; 17 procedures) was rated excellent or good in 43 of 44 procedures performed in 41 patients aged ≥5 years undergoing surgical or invasive dental procedures.[14]
- Mean preoperative loading doses of 48.4, 54.8 and 71.6 IU/kg for dental (n = 8), minor (n = 18) and major (n = 18) surgeries, respectively, produced plasma factor VIII levels that met or exceeded target levels within 10–30 minutes in 39 of 42 evaluable procedures.[14] Estimated actual blood loss was within or less than the predicted range for 38 of 40 evaluable procedures.[14]

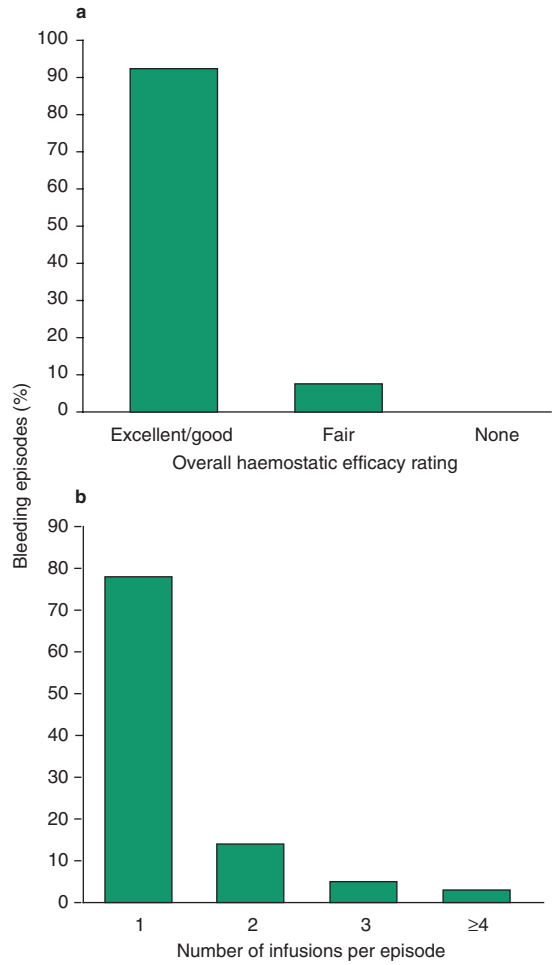

Fig. 2. Haemostatic efficacy of octocog alfa, plasma/albumin-free method (octocog alfa-PFM) in children, aged <6 years, with severe to moderately severe haemophilia A, who had previously been treated with factor VIII (interim analysis).[13] Children of mean age 3.1 years received standard prophylaxis (25–50 IU/kg three to four times per week; n = 11), intermittent/modified prophylaxis (n = 26) or on-demand treatment (n = 3) with octocog alfa-PFM for ≥50 days. Thirty patients experienced 234 new bleeding episodes during treatment (12% spontaneous, 52% trauma-related and 36% unknown) of which 210 were treated.[13] (**a**) Overall haemostatic efficacy rating for the treatment of each new bleeding episode on a 4-point scale (excellent, good, fair or none). (**b**) Number of infusions of octocog alfa-PFM required to achieve adequate haemostasis for each new bleeding episode.

Pharmacoeconomic Considerations

- Modelling based on clinical efficacy studies suggested that on-demand treatment with octocog alfa-

PFM rather than B-domain deleted octocog alfa in the US could result in a 12.2% reduction ($p < 0.05$) in the dose required to resolve a bleeding episode.[15] Therefore, in patients not self-administering therapy, but utilising primary care and/or hospital services according to one of five different scenarios, the use of octocog alfa-PFM rather than B-domain deleted octocog alfa could reduce primary care and/or hospital costs from a healthcare payor's perspective by 13.74% to 39.34% ($p < 0.05$).[15]

- The fiscal utility attributable to the plasma/albumin-free status of octocog alfa-PFM relative to a plasma/albumin-containing product was estimated in models assuming the emergence of a novel, infectious, plasma-borne virus, such as HIV.[15] Scenarios were related to on-demand treatment of bleeding episodes and they all resulted in potential cost savings for octocog alfa-PFM from a US healthcare payor's perspective. For instance, assuming the cost of a transmitted infection to be 5% that of HIV/AIDS, the potential savings in an 80kg male experiencing 6, 9 or 12 bleeding episodes per year were $US0.12, $US0.08 and $US0.06 per IU of octocog alfa-PFM (year of costing unclear).[15]

