Utah Medicaid Pharmacy and Therapeutics Committee
Drug Class Review

Factor VIII Replacement Products
Indicated for Hemophilia A

Antihemophilic Factor, Human

Hemofil M
Koate
Koate DVI
Monoclate-P

Antihemophilic Factor, Recombinant

Advate
Adynovate
Afstyla
Eloctate
Helixate FS
Kogenate FS
Kovaltry
Novoeight
Nuwiq
Recombinate
Xyntha

AHFS Classification: 20:28.16 Hemostatics

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Executive Summary

Hemophilia A is an X-linked inherited, lifelong bleeding disorder.[1] Patients with this disorder have deficient levels of the blood-clotting factor VIII (FVIII), a protein essential for maintaining hemostasis. In these patients, bleeding episodes can be triggered by trauma or surgery. Patients may experience recurrent, spontaneous bleeding into joints or muscle—most common with severe disease.[2] Quality of life is diminished as the long-term effects of recurrent bleeding episodes manifest as chronic joint disease, pain, and disability. If left untreated, patients face potential loss of life from bleeds into the central nervous system or vital organs, or due to prolonged bleeding. Disease management strategies aim to not only prevent and treat potentially life-threatening bleeds on an episodic basis, but also include routine prophylaxis for the prevention of recurrent bleeds and arthropathy.[3-5]

Plasma-derived FVIII (pdFVIII) and recombinant-DNA technology derived FVIII (rFVIII) products are available. All agents are administered intravenously. Manufacturing processes have improved over time to eliminate the use of human or animal additives that can introduce viruses. First-generation rFVIII products contain human and/or animal proteins in the production process and final product. Second generation rFVIII products are exposed to human or animal proteins in the cell culture medium but not in the final product. Third generation rFVIII products do not have human or animal proteins added into the cell-growth medium or final product.[6] Table 1 lists the FVIII product indications and Table 2 includes product description, technology, and packaging information for the FVIII replacement products.

The risk of disease transmission is theoretically less with rFVIII products compared to pdFVIII products; thus, rFVIII is recommended over pdFVIII as the standard of care per the National Hemophilia Foundation's Medical and Scientific Advisory Committee (MASAC).[6] Other organizations such as the Australian Haemophilia Centre Directors' Organisation[7] and the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO),[8] also recommend using rFVIII products over pdFVIII products. Guidelines do not specify a preference for one rFVIII product over another, nor is preference stated for one pdFVIII factor over another. The product chosen depends on individual pharmacokinetics, and patient circumstances.[9,10]

Routine prophylaxis dosing is determined based on the individual's disease severity and clinical response, since there is wide interpatient half-life variability among FVIII products. Some products were developed with the aim of lengthening the FVIII half-life to improve convenience and adherence to therapy; however, there is no widely-accepted definition for what constitutes as an extended-half-life FVIII (EHL-FVIII) product. The potential benefit of using a longer-acting product (e.g., a reduction in administration frequency) depends on the drug's patient-specific pharmacokinetic profile.

The most challenging aspect to the management of hemophilia is the development of inhibitors (neutralizing antibodies) to the replacement factor product, which diminishes or ultimately renders the particular product in use ineffective.[11] Decisions regarding the appropriate treatment regimen for managing a patient with an inhibitor depends on

several factors including the inhibitor titer (i.e. inhibitor concentration), whether the patient is experiencing an active bleed, and the previous response to inhibitor mitigation. Treatment options include immune tolerance induction (ITI) with higher doses of FVIII, the employment of bypassing agents (e.g. recombinant activated FVII [rFVIIa] and activated prothrombin complex concentrate [aPCC]), or the use of the monoclonal antibody, emicizumab.[6]

MASAC states that ITI is the best option for high-titer inhibitor eradication,[6] and that physicians should consider prophylaxis with bypassing agents (aPCC and rFVIIa) in patients with inhibitors.[12] In a 2015 guideline on ITI for patients with inhibitors, the authors stated that there is insufficient evidence regarding which FVIII agent should be used for ITI. Consequently, they do not recommend one product over another.[11] The 2013 UKHCDO guideline states that "[f]irst-line ITI should be conducted using rFVIII concentrate, unless as part of a clinical trial, and is usually performed with the product used by the patient at the time of inhibitor development."[8]

A systematic review of the literature for head-to-head randomized controlled trial (RCT) evidence addressing the possible treatment-effect differences between the FVIII products was performed. A total of 1271 unique titles/abstracts identified in PubMed and Embase were screened.

No head-to-head RCTs comparing the efficacy or safety of individual FVIII products with one another in the setting of on-demand therapy or routine prophylaxis therapy were identified. Overall, evidence is insufficient to conclude that there are differences in potential treatment effects among the FVIII products included in this review in terms of clinical endpoints (e.g. bleeding frequency, joint damage, joint function, pain, quality of life, and inhibitor development) for the treatment of hemophilia A.

This review address products labeled as human- or recombinant-derived antihemophilic factor (i.e., FVIII). Products labeled as pdFVIII/von Willebrand Factor complexes (Alphanate, Humate P, and Wilate) or recombinant von Willebrand Factor (Vonvendi) will be included in the September 2018 drug-class review.

Introduction

The single-ingredient factor VIII (FVIII) products addressed in this review are indicated to treat hemophilia A, a rare X-linked bleeding disorder.[1] Patients with hemophilia A have deficient levels of the clotting factor VIII, and thus benefit from substitution therapy with replacement FVIII products.[13,14] Disease management strategies aim to not only prevent and treat potentially life-threatening bleeds on an episodic basis, but also include routine prophylaxis for the prevention of bleeding, especially recurrent intra-articular bleeds which induce joint deformation and long-term motor impairment and disability in patients with hemophilia.

Replacement products are either derived from human plasma (plasma-derived FVIII [pdFVIII]), or are produced via genetic recombination technology (recombinant FVIII [rFVIII]). FVIII products are administered intravenously either on-demand, or for routine prophylaxis several times a week to reduce the frequency of bleeding episodes.

On-demand dosing for the control of bleeding episodes depends on the severity and location. Dosing for perioperative management depends on the type of surgery. With regard to routine prophylaxis, doses and frequencies must be based on the individual's disease severity and clinical response, especially since there is wide interpatient half-life variability with all FVIII products. Implantable venous access devices may be utilized for routine prophylaxis. Patients and/or caregivers must learn aseptic administration techniques to allow for at-home administration of FVIII several times a week.

This report will include a systematic review for head-to-head comparative evidence addressing the possible treatment-effect differences between the FVIII products listed in Table 1. We will also discuss safety concerns related to the use of these agents. The Utah Medicaid Preferred Drug List currently does not include these products. The Utah Drug Regimen Review Board reviewed some of the FVIII products in January of 2017; however, no prior authorization criteria were established at that time. Products labeled as pdFVIII/von Willebrand Factor complexes or recombinant von Willebrand Factor will be included in the September 2018 drug-class review. These products (Alphanate, Humate P, Wilate, and Vonvendi) are indicated for von Willebrand Disease; Alphanate and Humate P also have Hemophilia A indications.

