Comparison of Real-World Dose and Consumption for Two Extended Half-Life Recombinant Factor VIII Products for the Treatment of Hemophilia A in the United States

Yanyu Wu1, Shawn X Sun1, Tao Fan2

1Global Evidence & Outcomes, Data Sciences Institute, Research and Development, Takeda Development Center Americas, Inc, Cambridge, MA, USA; 2US Health Economics and Outcomes Research, Takeda Pharmaceuticals USA, Inc, Lexington, MA, USA

Correspondence: Yanyu Wu, Global Evidence & Outcomes, Data Sciences Institute, Research and Development, Takeda Development Center Americas, Inc, 40 Landsdowne Street, Cambridge, MA, USA, Tel +1 617-955-6408, Email yanyu.wu@takeda.com

Background: US patients with hemophilia A can receive prophylaxis with extended half-life recombinant factor VIII (rFVIII) products, including efmoroctocog alfa (fragment crystallizable fusion protein) and rurioctocog alfa pegol (antihemophilic factor [recombinant], PEGylated).

Objective: To evaluate dosing patterns and weekly consumption of extended half-life rFVIII products in the United States.

Methods: We performed a retrospective analysis using the US Specialty Pharmacy Database (2015–2018). Included patients had a diagnosis of hemophilia A, ≥2 consecutive monthly claims for efmoroctocog alfa or rurioctocog alfa pegol for prophylaxis, and weight data. Outcome measures included weekly dosing frequency and dispensed weekly dose.

Results: The analysis included 774 patients (efmoroctocog alfa, 506; rurioctocog alfa pegol, 268). Mean (SD) age was 24.2 (15.8) and 26.3 (14.9) years for patients receiving efmoroctocog alfa and rurioctocog alfa pegol, respectively; mean (SD) weight was 68.4 (36.8) and 79.8 (37.7) kg, respectively. The most frequent efmoroctocog alfa regimen was twice weekly (45.7%), followed by every 4 days (20.6%), every 3 days (9.1%), and 3 times per week (7.5%). The most frequent rurioctocog alfa pegol regimen was twice weekly (72.4%), followed by 3 times per week (8.7%), every 4 days (7.6%), and every 3 days (5.5%). The proportion of efmoroctocog alfa twice-weekly dispensing records increased from 31.5% to 50.9%, and every 4 days dispensing records decreased from 31.3% to 14.5% (2015–2018). The proportion of rurioctocog alfa pegol dispensing records remained broadly stable (2016–2018). Overall, mean (SD; median) weekly prophylactic dose was 105.4 (77.9; 92.6) IU/kg with efmoroctocog alfa, and 96.8 (41.9; 90.9) IU/kg with rurioctocog alfa pegol.

Conclusion: In this database study, the most frequently observed dosing frequency was twice weekly for patients receiving efmoroctocog alfa or rurioctocog alfa pegol. The observed mean weekly consumption was slightly higher, and variation was greater, in patients receiving efmoroctocog alfa versus rurioctocog alfa pegol.

Keywords: hemophilia A, fragment crystallizable fusion protein, efmoroctocog alfa, antihemophilic factor (recombinant), PEGylated, rurioctocog alfa pegol, dosing patterns

Introduction

Hemophilia A is a recessive congenital bleeding disorder caused by a deficiency of factor VIII (FVIII).1 The estimated worldwide prevalence is 17.1 cases per 100,000 males.2 The recommended care for patients with severe hemophilia A is prophylactic replacement therapy with recombinant FVIII (rFVIII) to prevent bleeding and maintain joint health.3,4 However, conventional factor concentrates have a short half-life of 8–12 hours,5 which necessitates frequent intravenous infusions. Therefore, standard half-life (SHL) rFVIII concentrates can result in a high treatment burden for patients, which can have a negative impact on treatment adherence,6 potentially leading to poorer bleeding outcomes. Extended...
half-life (EHL) rFVIII products with improved pharmacokinetic profiles have been developed, allowing patients to extend the interval between treatments. The plasma half-life of FVIII has been extended through recombinant technology, either by fusion with the fragment crystallizable (Fc) region of the immunoglobulin G1 molecule or by conjugation with the polymer polyethylene glycol (PEG). Efmaroctocog alfa (Eloctate; Bioverativ Therapeutics Inc., Waltham, MA, USA) is a rFVIII-Fc fusion protein. A phase 3 trial analyzed the pharmacokinetics of efmaroctocog alfa and reported that the terminal half-life was extended 1.5-fold versus a commercially available rFVIII product, octocog alfa (antihemophilic factor [recombinant], plasma/albumin-free method [Advate [Europe]; Takeda Manufacturing Austria AG] geometric mean = 19.0 vs 12.4 hours, respectively). Rurioctocog alfa pegol, antihemophilic factor (recombinant), PEGylated (Adynovate [United States]/Adynovi [Europe]; Baxalta Inc., a Takeda company, Lexington, MA, USA) is a recombinant full-length human coagulation FVIII covalently conjugated with at least one molecule of PEG. A pivotal study showed that the half-life for rurioctocog alfa pegol increased 1.4-fold versus octocog alfa (14.3 vs 10.4 hours, respectively) in patients aged ≥12 years.