4. Tolerability

- In the clinical study programme consisting of the pivotal, continuation, surgery and paediatric studies involving 285 patients (see section 3), the tolerability of octocog alfa-PFM was assessed for a total of 18 555 exposure days (>27 750 infusions).[16] Overall, there were 25 serious adverse events, none of which were judged to be related to octocog alfa-PFM.[16]
- Thirty non-serious adverse events considered related to octocog alfa-PFM were reported in 14 patients.[16] Of these events, 9 were mild, 17 were moderate and 4 were severe (high fever, headache, decreased factor VIII level and haematoma).[3,16] In addition, 2 mild adverse events were reported in a Japanese study involving 15 previously treated patients.[16]
- The most common adverse events with octocog alfa-PFM were headache and dizziness (three patients each), each of which occurred with an incidence of 1.7%.[16] All other adverse events occurred in only one patient each (incidence of 0.6%).
- Post-marketing surveillance during the first 15 months after launch identified 27 adverse events with octocog alfa-PFM.[16] In this period, >260 million IU (MIU) of the drug had been distributed worldwide. Only 17 of the adverse events were considered probably (2) or possibly (15) related to octocog alfa-PFM. Of these, 10 were serious (9 instances of factor VIII inhibitor and 1 case of anaphylaxis) and 7 were non-serious, including reports of allergic reactions, localised skin redness and facial flushing.[16]
- Only one patient in the pre-marketing clinical programme, consisting almost entirely of previously treated patients, developed inhibitors (antibodies) to factor VIII.[16] This previously treated male, aged 55 years, developed low titre inhibitor (2 Bethesda Units) after 26 exposure days.[12] The patient was asymptomatic and the inhibitor disappeared within 8 weeks.[16]
- The estimated incidence of factor VIII inhibitor development in a mixed population of previously treated and untreated patients, based on reported cases in the 18 months following launch, was 0.035 per MIU of octocog alfa-PFM distributed.[17] The equivalent previously estimated incidence with octocog alfa-A was 0.077 per MIU.[17]
- The incidence of inhibitors to octocog alfa is generally considerably lower with previously treated patients than with previously untreated patients.[18] Of the 14 patients developing inhibitors that were considered at least possibly related to octocog alfa-PFM administration in the 18-month post-marketing period, 11 were previously untreated or minimally treated patients and one was a previously treated patient, aged 13 years, with a history of inhibitor development.[17] The extent of previous exposure to factor VIII was uncertain in two patients.[17]

5. Dosage and Administration

The dosage of octocog alfa-PFM required in acute bleeding episodes depends upon the severity of factor VIII deficiency, the site and extent of

bleeding and the patient's clinical condition. The required dose (IU) is generally calculated by multiplying the patient's body weight (kg) by the desired increase (% or IU/dL) in factor VIII multiplied by 0.5 (since administering 1 IU/kg raises the plasma factor VIII activity by 2 IU/dL).[7,19] Routine determination of plasma factor VIII levels is advised in order to guide dosage requirements.

Octocog alfa-PFM is administered by intravenous infusion (≤10mL/min), commonly every 6 to 24 hours during acute bleeding episodes until bleeding is resolved.[7,19]

The dosages recommended in the EU prescribing information for long-term prophylaxis against bleeding in patients with severe haemophilia A are 20–40 IU/kg every 2–3 days in older children and adults and 20–50 IU/kg three to four times per week in children aged <6 years.[7]

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Octocog alfa-PFM: Current Status

Octocog alfa-PFM (Advate®) is approved in the US, the EU, Switzerland and Australia for the prevention and control of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency), and in the US for the perioperative management of patients with haemophilia A.[7,19-21] Octocog alfa-PFM was shown to have AUC_{48} values and *in vivo* recoveries similar to those of the previously marketed albumin-containing formulation (Recombinate®) and to be effective in treating and preventing bleeding episodes in patients of all age ranges, regardless of the origin or the site of the bleeding. Octocog alfa-PFM was well tolerated, with a low incidence of inhibitors to factor VIII.

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