Table 1 lists the single-ingredient FVIII products available in the United States (US) and their labeled indications. These products are available in single-dose vials and are labeled with the factor VIII potency expressed in international units (IU) since this varies from batch to batch. One IU is defined as the concentration equivalent to the level of FVIII activity in 1 mL of human plasma.[15,16]

Table 1. Single Ingredient Factor VIII Replacement Products Indicated for Hemophilia A

Product (approval year)	Labeled Indications for Hemophilia A[a]						
	Routine Prophylaxis to Prevent or Reduce the Frequency of Bleeding Episodes	Prevention of Bleeding	Control of Hemorrhagic Episodes	Peri-operative Management	Indicated for Children	Indicated for Adults	Single-dose vials (IU nominal potency)
Human Plasma Derived Antihemophilic Factor Products							
Hemofil M[17] (1966)		X	X		Age group unspecified		250, 500, 1,000, 1700
Koate[18] (1974)	X[b]	X	X	X	Age group unspecified		250, 500, 1,000
Koate DVI[19] (1974)	X[b]	X	X	X	[c] See note	X	
Monoclate P[20] (1972)[d]			X	X	Age group unspecified		250, 500, 1,000, 1500
Recombinant Antihemophilic Factor Products							
Advate[21] (2003)	X	X	X	X	X	X	250, 500, 1,000, 1500, 2000, 3000, 4000
Adynovate[22] (2015)	X		X	X	X	X	250, 500, 750, 1,000, 1500, 2000, 3000
Afstyla[23] (2016)	X		X	X	X	X	250, 500, 1000, 1500 2000, 2500, 3000
Eloctate[15] (2014)	X		X	X	X	X	250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000, 6000

Table 1. Single Ingredient Factor VIII Replacement Products Indicated for Hemophilia A

Product (approval year)	Labeled Indications for Hemophilia A[a]				Indicated for Children	Indicated for Adults	Single-dose vials (IU nominal potency)
	Routine Prophylaxis to Prevent or Reduce the Frequency of Bleeding Episodes	Prevention of Bleeding	Control of Hemorrhagic Episodes	Peri-operative Management			
Helixate FS[16] (1993)	X (additionally, to reduce the risk of joint damage in children without pre-existing joint damage)		X	X	X	X	250, 500, 1000, 2000, 3000
Kogenate FS[24] (1993)			X	X	X	X	250, 500, 1000, 2000, 3000
Kovaltry[25] (2016)	X		X	X	X	X	250, 500, 1000, 2000, 3000
Novoeight[26] (2013)	X	X	X	X	X	X	250, 500, 1000, 1500, 2000, 3000
Nuwiq[27] (2015)	X		X	X	X	X	250, 500, 1000, 2000, 2500, 3000, 4000
Recombinate[28] (1992)		X	X	X	X	X	250, 500, 1000, 1500, 2000
Xyntha[29] (2008)		X	X	X	X	X	250, 500, 1000, 2000

Abbreviation: IU, international units

[a] Products listed in Table 1 are not indicated for von Willebrand Disease

[b] Routine prophylaxis is mentioned in the dosing section or special population section; however, not specifically stated in the indication section of the product labeling

[c] Koate DVI labeling notes that the DVI version has not been studied in pediatrics; however, the Koate HP version has

[d] CSL Behring will discontinue manufacturing Monoclate P; supplies are estimated to last till December 2018[30]

Table 2 includes product description, technology, and packaging information for the FVIII replacement products. The manufacturing process of rFVIII products has evolved over time in order to minimize the potential for pathogen transmission. Risk of viral transmission with plasma-derived products is mitigated using blood donor screening, heat treatments, solvent-detergent treatment, and nanofiltration in the manufacturing process. Nonetheless, the risk of viral transmission remains a possibility with plasma-derived factors, with first and second generation recombinant FVIII products which employ animal or human proteins in the cell growth medium, and with third generation products if contaminated by other routes.[6,31]

First-generation rFVIII products (e.g. Recombinate, approved in 1992) contain human and/or animal proteins in the production process and final product. Second generation rFVIII products (e.g. Kogenate FS, approved in 1993) are exposed to human or animal proteins in the cell culture medium but not in the final product. FVIII products developed in the last 5 years are classified as third generation rFVIII products (e.g., Adynovate, approved in 2015) and do not have added human or animal proteins in the cell-growth medium and final product.[6]

Table 2. Description of Factor VIII Replacement Products

Products[a]	FVIII Description	Production Technique	Viral Inactivation & Nanofiltration Step(s)	Packaging
Human Plasma Derived Antihemophilic Factor Products (hpFVIII)				
Hemofil M[17]	Full length FVIII	Produced from pooled human plasma; contains human albumin	- Solvent-detergent treatment - Nanofiltration	Double ended needle and a filter needle
Koate[18]	Full length FVIII	Produced from pooled human plasma; contains human albumin and naturally occurring VWF	- Solvent-detergent treatment - Heat treatment - PEG precipitation/ depth filtration	- Mix2Vial filter transfer set for reconstitution
Koate DVI[19]			- Solvent-detergent treatment - Heat treatment	- One sterile double-ended transfer needle - One sterile filter needle - One sterile administration set
Monoclate P[20]	Full length FVIII	Produced from pooled human plasma; contains human albumin	- Heat treatment in aqueous solution (pasteurized)	- Double-ended needle for reconstitution - Vented filter spike for withdrawal - Filter needle for withdrawal Winged infusion set

Table 2. Description of Factor VIII Replacement Products

Products[a]	FVIII Description	Production Technique	Viral Inactivation & Nanofiltration Step(s)	Packaging
Recombinant DNA Technology Derived Antihemophilic Factor Products (rFVIII)				
Advate[21] 3rd Generation	Full length FVIII	- CHO cell line that expresses the rFVIII - Contains low quantity of VWF	Solvent-detergent treatment	Baxject III reconstitution System[b] with one Terumo Microbore Infusion set
Adynovate[22] 3rd Generation	Full-length FVIII; PEGylated (PEGylation of Advate parent molecule)	CHO cell line that expresses the rFVIII. PEG moiety is attached to FVIII, extending the half-life	- Solvent-detergent treatment	Baxject III reconstitution System[b] with one Terumo Microbore Infusion set
Afstyla[23] 3rd Generation	Single chain FVIII; B-domain truncated	CHO cell line that expresses the rFVIII	- 2 virus reduction steps (Not specified)	Mix2Vial filter transfer set for reconstitution
Eloctate[15] 3rd Generation	B-domain deleted rFVIII linked to the human IgG_1 Fc-domain fusion protein (BDD-rFVIIIFc)	HEK cell line that expresses BDD-rFVIIIFc	- Solvent-detergent treatment - Nanofiltration	Sterile vial adapter reconstitution device
Helixate FS[16] 2nd Generation	Full length FVIII	- BHK cell line that expresses rFVIII - The cell culture medium contains human plasma protein and recombinant insulin - No human or animal proteins, such as albumin added during the purification and formulation processes	- Solvent-detergent treatment	Mix2Vial filter transfer device for reconstitution
Kogenate FS[24] 2nd Generation	Full length FVIII		Solvent/detergent treatment	- Sterile vial adapter (with 15-µm filter) for needleless reconstitution or Bio-Set[b] reconstitution system - Administration set

Table 2. Description of Factor VIII Replacement Products

Products[a]	FVIII Description	Production Technique	Viral Inactivation & Nanofiltration Step(s)	Packaging
Kovaltry[25] 3rd Generation	Full length FVIII	BHK cell line (with FVIII gene and human heat shock protein 70 gene introduced)	- Detergent treatment - Nanofiltration (20nm)	- Sterile vial adapter (with 15-µm filter) for needleless reconstitution or Bio-Set[b] reconstitution system - Administration set
Novoeight[26] 3rd Generation	B-domain trucated FVIII	CHO cell line that expresses the rFVIII	- Detergent treatment - Nanofiltration (20nm)	Sterile vial adapter (with 25-µm filter) for needleless reconstitution
Nuwiq[27] 3rd Generation	B-domain deleted FVIII	HEK cell line that expresses the rFVIII	- Solvent/detergent treatment - Nanofiltration (20nm)	- Vial adapter - Butterfly needle
Recombinate[28] 1st Generation	Full length FVIII	- CHO cell line that expresses the rFVIII - Contains bovine protein, human albumin, and rVWF (≤2 ng per IU rFVIII)	none	Baxject II needleless transfer device
Xyntha[29] 3rd Generation	B-domain deleted FVIII	CHO cell line that expresses the rFVIII	- Solvent/detergent treatment - Nanofiltration (35nm)	- Vial adapter for reconstitution or Solofuse[b] dual chamber syringe - Sterile infusion set

Abbreviation: BHK, baby hamster kidney; CHO, Chinese hamster ovary; HEK, human embryonic kidney; IU, international units; PEG, polyethylene glycol; rFVIII, recombinant factor VIII

[a] Recombinant FVIII generations:

- 1st generation: contains human or animal proteins in the cell culture medium and in the final product
- 2nd generation: contains human or animal proteins in the cell culture medium but not in the final product
- 3rd generation: no human or animal protein added in the cell culture and production process

[b] The Baxject III, Bio-Set and Solofuse transfer systems eliminate the need to manually disinfect vials prior to administration

Methods

Systematic Literature Search

Search strategies were developed for PubMed (Medline) and EMBASE. Strategies consisted of controlled vocabulary, such as MeSH ("F8 protein, human"[Supplementary Concept] OR "Factor VIII"[Mesh] OR "recombinant factor VIII SQ"[Supplementary Concept]) OR ("von Willebrand Factor"[Mesh] OR "factor VIII, von Willebrand factor drug combination"[Supplementary Concept]), and keyword phrases (including product names or antihemophilic factor).