Efmaroctocog alfa was approved in the United States in 2014 for use in adults and children with hemophilia A. According to the product label, the recommended starting regimen for prophylaxis (at the time of the study) in patients aged ≥6 years is 50 IU/kg administered every 4 days. The dose can be adjusted, based on the patient response, within a range of 25–65 IU/kg every 3–5 days. For patients aged <6 years, the recommended starting regimen is 50 IU/kg administered twice weekly. The regimen can be adjusted based on patient response, with dosing in the range of 25–65 IU/kg at 3–5-day intervals, with more frequent or higher doses up to 80 IU/kg if required. A pivotal phase 3 study of males aged ≥12 years with severe hemophilia A found that prophylaxis with efmaroctocog alfa was well tolerated and effective in the prevention and treatment of bleeding and did not result in increased immunogenicity.

Rurioctocog alfa pegol was first approved for use in November 2015. The prescribing information recommends a dose of 40–50 IU/kg twice weekly for patients aged ≥12 years. For patients aged <12 years, the recommended starting dose is 55 IU/kg twice weekly. The dose can be adjusted based on the patient’s clinical response, with a maximum of 70 IU/kg. A phase 3b study among patients with severe hemophilia A found that rurioctocog alfa pegol as long-term prophylaxis provided good hemostatic efficacy and had a similar safety and immunogenicity profile to previously published data.

There is a lack of published studies of real-world treatment patterns for EHL rFVIII among patients with hemophilia A. In 2020, an observational study of US patients with hemophilia A reported a reduction in the frequency of treatment administration (mean days/week) after patients switched from an SHL rFVIII to rurioctocog alfa pegol (from 2.8 to 2.2 days). The authors also reported lower consumption by patients who switched from SHL rFVIII to rurioctocog alfa pegol (from 109.8 to 100.6 IU/kg). A Canadian report of efmaroctocog alfa utilization for the first 8 months following availability in 2014 showed a 19% reduction in factor utilization (based on weekly IU/kg) among patients with severe hemophilia A who switched from SHL rFVIII to efmaroctocog alfa. Another Canadian study reported a retrospective analysis of pharmacokinetic data from 23 patients with hemophilia A who were switched from efmaroctocog alfa to rurioctocog alfa pegol. The results showed minor differences in the pharmacokinetic profile of the two agents, which were statistically significant (p<0.05 for all) for in vivo recovery (mean 2.73 vs 2.41 IU/dL per IU/kg), clearance (mean 0.163 vs 0.194 mL/h), and volume of distribution at steady state (mean 42.5 vs 49.8 mL/kg), respectively. The authors commented, however, that the clinical implications of these differences are uncertain. Indeed, an earlier study from the same centers showed that the pharmacokinetic profiles of efmaroctocog alfa to rurioctocog alfa pegol in adolescents with hemophilia A were almost identical (mean [range] terminal half-life 16.1 (10.4–23.4) hours vs 16.7 (11.0–23.6) hours, respectively [p=NS]).

There is a need for further real-world evidence on EHL products to improve the understanding of prophylaxis dosing patterns associated with each EHL rFVIII to inform health care decision-making and identify the most appropriate treatment regimens for different patient groups. We therefore undertook a retrospective analysis of US specialty pharmacy data to evaluate real-world dosing patterns (weekly dose, infusion frequency) of efmaroctocog alfa and rurioctocog alfa pegol for the prophylactic treatment of patients with hemophilia A without inhibitors.
Methods

Study Design and Data Source
This study was a retrospective analysis of prescription dispensing data from the US Specialty Pharmacy Database and includes >2400 patients with hemophilia from all 50 states. The database comprises de-identified data including patient demographics, detailed prescription information, and clinical data such as diagnosis, disease severity, and inhibitor status, and is fully compliant with regulations from the Health Insurance Portability and Accountability Act (HIPAA) of 1996. De-identified prescription dispensing data were collected for the period between January 1, 2015 and December 31, 2018.

Patient Population
Patients were included in the analysis if they had a diagnosis of hemophilia A using International Classification of Diseases (ICD)-9 code 286.0 or ICD-10 code D66. For registration in the database, patients were required to have received medication for hemophilia A from one of the Specialty Pharmacy Providers included in the database. This study included patients from the database that had at least two consecutive monthly pharmacy dispensing records for efmoroctocog alfa or rurioctocog alfa pegol administered for prophylaxis during the study period. Body weight data and valid dispensing units in the patient record were also required. Patients were excluded if they received immune tolerance induction therapy or more than one dose per day, because this is given to patients receiving immune tolerance induction therapy or could be a coding error. Patients receiving perioperative management were not included in the database.

Outcome Measures
We evaluated the weekly consumption (IU/kg) of efmoroctocog alfa or rurioctocog alfa pegol. The frequency of dosing was evaluated according to the number and percentage of patients with a prophylactic dose recorded (once weekly, twice weekly, 3 times per week, every 3 days, every 4 days, every 5 days). Infusion frequency data for efmoroctocog alfa were available from 2015 to 2018; data for rurioctocog alfa pegol were available from 2016 to 2018. We evaluated the number and percentage of pharmacy dispensing records with doses ≤50 and >50 IU/kg. For the purposes of comparison between the two drugs, this threshold was chosen because 50 IU/kg is the starting dose for efmoroctocog alfa, per the label. The above outcomes (consumption, frequency of dosing) were analyzed for patients in each treatment group; consumption was also analyzed by age category (<12 and ≥12 years).

Statistical Analyses
Descriptive analyses were performed for patient demographic characteristics and clinical conditions. Patient characteristics were summarized using mean (SD) for continuous outcomes and counts, while proportions and counts described categorical variables. Consumption was described by the mean (SD) and median (interquartile range). Between-group comparisons were made using t-test for the weekly consumption (continuous variable) and chi-square test for dosing frequency (categorical variable).

Mean weekly prophylaxis was calculated based on the following:
\[
\text{dispensed units} \times \frac{\text{patient weight}}{\text{number of days between pharmacy dispensing records}} \times 7
\]

The dose from the last observed pharmacy dispensing claim was excluded because the number of days covered by that record could not be calculated. Only consecutive claims were included; claims with more than a 1-month gap to the next claim were excluded.

The proportion of patients receiving efmoroctocog alfa and rurioctocog alfa pegol doses that were above, below, and equal to the prophylactic dose of 50 IU/kg was calculated. Subgroup analyses according to age groups (<12 and ≥12 years) were performed for patients who received efmoroctocog alfa or rurioctocog alfa pegol using pharmacy dispensing records from 2017, when both EHL products had been approved for use in the United States for ≥1 year.
Results

Patient Characteristics

A total of 774 patients were included in the study (efmoroctocog alfa, n=506; rurioctocog alfa pegol, n=268) (Table 1). The mean (SD) ages of patients who received efmoroctocog alfa and rurioctocog alfa pegol were 24.2 (15.8) and 26.3 (14.9) years, respectively.

A higher proportion of patients aged 0 to <12 years was observed in the efmoroctocog alfa group versus the rurioctocog alfa pegol group (24.3% vs 14.6%, respectively). Among patients aged ≥12 years, the mean age was 31.2 years in the efmoroctocog alfa group and 29.7 years in the rurioctocog alfa pegol group, with a similar age distribution between groups. The mean (SD) weight was 68.4 (36.8) and 79.8 (37.7) kg for patients receiving efmoroctocog alfa and rurioctocog alfa pegol, respectively. A higher proportion of patients receiving rurioctocog alfa pegol had severe hemophilia A versus those receiving efmoroctocog alfa (79.9% vs 57.5%). The states with the most patients in the database were California, Florida, Massachusetts, and Ohio. Florida had the highest proportion of patients receiving efmoroctocog alfa (20.2%), while Ohio had the highest proportion of patients receiving rurioctocog alfa pegol (16.0%).