Two methodological filters were used for systematic reviews in PubMed: the University of McMaster's review filter for maximized specificity,[32] and the PubMed filter for systematic reviews (AND systematic [sb]).[33] The Cochrane filter for identifying randomized controlled trials in PubMed was used (sensitivity- and precision-maximizing version [2008 revision]; PubMed format).[34] PubMed was searched through May 30th, 2018 for systematic reviews (SRs) and through June 7th, 2018 for RCTs. EMBASE was searched through June 5th, 2018 for SRs and through June 11th, 2018 for RCTs. In EMBASE, we excluded conference abstracts. Articles were de-duplicated in Covidence. The complete search strategies and terms are available in **Appendix A**.

Authors also conducted grey literature searching to identify systematic reviews (SRs), such as publications by the Oregon Drug Effectiveness Review Project group and the Agency for Healthcare Research and Quality (AHRQ). We also screened the reference lists and other relevant websites for further information:

I. For treatment guidelines addressing Hemophilia A therapy: websites of the American National Hemophilia Foundation (NHF), the National Guideline Clearinghouse, the Haemophilia Foundation of Australia (HFA), the United Kingdom Haemophilia Centres Doctors' Organization (UKHCDO), and the World Federation of Hemophilia.
II. For prescribing information product labeling: the DailyMed website, (an official provider of US Food and Drug Administration [FDA] drug-label information), and product websites maintained by the manufacturer.
III. Drug information database: Micromedex

Screening

Two reviewers screened publication titles, abstracts, and full texts. Conflicts were resolved upon discussion between reviewers. **Figure 1** on page 22 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

Inclusion and Exclusion Criteria

Only SRs or RCTs providing head-to-head efficacy or safety comparisons (for Hemophilia A treatment) among the agents listed in Table 1 were included. Direct pair-wise meta-analysis data was considered, while indirect statistical data was excluded. A list containing excluded references is provided in **Appendix B**.

Disease Overview

Congenital hemophilia is a rare, inherited, lifelong bleeding disorder.[1] Patients with hemophilia have a deficiency of factor VIII or IX clotting factors which results in spontaneous bleeding or life-threatening prolonged bleeding following injury or surgery.[1] The number of affected individuals with hemophilia in the US is estimated by the Centers for Disease Control and Prevention (CDC) to be approximately 20,000 individuals.[1] Patients are diagnosed at a young age, usually in the first month of life for severe hemophilia, and by 36 months of age for mild hemophilia. About two-thirds of cases have a known family history.[1,7]

Although there are several different types of factor deficiencies, hemophilia type A and B, which are X-linked recessive diseases, are the most common.[35] Approximately 80% of patients with hemophilia have type A, while about 20% have hemophilia B.[1,7] Hemophilia A occurs in all racial and ethnic groups, and is primarily seen in men (with only one copy the X chromosome) occurring in about 1 out of every 5,000 male births in the US.[1] Although rare, females may also be diagnosed with hemophilia, but they are most often asymptomatic carriers of the disease.[1]

A deficiency of factor VIII prolongs the activated partial thromboplastin time (aPTT) and is diagnosed using factor activity assays and genetic testing.[2,35] Bleeding manifestations are generally dependent on the degree of factor deficiency. **Table 3** describes the classification of hemophilia severity endorsed by the International Society on Thrombosis and Haemostasis.[36]

Table 3. Hemophilia A Severity Classification[2,36]

Severity	Clotting Factor Activity Level (plasma concentration)	Percentage breakdown of the hemophilia A population[37]
Mild	5 to <40% of normal (5-40 IU/dL)	About 25% of cases
Moderate	1 to <5% of normal (1-5 IU/dL)	About 15% of cases
Severe	<1% of normal (<1 IU/dL)	About 60% of cases

Bleeding episodes can be induced by trauma or surgery. Patients may also experience recurrent, spontaneous bleeding into joints or muscles which is most common in severe disease.[2] Patients with severe disease may experience as many as 20 to 30 bleeding episodes a year (mostly intra-articular bleeds); however, about 10% of patients with severe hemophilia demonstrate a lower bleeding frequency.[38]

Complications include chronic joint disease, pain, seizures and paralysis if bleeds occur in the brain, or death due to unstoppable bleeding or from bleeding into a vital organ.[39] Bleeding often re-occurs in the same joint causing degradation, decreased range of motion, and reduced quality of life. Disease progression can lead to the patient needing a

radiosynovectomy, joint fusion, or joint replacement procedure.[7,40] Early initiation of continuous prophylactic treatment with blood factors reduces bleeding episodes and therefore prevents joint disease and other complications.[3-5] With adequate substitution FVIII therapy, "…children can look forward to a normal life expectancy."[41]

Acquired Hemophilia A— Another form of FVIII hemophilia is an acquired autoimmune disorder caused by the development of autoantibodies that inactivate FVIII. It mostly occurs in the elderly, but is also associated with pregnancy, malignancy, other autoimmune disorders (i.e. rheumatoid arthritis), or may be triggered by an allergic reaction to a medication.[42] Acquired hemophilia manifests with extensive cutaneous purpura, gastrointestinal bleeding, and muscle bleeding.[42,43] This condition often resolves upon treatment with hemostatic agents and immunosuppressants.[42,43]

Treatment for Congenital Hemophilia A

Patients with hemophilia A require replacement FVIII products either on an episodic basis, for acute bleeding or surgery, or as a prophylaxis to limit bleeding frequency and prevent arthropathy. **Table 4** defines terms regarding therapy approaches for administering replacement products.

Table 4. Terms Regarding the Therapy Approach for Administering Replacement Products[7]

Episodic or On-Demand Treatment

Treatment with replacement factors are provided at the time of an active bleed

- Helps improve pain and serious bleeding

Continuous Prophylaxis

Under continuous therapy (exposure to replacement factor) for a minimum of 85% of the year, with the intent to treat for 52 weeks/year

1. **Primary prophylaxis**: Continuous prophylaxis "…initiated in the absence of documented osteochondral joint disease, determined by physical examination or imaging studies (or both), and started before the second clinically evident large joint bleed and age 3 years"
    - Reduces bleeding frequency and progression of musculoskeletal disease
2. **Secondary prophylaxis:** Continuous prophylaxis initiated "…after two or more bleeds into large joints, and before the onset of joint disease documented by physical examination and imaging studies"
    - May help minimize progression of musculoskeletal disease
3. **Tertiary prophylaxis**: Continuous prophylaxis "started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints"
    - May help improve normal activities of daily living

Intermittent or Periodic Prophylaxis

Treatment with replacement factors for periods not exceeding 45 weeks in a year

- May help improve pain, serious bleeding, and progression of joint deterioration in target joints