Dosing Frequency

From 2015 to 2018, the most frequent dosing regimens overall were twice weekly for both efmoroctocog alfa (45.7%) and rurioctocog alfa pegol (72.4%) (Supplementary Figure 1). For efmoroctocog alfa, this was followed by every 4 days (20.6%), every 3 days (9.1%), and 3 times per week (7.5%). For rurioctocog alfa pegol, it was followed by 3 times per week (8.7%), every 4 days (7.6%), and every 3 days (5.5%) (p<0.001 for distribution of dose frequencies between efmoroctocog alfa and rurioctocog alfa pegol). During 2015–2018 (after US approval in June 2014), the proportion of efmoroctocog alfa twice-weekly dispensing records increased from 31.5% in 2015 to 50.9% in 2018, and every 4 days dispensing records decreased from 31.3% in 2015 to 14.5% in 2018. During 2016–2018 (after US approval in November 2015), the proportion of rurioctocog alfa pegol dispensing records remained broadly stable.

| Characteristic                      | Efmoroctocog Alfa n=506 | Rurioctocog Alfa Pegol n=268 |
|-------------------------------------|--------------------------|------------------------------|
| Age group (as of 2018), n (%)       |                          |                              |
| 0 to <6 years                       | 38 (7.5)                 | 10 (3.7)                     |
| 6 to <12 years                      | 85 (16.8)                | 29 (10.8)                    |
| 12 to <18 years                     | 75 (14.8)                | 45 (16.8)                    |
| ≥18 years                           | 267 (52.8)               | 182 (67.9)                   |
| Missing                             | 41 (8.1)                 | 2 (0.8)                      |
| Hemophilia A severity, n (%)*       |                          |                              |
| Mild (>5–30%)                       | 10 (2.0)                 | 4 (1.5)                      |
| Moderate (1–5%)                     | 26 (5.1)                 | 15 (5.6)                     |
| Severe (<1%)                        | 291 (57.5)               | 214 (79.9)                   |
| Unknown                             | 179 (35.4)               | 35 (13.1)                    |
| Top four health care provider states, n (%)* |  |                              |
| California                          | 48 (9.5)                 | 26 (9.7)                     |
| Florida                             | 102 (20.2)               | 23 (8.6)                     |
| Massachusetts                       | 23 (4.6)                 | 27 (10.1)                    |
| Ohio                                | 41 (8.1)                 | 43 (16.0)                    |

Notes: *Disease severity as recorded in the database records. aValues in parentheses indicate FVIII levels, percentage of normal. bBased on data from all 50 states.
Overall, for patients receiving efmoroctocog alfa, the mean (SD) weekly consumption was 105.4 (77.9) IU/kg; the weekly consumption for patients receiving rurioctocog alfa pegol was 96.8 (41.9) IU/kg (p<0.001 vs efmoroctocog alfa). Mean weekly consumption was slightly higher in patients aged <12 versus ≥12 years for both efmoroctocog alfa and rurioctocog alfa pegol from 2015 to 2018. By age category, mean weekly consumption was 109.5 (108.2) IU/kg for patients aged <12 years and 103.3 (57.9) IU/kg for patients aged ≥12 years receiving efmoroctocog alfa. For patients receiving rurioctocog alfa pegol, mean weekly consumption was 108.5 (48) IU/kg for patients aged <12 years and 94.6 (40.4) IU/kg for patients aged ≥12 years (Figure 1).

Subgroup Analysis
The subgroup analysis using 2017 data showed higher mean weekly consumption for patients who received efmoroctocog alfa versus those who received rurioctocog alfa pegol. By age category, the mean consumption for patients aged ≥12 years or <12 years was higher for patients receiving efmoroctocog alfa versus rurioctocog alfa pegol (Supplementary Table 1).