Several hemophilia organizations including National Hemophilia foundation Medical and Scientific Advisory Council (MASAC) and the World Federation of Hemophilia

recommend routine prophylaxis therapy (continuous administration of replacement factors) as the most optimal approach for persons with severe hemophilia.[2,44] The 2016 guideline by the Australian Haemophilia Centre Directors' Organisation recommends more specifically that *primary* prophylaxis is the standard of care for severe hemophilia.[7] The 2010 United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) guideline recommends that prophylaxis should be initiated, ideally before the second joint bleed, for children with severe hemophilia and continued at least until reaching physical maturity.[45]

In 2011, a Cochrane review was published regarding the effectiveness of clotting factor prophylaxis versus on-demand therapy for the management of hemophilia.[46] Authors found that randomized controlled trials (RCTs) were congruent with observational studies, showing increased benefit for children with moderate and severe hemophilia A treated with prophylaxis regimens. Prophylaxis significantly reduced bleeding frequency and joint bleeds compared to on-demand therapy. Moreover, an RCT by Gringeri et al showed significantly improved quality of life and joint function protection when FVIII agents were employed for primary prophylaxis of severe hemophilia A compared to on-demand treatment.[47] For patients with existing joint damage, there was insufficient information from RCTs to confirm a reduction in bleeding or long-term joint damage, a benefit that had been suggested from observational studies.[46]

More recently in 2017, Manco-Johnson et al[13] published an RCT comparing 3 years of on-demand versus routine prophylaxis therapy in adolescents and adult patients with severe hemophilia A and pre-existing joint arthropathy. While prophylaxis did not reverse or halt arthropathy progression (i.e., deterioration initiated from previous joint bleeding episodes prior to study entry), compared to on-demand therapy, prophylaxis did yield a benefit in terms of significant reductions in bleeding, pain, and healthcare resource utilization, as well as significant improvements in joint health (measured by the Colorado Adult Joint Assessment Scale), activity level, satisfaction, and health-related quality of life.[13]

While it is unclear when to stop prophylaxis,[2,44] continuation is generally tailored to the patient's bleeding frequency and preferences. The UKHCDO recommends re-evaluating the prophylaxis regimen every 6 months, and adjusting dosages based on the frequency of breakthrough bleeds.[45] Continuation of prophylaxis is recommended if the patient experiences any of the following while not receiving prophylaxis: (a) hemarthrosis, (b) bleeding episodes that negatively impact the patient's mobility or ability to work, or (c) a recurrence of intracranial hemorrhage.[45] Overall, decisions regarding the treatment strategy, and dose modifications as the patient ages are determined on an individual basis, based on the patient's bleeding phenotype, response to therapy, co-morbidities, and patient/caregiver preferences.

Guidelines published in the last 5 years, including a 2018 guideline by the National Hemophilia Foundation's Medical and Scientific Advisory Council (NHF-MASAC),[6] a 2016 guideline by the Australian Haemophilia Centre Directors' Organisation (2016),[7] and a 2013 guideline by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO),[8] recommend using recombinant FVIII products over plasma-derived FVIII products.[6,7] Recommendations seem to stem mostly from concerns about the theoretical increased risk of viral disease transmission with plasma products compared to

recombinant products.[31] Guidelines do not specify a preference for one recombinant product FVIII over another; they state that the chosen product is dependent on individual pharmacokinetics, and patient circumstances.[9,10]

Recommendations from the NHF-MSAC for the management of Hemophilia A are outlined in **Table 5.**

Table 5. Treatment Recommendations by the American National Hemophilia Foundation (NHF), Medical and Scientific Advisory Council (MASAC)

MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders (April 2018; Document #253)[6]
• **Recombinant FVIII products are the recommended treatment of choice for patients with Hemophilia A** o Authors express that "[t]he risk of human viral contamination associated with recombinant FVIII is definitely much lower than for plasma-derived FVIII products."[6] MASAC guidelines state elsewhere that "[p]lasma-derived products continue to carry the theoretical risk of viral transmission,"[10] especially considering non-enveloped viruses such as parvovirus B19 and prion-related diseases.[31] Authors state that no seroconversions to HIV, HBV, or HCV have been reported with any of the currently available plasma-derived or recombinant FVIII products.[6] • "Desmopressin (DDAVP) may be used for patients with mild hemophilia A who have been documented by a DDAVP trial to have a significant rise in FVIII." However, this is not an option for patients under 2 years old, and should be used with caution if chosen for pregnant women. Hyponatremia is a risk with this option. • *Treatment of patients with inhibitors to FVIII*: The guideline points out the licensed products for this scenario (Feiba, NovoSeven RT, and Hemlibra) and highlights that the choice of product depends on the type of inhibitor, the patient's titer of inhibitor, location of bleeding, and previous response to these products. For high-titer inhibitors: immune tolerance induction (ITI) is the best option for inhibitor eradication
MASAC Guidelines for Emergency Department Management of Individuals with Hemophilia and Other Bleeding Disorders (September 2017; Document #252)[48]
Patients with Hemophilia A without Inhibitors • Patients should be offered recombinant factor VIII or their product of choice. Plasma-derived concentrate may be used in an emergency situation when recombinant products are unavailable. Cryoprecipate and fresh frozen plasma are not recommended.
MASAC Recommendations Concerning Prophylaxis (February 2016; Document # 241)[44]
• Prophylaxis is considered optimal therapy for individuals with severe hemophilia A or B • Initiation and target: *"Prophylactic therapy should be instituted early (prior to the onset of frequent bleeding), with the aim of keeping the trough FVIII or FIX level above 1% between doses."* • Dosing should be individualized based on clinical response and laboratory monitoring • Prophylaxis duration: *"There are no clear cut guidelines as to when to stop prophylaxis. Joint bleeds with subsequent joint destruction are a lifelong problem for these individuals. Therefore, they may continue to benefit from prophylaxis throughout their life."*

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MASAC, Medical and Scientific Advisory Council

Previously Untreated Patients

Previously untreated patients (PUPs) are a unique subpopulation that is of interest because the risk of developing inhibitors, or neutralizing antibodies, is considered "unacceptably high."[10] The risk of developing inhibitors is about 30% in PUPs.[10] The randomized controlled SIPPET trial resulted in a lower risk of inhibitor development, as seen in some observational studies, in PUPs treated with pdFVIII/VWF products (Alphanate and other agents not currently available in the US), compared to rFVIII products (Advate, Recombinate, Kogenate, and Refacto AF [a brand approved in the European Union]).[49] Following this study MASAC provided recommendations summarized in **Table 6**. The authors did not go as far to specifically recommend one class of FVIII over another, however, lists both plasma-derived and recombinant FVIII products as options in newly diagnosed patients.[10] The combination pdFVIII with von Willebrand factor products will be discussed further in the September 2018 drug-class review.