Discussion
This analysis of the US Specialty Pharmacy Database showed that the most frequently observed dispensed treatment regimen between 2015 and 2018 was twice weekly for both efomorococog alfa and rurioctocog alfa pegol. This aligns with previously published clinical trial efficacy data, where twice-weekly prophylaxis regimens of efomorocog alfa and rurioctocog alfa pegol resulted in low annualized bleeding rates.7,10,12 Further, in separate trials prophylaxis with rurioctocog alfa pegol twice-weekly or efomorococog alfa every 3–5 days resulted in 40% and 45% of patients, respectively, having zero bleeds.10,12 It seems likely that the choice of twice-weekly dosing was made for convenience.
reasons, as it is less challenging for patients than dosing every 4 days. The advantage of dosing every 4 days, however, is the reduction in the number of total infusions by 1–2 per month, particularly as reduction in dosing frequency is seen as highly desirable by patients and caregivers. In patients who are highly active or have other clinical needs, more frequent dosing than every 4 days may be necessary even with EHL products, and studies have demonstrated the importance of individualized dosing.

In the present study, overall weekly consumption was slightly higher for efmoroctocog alfa versus rurioctocog alfa pegol. Twice-weekly dosing for efmoroctocog alfa increased from 31.5% in 2015 to 50.9% in 2018 but remained broadly stable for rurioctocog alfa pegol (67.0% to 72.2%). A possible explanation for this is that efmoroctocog alfa was approved in June 2014 and clinicians may have become familiar with its use before rurioctocog alfa was approved ~1.5 years later. It has been estimated that the use of EHL rFVIII products results in a 30% reduction in the numbers of annual infusions versus SHL products. The results of the current study provide real-world evidence to support the finding that EHL rFVIII allows patients with hemophilia A to extend the time periods between intravenous injections.

Notably, most patients receiving efmoroctocog alfa and rurioctocog alfa pegol resided in Florida and Ohio, respectively, likely due to different drug formularies between regions/states. A higher mean weekly consumption was observed for patients receiving efmoroctocog alfa (105.4 IU/kg) versus rurioctocog alfa pegol (96.8 IU/kg), a finding that is meaningful economically. These results are broadly consistent with a published real-world exploratory analysis of SHL products (morocotocog alfa, octocog alfa, simoctocog alfa, turoctocog alfa) versus EHL products (efmoroctocog alfa and rurioctocog alfa pegol).

Our consumption results for efmoroctocog alfa are very similar to those presented previously, where the authors reported a mean weekly consumption (all ages) of 104 (79.4) IU/kg. Our observed consumption findings for rurioctocog alfa pegol are also similar to the findings of a real-world study published in 2020 of patients with hemophilia A who received rurioctocog alfa pegol after switching from an SHL rFVIII (overall mean weekly dose, 100.6 IU/kg). The slight increase in consumption for patients receiving efmoroctocog alfa versus rurioctocog alfa pegol in the current study is likely explained by the higher dose and infusion frequency recommended in the prescribing information for efmoroctocog alfa (according to the label, the dosing frequency for adults is every 4 days). In contrast to the prescribing information, our real-world data show that twice weekly is the most frequently used infusion frequency, which is likely due to convenience as it is less challenging for patients to follow than dosing every 4 days.

The proportion of children aged <12 years was substantially higher in the efmoroctocog alfa group than the rurioctocog alfa pegol group. We observed that mean weekly consumption was slightly higher in patients aged <12 versus ≥12 years for both efmoroctocog alfa and rurioctocog alfa pegol, which could have affected our observed results, given the possibility of age-dependent pharmacokinetic variation and the shorter half-life of FVIII in young children than in adults. Our finding of greater consumption variability among patients receiving efmoroctocog alfa suggests less predictable utilization and indicates differences in the prescribing information for efmoroctocog alfa versus rurioctocog alfa pegol (eg, different dosing frequencies for patients aged ≥6 vs <6 years). It may also reflect greater use of personalized treatment regimens with efmoroctocog alfa, based on its longer period of availability and data obtained from clinical trials and presented in the prescribing information.

**Limitations**

We acknowledge some limitations that are inherent to database analyses. The US Specialty Pharmacy Database does not include all specialty pharmacy providers and therefore may not be representative of the total US population with hemophilia A. The recording of treatment regimen, infusion frequency, and disease severity may be inconsistent in a pharmacy dispensing records database. For example, no information on disease severity was recorded for 35% of patients in the efmoroctocog alfa group and 13% in the rurioctocog alfa pegol group. In addition, the treatment selection and clinical response may affect dosing patterns. These factors were not investigated owing to lack of information in the pharmacy dispensing records data. The current analysis focused on FVIII utilization (frequency of infusions, consumption), but did not link the data to clinical outcomes. Finally, it should be noted that there were important differences between the two treatment groups, potentially affecting comparisons between the two agents. For example, there were
almost twice as many patients in the efomoroctocog alfa group than the rurioctocog alfa pegol group, reflecting the longer availability, and therefore potential study period, of efomoroctocog alfa. There was also a higher percentage of children aged <12 years in the efomoroctocog alfa group (24%) compared with the rurioctocog alfa pegol group (15%), and a higher proportion of patients receiving rurioctocog alfa pegol had severe hemophilia A (79.9%) versus those receiving efomoroctocog alfa (57.5%).

Conclusions
This retrospective database analysis provides additional evidence to increase the understanding of real-world dosing and utilization patterns of EHL rFVIII in patients with hemophilia A without inhibitors, which may help providers to understand clinical effectiveness implications for these therapies. Together, the results of this real-world study and those of clinical trial data suggest that the use of EHL rFVIII may reduce the treatment burden for patients. Additional research is needed to evaluate the reasons for changes in dosing patterns over time and the associated clinical outcomes.

Abbreviations
EHL, extended half-life; FVIII, factor VIII; HIPAA, Health Insurance Portability and Accountability Act; ICD, International Classification of Diseases; IQR, interquartile range; PEG, polyethylene glycol; rFVIII, recombinant factor VIII; SHL, standard half-life.

Data Sharing Statement
The data that support the findings of this study are available from Specialty Pharmacy Database records from individual states, but restrictions apply to the availability of these data due to applicable privacy laws and data use agreements. The data were used pursuant to data use agreements between Shire US Inc., a Takeda company, and the individual states.

Ethics Approval and Informed Consent
No institutional review board approval was required for this retrospective database analysis because only de-identified data were used. All data analyzed in the present study complied with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 for fully de-identified datasets.

Acknowledgments
Medical writing and editorial support were provided by Lisa O’Brien, PharmD, and Roz Bonomally, MSc, employees of Excel Medical Affairs (Fairfield, CT, USA) and funded by Takeda Development Center Americas, Inc., Lexington, MA, USA.

Author Contributions
All authors made a significant contribution to the conception, study design, execution, acquisition of data, analysis and/or interpretation of the manuscript. In addition, all authors took part in drafting, revising, and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding
This study was funded by Takeda Pharmaceutical Company Limited, Cambridge, MA, USA. The study sponsor was involved with the study design, analysis and interpretation of data, writing of the manuscript, and decision to publish the article.

Disclosure
Y. Wu and S.X. Sun are employees of Takeda Development Center Americas, Inc., Cambridge, MA, USA, and Takeda stock owners. T. Fan is an employee of Takeda Pharmaceuticals USA, Inc., Lexington, MA, USA, and Takeda stock owner. The authors report no other conflicts of interest in this work.
References

1. Mannucci PM, Tuddenham EG. The hemophilias — from royal genes to gene therapy. N Engl J Med. 2001;344(23):1773–1779. doi:10.1056/NEJM200010063442307

2. Iorio A, Stonebraker JS, Chambost H, et al.; Data Demographics Committee of the World Federation of Hemophilia. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. Ann Intern Med. 2019;171(8):540–546. doi:10.7326/M19-1208

3. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. Blood. 2015;125(13):2038–2044. doi:10.1182/blood-2015-01-528414

4. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia panelists and co-authors. WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia. 2020;26(Suppl6):1–158. doi:10.1111/hae.14046

5. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al.; Treatment Guidelines Working Group on Behalf Of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1–47. doi:10.1111/hae.1356-2516.2012.02909.x

6. Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. Haemophilia. 2001;7(4):392–396. doi:10.1046/j.1365-2516.2001.00534.x

7. Mannucci PM. Benefits and limitations of extended plasma half-life factor VIII products in hemophilia A. Expert Opin Investig Drugs. 2020;29(3):303–309. doi:10.1080/13546808.2020.1723547

8. Mahdi AJ, Obaji SG, Collins PW. Role of enhanced half-life factor VIII and IX in the treatment of haemophilia. Br J Haematol. 2015;169(6):766–776. doi:10.1111/bjh.13360

9. Biogen Inc. ELOCTATE® [antihemophilic factor (recombinant), Fc fusion protein] lyophilized powder for solution for intravenous injection; 2014. Available from: https://www.fda.gov/media/98746/download. Accessed January 27, 2020.