Table 6. MASAC Recommendations on Previously Untreated Patients (June 2016; Document #243)[10]

- Consider leaving patients on their current product if they have had >50 exposure days (ED) to any recombinant product (these are known as previously treated patients [PTP]); risk for inhibitor development with any FVIII product is markedly diminished after 50 EDs.
- Consider leaving patients on their current product if they have 1 to < 50 EDs
- When choosing a FVIII product for newly diagnosed patients, consider the new data from the SIPPET study, all other data on inhibitor formation in previously untreated patients (PUP)s, and the pathogen safety risk/benefit of the two product classes (pdFVIII/VWF or rFVIII products)
- Enroll all PUPs in a data collection system or a clinical trial to assess inhibitor development outcomes on a population level

Abbreviations: ED, exposure days; HBV,; MASAC, Medical and Scientific Advisory Council; pdFVIII/VWF, plasma-derived factor VIII with von Willebrand Factor; PUPs, previously untreated patients; rFVIII, recombinant factor VIII

Treatment Setting

Infusions for routine prophylaxis can be performed in the home by the patient or caregiver. A comprehensive Hemophilia Treatment Center (HTC) can offer the best care and education for patients with hemophilia whom must learn aseptic infusion techniques and medication storage requirements.[50] Patients or caregivers may contact the HTC upon an episodic bleed for consultation regarding the appropriate dosing strategy for resolving bleeding. Life- or limb-threatening bleeding usually requires in-patient management.[51]

Implantable Venous Access Device (VAD) or Port-A-Cath

Continuous prophylaxis therapy involves venipuncture carried out by a trained patient or caregiver several times per week for intravenous administration of replacement factor. Implantable central venous access devices may be employed to improve venous accessibility or treatment adherence.[41] Risks involved with venous access devices include infections and potential embolism from clot formation at the tip of the catheter.[41]

Monitoring Treatment Response

Assessment of plasma factor VIII activity, prior to and during treatment, to confirm that adequate levels have been achieved and maintained can be measured via chromogenic assay or one-stage clotting test.[15,22,23,25] If the development of factor VIII inhibitors is

suspected (i.e., if expected FVIII levels are not attained or if bleeding is not controlled upon administration of factor) the Nijmegen Bethesda inhibitor assay is employed.[36]

Dosing of FVIII Replacement Factor Products

The half-life of a product varies widely between individuals. Children generally clear FVIII faster than adults.[9,38] Dosing frequency is individualized and titrated per the patient's response, physical activity level, and preferences.[9,38] A pharmacokinetic half-life study can be performed and used to guide decisions based on the specific individual's individual clearance rate. Continuous prophylaxis dosing may be initially titrated to maintain a factor trough level of >1 IU/dL; however, the optimal level and dosing frequency is adjusted according to the patient's response.[52,53] Ultimately, "[c]linical outcome, not the achieved trough level, determines whether a dosage is adequate."[53,54]

Table 7 includes the labeled recommended initial dosages for routine prophylaxis for the FVIII products. Several product labels— those for Hemofil M, Monoclate-P, Recombinate, and Xyntha— do not provide specific information for routine prophylaxis dosing.

Episodic bleeding requirements are based on the location of the bleed. The equation used to estimate the dose required is as follows:[15,17,29]

- *Dose (IU/kg body weight) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)*

A major dose, defined as enough clotting factor to achieve a factor VIII activity level of 60% to ≥100%, is given if the bleed location poses a high risk of significant sequelae (e.g. hip, head, gastrointestinal, fractures, etc.). A moderate dose, enough clotting factor to achieve a factor VIII activity level of 30% to 60%, is given if the bleed location involves less critical sites (e.g. muscles [except iliopsoas], hemarthrosis, oral cavity, mild trauma).[23] A minor dose, enough clotting factor to achieve a factor VIII activity level of 20% to 40%, is given if the location of the bleed is in a non-critical area (e.g. in mild muscle or skin/soft tissue bleeds). The MASAC guideline highlights that a "…treating physician is best able to determine the number of doses required for each patient based upon their diagnosis, co-morbidities, clinical circumstances, product(s) utilized, and historical bleeding patterns."[51]

Table 7. Labeled Dosing Regarding Routine Prophylaxis for Hemophilia A

Human Plasma Derived Antihemophilic Products	
Hemofil M[17]	No information is provided regarding dosing for routine prophylaxis
Koate[18]	No information is provided regarding dosing for routine prophylaxis
Koate DVI[19]	No specific dosing recommendations besides the general statement that "[f]actor VIII concentrates may also be administered on a regular schedule for prophylaxis of bleeding…"[19]
Monoclate P[20]	No information is provided regarding dosing for routine prophylaxis
Recombinant Antihemophilic Factor Products	
Advate[21]	20 to 40 IU/kg every other day, or 3 to 4 times weekly May use every third day dosing regimen targeted to maintain FVIII trough levels ≥1% Adjust dose based on the patient's clinical response
Adynovate[22]	Children and adults ≥12 years: 40 to 50 IU/kg, 2 times per week Children < 12 years: 55 IU/kg, 2 times per week (maximum of 70 IU/kg) Adjust the dose based on the patient's clinical response
Afstyla[23]	Adults and adolescents ≥12 years: 20 to 50 IU/kg given 2 to 3 times weekly Children <12 years: 30 to 50 IU/kg 2 to 3 times weekly Adjust regimen based on patient response; more frequent or higher doses may be required in children <12 years of age
Eloctate[15]	Initiate at 50 IU/kg every 4 days; adjust regimen based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals Children <6 years of age: initiate at 50 IU/kg twice weekly and adjust per patient response (expected dosing range of 25-65 IU/kg at 3-5 day intervals; however, more frequent or higher doses up to 80 IU/kg may be required)
Helixate FS[16]	Adults: 25 IU/kg, 3 times per week Children: 25 IU/kg, every other day
Kogenate FS[24]	Adults: 25 IU/kg, 3 times per week Children: 25 IU/kg, every other day
Kovaltry[25]	Individualize the patient's dose based on clinical response Adults and adolescents: 20 to 40 IU/kg, 2 to 3 times per week Children ≤12 years old: 25 to 50 IU/kg, 3 times weekly, or every other day
Novoeight[26]	Adults and adolescents ≥12 years: 20 to 50 IU/kg, 3 times weekly OR 20 to 40 IU/kg, every other day Children < 12 years: 25 to 60 IU/kg, 3 times weekly OR 25 to 50 IU/kg every other day
Nuwiq[27]	Patients ≥ 12 years: 30 -40 IU/kg every other day Children 2 to 11 years: 30 -50 IU/kg every other day or 3 times per week
Recombinate[28]	No information is provided regarding routine prophylaxis
Xyntha[29]	No information is provided regarding dosing for routine prophylaxis. The clinical trial section, at least states Xyntha was used for routine prophylaxis

Pharmacology

Factor VIII is required for the proper functioning of the clotting cascade, the pathway that ultimately produces a stabilized fibrin clot at the site of vascular endothelial injury. Patients who are severely deficient in FVIII cannot maintain hemostasis and require treatment with replacement factor VIII products. A single administered treatment dose of a FVIII product allows for a temporary increase in the plasma FVIII to a therapeutic level that is needed to manage bleeding. Prophylaxis FVIII regimens are used to prevent bleeds, and employ an administration frequency of multiple-times-per-week.[9,38]

Products have recently been developed with the aim of lengthening the FVIII half-life to improve convenience and adherence to therapy. Bioengineering strategies for half-life extension include attaching polyethylene glycol to the rFVIII molecule (as for Adynovate), or fusing rFVIII to the Fc region of immunoglobulin G_1 (as for Eloctate).[6] Afstyla is a stabilized single-chain FVIII product with increased affinity for von Willebrand factor, which seems to improve the half-life.[55,56] A higher degree of FVIII glycosylation/sialylation (as with Kovaltry versus Kogenate FS) is also considered to positively influence PK parameters.[56-59] At this time, there is no widely-accepted definition for classifying a product as an "extended-half-life" FVIII (EHL-FVIII).[56] This is further complicated by the fact that the half-life of a product can vary widely from patient to patient.[9,56]

Considering the wide interpatient variability of FVIII-half-life expression, and the variance in assays or statistical analysis methods across clinical studies, Mahlangu et al explain that newer products should be evaluated against a conventional product in the same individual to adequately differentiate agents based on their half-life, as also recommended by the International Society on Thrombosis and Haemostasis (ISTH), European Medicines Agency (EMA), and US FDA.[56]

Mahlangu et al (2018) propose a definition for an EHL-FVIII in which the product must meet the following 3 criteria:

1. "Designed with technology to extend circulating biological half-life"[56]
2. "Demonstration of difference from a standard rFVIII comparator for the majority of patients according to proposed "biodifference" criteria based on the lower limit of the 90% CI for the AUC ratio being above the FDA/EMA cut-off for bioequivalence (1.25 or 125%)"[56]
3. "Having a half-life ratio [of the study product: comparator product] of 1.3 or higher, based on modelling."[56]

Based on these criteria, only Adynovate and Eloctate would be classified as extended-half life products.[56]

Table 8 contains pharmacokinetic half-life information from the FDA-approved package labeling. Children demonstrate a shorter FVIII half-life compared to older patients, and, as a result, they may require higher or more frequent dosing. For additional background information, Table 1 of **Appendix C** includes pharmacokinetic comparison studies identified from the literature search.

Routine prophylaxis dosing with traditional products requires administration 3 times weekly or via alternate-day dosing. Labeling for several newer products recommends initiating prophylaxis regimens with an administration frequency of 2 to 3 times weekly for Afstyla and Kovaltry; twice weekly for Adynovate; and every 4 days (or twice weekly for patients < 6 years) for Eloctate.

Table 8. Labeled Half-Life for the Factor VIII Replacement Products

Product	Half-Life (hours)
Human Plasma Derived Antihemophilic Products	
Hemofil M	14.8 ± 3.0 hours (no specifics with regard to population age or dose)
Koate, Koate DVI	Mean half-life: 16.1 hours (no specifics with regard to population age or dose)
Monoclate P	Mean half-life: 17.5 hours (no specifics with regard to population age or dose)
Recombinant Antihemophilic Factor Products	
Advate[a]	Patients > 16 years: 12.0 ±4.2 Adolescence 12 to < 16 years: 12.0 ±2.9 Children 5 to < 12 years: 11.2 ±3.5 Children 2 to < 5 years: 9.5 ±1.8 Infants 1 month to < 2 years: 8.7 ±1.4
Adynovate	(Following a dose of 45 IU/kg) Patients ≥ 18 years: 14.7 ±3.8 Adolescence 12 to < 18 years: 13.4 ±4.1 Children 6 to < 12 years: 12.4 ±1.7 Children < 6 years: 11.8 ±2.4
Afstyla[a]	Patients ≥ 18 years: 14.2 Adolescence 12 to < 18 years: 14.3 Children 6 to < 12 years: 10.2 Children < 6 years: 10.4
Eloctate[a]	Patients ≥ 18 years: 19.7 (17.4 - 22.0) Adolescence 12 to < 18 years: 16.4 (14.1 - 18.6) Children 6 to < 12 years: 14.9 (12.0 - 17.8) Children 1 to 5 years: 12.7 (11.2 - 14.1)
Helixate FS[a]	Patients (12 to 33 years): 14.7 ±2.6 Patients (4 to 18 years): 10.7 (7.8 to 15.3)
Kogenate FS[a]	Adolescents and Adults: 13.7 to 14.6 ± 4.38 Children: 10.7 hours (7.8 to 15.3)
Kovaltry[a]	Patients ≥ 18 years: 14.2 ±3.5 Adolescence 12 to < 18 years: 14.4 ±5.5 Children 6 to < 12 years: 12.0 ±2.1 Children < 6 years: 12.1 ±2.7
Novoeight[a]	Adults/Adolescents: 11-12 hours Children 6 to < 12 years: 8.0 - 9.4 Children < 6 years: 7.7-10.0
Nuwiq[a]	Adults/Adolescents: 17.1 ± 11.2 Children Age 6 to 12 years: 13.1 ± 2.6 Children Age 2 to 5 years: 11.9 ± 5.4
Recombinate	14.6±4.9 (no specifics with regard to population age or dose)

Xyntha[a]	Adults/Adolescents > 12 years: 11.2 to 16.7 Young Children and Adolescents 6.9 to 8.3

[a] Following a dose of 50 IU/kg

Table 9 contains special population information from the FDA-approved package labeling.

Table 9. Labeled Specific Population Information

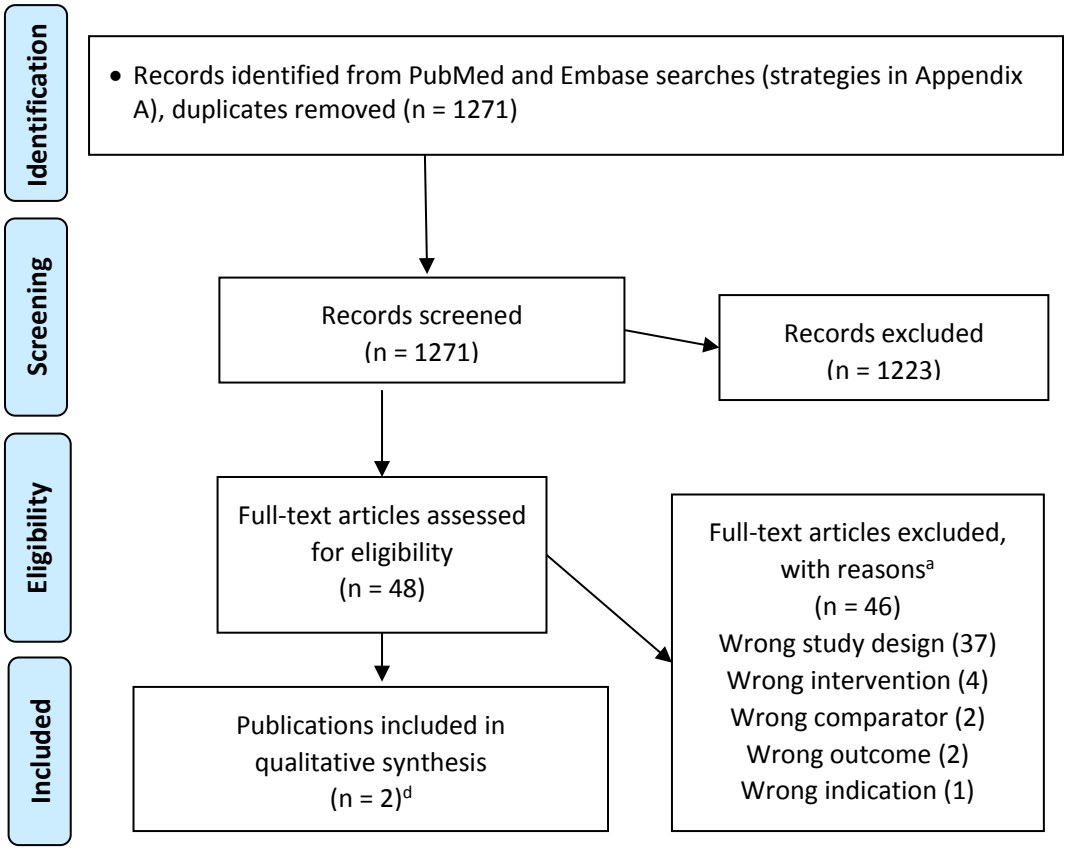
Human Plasma-Derived Antihemophilic Products	
Hemofil M	Pregnancy Category C: there is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: No information in the package labeling
Koate	Pregnancy: There is no human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed.
Koate DVI	Pregnancy Category C: there is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: No studies have been conducted in patients with Koate DVI; however, studies are available with Koate-HP formulation
Monoclate P	Pregnancy Category C: There is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: use weight based dosing
Recombinant Antihemophilic Factor Products	
Advate	Pregnancy: There is no human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed.
Adynovate	Pregnancy: There is no human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed
Afstyla	Pregnancy: There is no human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed

Eloctate	Pregnancy: There is no human data to inform about potential risks. It is unclear whether there is clinical relevance based on the finding in animal models where fetal blood exposure was approximately 1% of the maternal plasma concentration. Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed
Helixate FS	Pregnancy: There is no human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed
Kogenate FS	Pregnancy Category C: There is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed
Kovaltry	Pregnancy: There is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed
Novoeight	Pregnancy: There is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed
Nuwiq	Pregnancy: There is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed
Recombinate	Pregnancy Category C: There is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed
Xyntha	Pregnancy Category C: There is a lack of human or animal data to inform about potential risks; use only if clearly needed Lactation: It is unknown whether drug is excreted into human milk Pediatric Use: Pediatric patients demonstrate more rapid clearance compared to adults; dose adjustments may be needed

Literature Search Results

Our literature search for SRs and RCTs in PubMed and Embase yielded a total of 1271 unique titles. **Figure 1** displays the PRISMA flow chart for the publication screening process. **Appendix B** provides a list of studies excluded in the full-text review stage. Two systematic reviews were included; however, no RCTs were identified that meet our inclusion criteria.