10. Mahlangu J, Powell JS, Ragni MV; A-LONG Investigators. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014;123(3):317–325. doi:10.1182/blood-2013-10-529974

11. Baxalta US Inc. ADYNOVATE, antihemophilic factor (recombinant), PEGylated lyophilized powder for solution for intravenous injection; 2021. Available from: https://www.fda.gov/media/94470/download. Accessed January 27, 2020.

12. Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. Blood. 2015;126(9):1078–1085. doi:10.1182/blood-2015-03-630897

13. Chowdary P, Mullins ES, Konkle BA, et al. Long-term safety and efficacy results from the phase 3b, open-label, multicentre Continuation study of rurioctocog alfa pegol for prophylaxis in previously treated patients with severe haemophilia A. Haemophilia. 2020;26(4):e168–e178. doi:10.1111/hae.14052

14. Aledort L, Milligan S, Watt M, Booth J. A retrospective observational study of rurioctocog alfa pegol in clinical practice in the United States. J Manag Care Spec Pharm. 2020;26(4):492–503. doi:10.18553/jmcp.2020.26.4.492

15. Keepanasseril A, Stoffman J, Bouskill V, et al. Switching to extended half-life products in Canada - preliminary data. Haemophilia. 2017;23(4):e365–e367. doi:10.1111/hae.13245

16. Teitel J, Sholzberg M, Iorio A. Extended half-life factor VIII concentrates in adults with hemophilia A: comparative pharmacokinetics of two products. Res Pract Thromb Haemost. 2021;5(2):349–355. doi:10.1002/rth2.12476

17. Carcao MD, Chelle P, Clarke E, et al. Comparative pharmacokinetics of two extended half-life FVIII concentrates (Eloctate and Adynovate) in adolescents with hemophilia A: is there a difference? J Thromb Haemost. 2019;17(7):1085–1096. doi:10.1111/jth.14469

18. Su J, Li N, Joshi N, et al. Patient and caregiver preferences for haemophilia A treatments: a discrete choice experiment. Haemophilia. 2020;26(6):e291–e299. doi:10.1111/hae.14137

19. Valentino LA, Pipe SW, Collins PW, et al. Association of peak factor VIII levels and area under the curve with bleeding in patients with haemophilia A on every third day pharmacokinetic-guided prophylaxis. Haemophilia. 2016;22(4):514–520. doi:10.1111/hae.12905

20. Klamroth R, Windyga J, Radulescu V, et al. Rurioctocog alfa pegol PK-guided prophylaxis in hemophilia A: results from the phase 3 PROPEL study. Blood. 2021;137(13):1818–1827. doi:10.1182/blood.2020005673

21. Mannucci PM. Hemophilia therapy: the future has begun. Haematologica. 2020;105(3):545–553. doi:10.3324/haematol.2019.232132

22. Chhabra A, Spurden D, Frogarty PF, et al. Real-world outcomes associated with standard half-life and extended half-life factor replacement products for treatment of haemophilia A and B. Blood Coagul Fibrinolysis. 2020;31(3):186–192. doi:10.1097/MBC.0000000000000885

23. Booth J, Lu M, Bron M, Hafeman A. Real world dosing and therapy switching patterns of rFVIII-Fc from specialty pharmacy providers in the United States. Poster presented at: WFH World Congress; July 24–28; 2016; Orlando, FL, USA. Available from: https://www.postersessiononline.eu/173580348_eu/congresos/WFH2016/aula/PP-T_66_WFH2016.pdf. Accessed August 31, 2022.

24. Collins PW, Björkman S, Fischer K, et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens. J Thromb Haemost. 2010;8(2):269–275. doi:10.1111/j.1538-7836.2009.03703.x