Figure 1. PRISMA Flow Chart for Publication Screening



[a] See Appendix B for descriptions

[d] (n=2); 2 systematic reviews which showed no head-to-head comparisons among FVIII products

Head-to-head Efficacy Comparison

There were no head-to-head RCTs identified comparing the efficacy of individual FVIII products with one another in the setting of on-demand therapy or routine prophylaxis. This finding is consistent with other systematic reviews that set out to compare the efficacy of available FVIII products.[60,61] Thus, there is insufficient evidence available to determine whether there are differences in efficacy between FVIII products, in terms of clinical endpoints (e.g. bleeding frequency, joint damage, joint function, pain, or quality of life), for the treatment of hemophilia A.

Safety

Table 10 summarizes the warnings and most common adverse events provided in the labeling for FVIII products.

Table 10. Warnings and Adverse Reactions Labeling for FVIII Products[17-20]

General Warnings for FVIII Products[a]	▪ *Hypersensitivity, including anaphylaxis* ▪ *Neutralizing antibodies* ▪ *Cardiovascular risk* (stated in Kogenate FS and Hexilate FS)*:* "When clotting is normalized by treatment with factor VIII, development of cardiovascular risk factors may be the same as the risk for non-hemophilic patients"[24] Warnings for plasma derived factor products ▪ *Transmission of infectious disease* ▪ *Hemolysis* (Monoclate-P, Koate DVI, Koate): when large or frequently repeated doses of a plasma product are provided to patients with A, B or AB blood groups, patients should be monitored via direct Coombs test and hematocrit
Most Common Adverse Reactions (reported in patients in clinical trials)[b]	<u>Human Derived Products</u> ▪ Hemofil M: Factor VIII inhibitors (5.7%), dizziness (0.8%), headache (0.8%), dysgeusia (0.8%), pyrexia (0.8%), infusion site inflammation (1.6%) ▪ Koate: (reported in ≥ 5% of patients) nervousness, headache, abdominal pain, nausea, paresthesia and blurred vision ▪ Koate-DVI: 0.7% infusions were associated with adverse mild reactions including paraesthesia, blurred vision, headache, nausea, abdominal pain, and feeling jittery ▪ Monoclate- P: (general statement of product type) known to cause allergic reactions, mild chills, nausea, stinging at the infusion site, and inhibitors of FVIII may occur in some cases <u>Recombinant Products</u> ▪ Advate: (reported in > 5% of patients) pyrexia, headache, cough, nasopharyngitis, arthralgia, vomiting, upper respiratory tract infection, limb injury, nasal congestion, and diarrhea ▪ Adynovate: (reported in ≥1% of patients) headache and nausea ▪ Afstyla: (reported in >0.5% of patients) dizziness and hypersensitivity ▪ Eloctate: (reported in >0.5% of patients) arthralgia, malaise, myalgia, headache, and rash

Table 10. Warnings and Adverse Reactions Labeling for FVIII Products[17-20]

	▪ Helixate FS: (reported in ≥4% of patients) inhibitor formation in previously untreated and minimally treated patients (15%), skin-associated hypersensitivity reactions (e.g., rash, pruritus, urticaria), infusion site reactions (e.g., inflammation, pain), and central venous access device associated infections ▪ Kogenate FS: (reported in ≥4% of patients) inhibitor formation in previously untreated and minimally treated patients (15%), skin-associated hypersensitivity reactions (e.g., rash, pruritus, urticaria), infusion site reactions (e.g., inflammation, pain), and central venous access device associated infections ▪ Kovaltry: (reported in ≥3% of patients) headache, pyrexia, and pruritus. "In an actively enrolling clinical trial in PUPs, 6 of 14 treated subjects (42.9% with a 95% Confidence Interval of 17.7-71.1%) developed an inhibitor. Of these, 3 subjects (21.4%) had high titer inhibitors..."[25] ▪ Novoeight: (reported in ≥ 0.5% of patients) injection site reactions, increased hepatic enzymes, and pyrexia ▪ Nuwiq: (reported in>0.5% of patients) paresthesia, headache, injection site inflammation, injection site pain, non-neutralizing anti-Factor VIII antibody formation, back pain, vertigo, and dry mouth ▪ Recombinate: (most commonly reported adverse drug reactions) chills, flushing, rash and epistaxis. "Inhibitors have been reported following administration of Recombinate predominantly in previously untreated and minimally treated patients."[28] ▪ Xyntha: (reported in ≥ 10% of patients) headache, arthralgia, pyrexia, and cough; 3 subjects developed factor VIII inhibitors across all studies (2.1%)

[a] Refer to prescribing information for full details and recommended monitoring with respect to warnings/precautions
[b] "The detection of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, it may be misleading to compare the incidence of antibodies to KOVALTRY [or another FVIII product] with the incidence of antibodies to other products."

Inhibitor Development

The most challenging complication with use of FVIII therapy for the management of hemophilia is considered to be the development of inhibitors (i.e., neutralizing antibodies) to the replacement factor. Inhibitors can diminish the efficacy of the replacement factor product or ultimately render a product ineffective at the usual dose.[11] The development of inhibitors limits treatment options available for a patient, and drives up therapy costs.[1,62-64] An estimated 30% of newly treated patients (i.e. PUPs) have been shown to develop an inhibitor in the early stages (<50 exposure days to exogenous FVIII) of prophylaxis therapy.[10] Testing for inhibitors is performed regularly during therapy, especially during prophylaxis initiation, when switching between FVIII products, after intensive therapy, and when the patient's response to therapy is suboptimal.

Decisions regarding the appropriate treatment regimen for managing a patient with inhibitors depends on several factors including the inhibitor titer, whether the patient is experiencing an active bleed, and any previous response to inhibitor mitigation. Treatment options include immune tolerance induction (ITI) with higher doses of FVIII, the employment of bypassing agents (e.g. recombinant activated FVII and activated prothrombin complex concentrate), or the use of the monoclonal antibody, emicizumab.[6]

ITI consists of administering significantly higher than standard doses of a clotting factor (usually the factor for which the patient developed inhibitors) in order to induce tolerance and neutralize the inhibitor.[8] Hay et al summarized that some attributes correlated with ITI success include a lower pre-ITI inhibitor titer (<10 Bethesda units [BU]), lower historical peak inhibitor titer (<200 BU), and lower peak inhibitor titers on ITI.[65]

In a 2018 MASAC recommendation document the authors state that "[f]or high titer inhibitors, immune tolerance induction (ITI) is the best option for inhibitor eradication."[6] They also recommended, in 2013, considering prophylaxis with bypassing agents (aPCC and rFVIIa) in patients with inhibitors.[12] In a 2015 guideline on ITI for patients with inhibitors, the authors stated that there is insufficient evidence regarding which FVIII agent should be used for ITI, so they do not recommend one product over another.[11] The 2013 UKHCDO guideline states that "[f]irst-line ITI should be conducted using rFVIII concentrate, unless as part of a clinical trial, and is usually performed with the product used by the patient at the time of inhibitor development."[8]

There have been two Cochrane reviews with the objective of comparing regimens used to manage hemophilia patients with inhibitors.

a) The 2017 review assessed the efficacy of using bypassing agents prophylactically in patients with hemophilia and with inhibitors for the reduction of bleeding rates.[66] Four RCTs were included: 2 comparing aPCC for prophylaxis versus on-demand use, and 2 comparing high-dose versus low-dose rFVIIa regimens for prophylaxis. The authors concluded that while prophylaxis with bypassing agents may effectively reduce bleeding in patients with inhibitors compared to on-demand therapy, "there is a lack of evidence for the superiority of one agent over the other or for the optimal dosage regimen."[66]

b) A 2014 review considered RCTs comparing the efficacy of different ITI protocols, or the potential difference in efficacy between ITI versus bypassing agents alone.[67] Only one published study meeting inclusion criteria was identified. It did not show a difference between high- versus low-dose ITI protocols (200 IU/kg/day vs. 50 IU/kg/3 times weekly) with respect to percentages of patients achieving tolerance after a maximum of 33 months; however, the time to a negative titer was significantly shorter in the high-dose arm.[65] The Cochrane review authors concluded that "there is low-quality evidence to suggest that high-dose immune tolerance induction may induce tolerance more quickly which is associated with fewer bleeding complications."[67]

Genetic risk factors associated with inhibitor development include family history, African or Hispanic descent, genetic mutation type, and individual immune response traits.[8,63] Witmer et al summarized in 2013 that studies associating treatment-related factors (e.g. age at first exposure, the intensity of the first exposure, prophylaxis versus on-demand regimens, and the type of FVIII product [recombinant *versus* plasma derived]) with increased risk of inhibitor development are difficult to interpret due to retrospective designs, variable methodologies, and inadequate control of confounding factors.[63]

Disease Transmission Risk

Regarding disease transmission, MASAC holds that recombinant factors have less risk of disease transmission compared to plasma derived factors. Authors express that "[t]he risk of human viral contamination associated with recombinant FVIII is definitely much lower than for plasma-derived FVIII products."[6] MASAC guidelines state elsewhere that "[p]lasma-derived products continue to carry the theoretical risk of viral transmission,"[10] especially considering non-enveloped viruses such as parvovirus B19 and prion-related diseases.[31] Authors state that no seroconversions to HIV, HBV, or HCV have been reported with any of the currently available plasma-derived or recombinant FVIII products.[6]

Summary

Disease management strategies aim to not only prevent and treat potentially life-threatening bleeds on an episodic basis, but also include routine prophylaxis for the prevention of recurrent bleeds and arthropathy.[3-5] The risk of disease transmission is theoretically less with rFVIII products compared to pdFVIII products; thus rFVIII is recommended over pdFVIII as the standard of care in hemophilia per the National Hemophilia Foundation's Medical and Scientific Advisory Committee (MASAC). Guidelines do not specify a preference for one rFVIII product over another, nor is preference stated for one pdFVIII factor over another. The chosen product is dependent on individual pharmacokinetics, and patient circumstances.[9,10] Dosing for routine prophylaxis must be based on the individual's disease severity and clinical response, especially because there is wide interpatient half-life variability with all FVIII products.

The most serious complication in the management of hemophilia is considered to be the development of inhibitors.[11] Depending on the titer level of the inhibitor, the location of bleeding, and previous response to inhibitor mitigation, treatment may involve immune tolerance induction (ITI) with high-doses of the clotting factor, and/or the employment of bypassing agents such as recombinant activated FVII (rFVIIa) or activated prothrombin complex concentrate (aPCC).[6,68]

MASAC states that ITI is the best option for high-titer inhibitor eradication,[6] and that physicians should consider prophylaxis with bypassing agents (aPCC and rFVIIa) in patients with inhibitors.[12] In a 2015 guideline on ITI for patients with inhibitors, the authors stated that there is insufficient evidence regarding which FVIII agent should be used for ITI. Consequently, they do not recommend one product over another.[11] The 2013 UKHCDO guideline states that "[f]irst-line ITI should be conducted using rFVIII concentrate, unless as part of a clinical trial, and is usually performed with the product used by the patient at the time of inhibitor development."[8]

This report included a systematic review of literature for head-to-head randomized controlled trial (RCT) evidence addressing the possible treatment-effect differences between the FVIII products listed in Table 1 (page 5). There were no head-to-head RCTs identified comparing the efficacy of individual FVIII products with one another in the setting of on-demand therapy or routine prophylaxis therapy.

Appendix A: Literature Search Strategies

Table 1. PubMed Search Strategies

PubMed Systematic Reviews (SR) Search (May 30, 2018; 210 results returned)

- Employed a review filter developed by McMaster[a] University[32] with (combined as OR) the PubMed Filter for SRs[33]

((((((antihemophilic factor[Title/Abstract] OR antihaemophilic factor[Title/Abstract]) OR ((((((((((((("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "hemofil"[All Fields]) OR (koate[All Fields] OR koatech[All Fields] OR koatedvi[All Fields] OR koater[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "monoclate"[All Fields])) OR Advate[All Fields]) OR ("BAX 855"[Supplementary Concept] OR "BAX 855"[All Fields] OR "adynovate"[All Fields])) OR Afstyla[All Fields]) OR ("factor VIII-Fc fusion protein"[Supplementary Concept] OR "factor VIII-Fc fusion protein"[All Fields] OR "eloctate"[All Fields])) OR Helixate[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kogenate"[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kovaltry"[All Fields])) OR Novoeight[All Fields]) OR Nuwiq[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "recombinate"[All Fields])) OR ("recombinant factor VIII SQ"[Supplementary Concept] OR "recombinant factor VIII SQ"[All Fields] OR "refacto"[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "xyntha"[All Fields]))) NOT (Koater[Title/Abstract] OR Koatech[All Fields])) OR ("Factor VIII"[Mesh] OR "F8 protein, human"[Supplementary Concept] OR "recombinant factor VIII SQ"[Supplementary Concept])) AND systematic[sb]) OR (((((antihemophilic factor[Title/Abstract] OR antihaemophilic factor[Title/Abstract]) OR ((((((((((((("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "hemofil"[All Fields]) OR (koate[All Fields] OR koatech[All Fields] OR koatedvi[All Fields] OR koater[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "monoclate"[All Fields])) OR Advate[All Fields]) OR ("BAX 855"[Supplementary Concept] OR "BAX 855"[All Fields] OR "adynovate"[All Fields])) OR Afstyla[All Fields]) OR ("factor VIII-Fc fusion protein"[Supplementary Concept] OR "factor VIII-Fc fusion protein"[All Fields] OR "eloctate"[All Fields])) OR Helixate[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kogenate"[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kovaltry"[All Fields])) OR Novoeight[All Fields]) OR Nuwiq[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "recombinate"[All Fields])) OR ("recombinant factor VIII SQ"[Supplementary Concept] OR "recombinant factor VIII SQ"[All Fields] OR "refacto"[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "xyntha"[All Fields]))) NOT (Koater[Title/Abstract] OR Koatech[All Fields])) OR ("Factor VIII"[Mesh] OR "F8 protein, human"[Supplementary Concept] OR "recombinant factor VIII SQ"[Supplementary Concept])) AND (MEDLINE[Title/Abstract] OR (systematic[Title/Abstract] AND review[Title/Abstract]) OR meta analysis[Publication Type]))) OR (((((("F8 protein, human"[Supplementary Concept] OR "Factor VIII"[Mesh] OR "recombinant factor VIII SQ"[Supplementary Concept]) OR ("von Willebrand Factor"[Mesh] OR "factor VIII, von Willebrand factor drug combination"[Supplementary Concept])) OR ((("factor VIII, von Willebrand factor drug combination"[Supplementary Concept] OR "factor VIII, von Willebrand factor drug combination"[All Fields] OR "alphanate"[All Fields]) OR humatep[All Fields]) OR wilate[All Fields])) AND systematic[sb]) OR ((MEDLINE[Title/Abstract] OR (systematic[Title/Abstract] AND review[Title/Abstract]) OR meta analysis[Publication Type]) AND ((("F8 protein, human"[Supplementary Concept] OR "Factor VIII"[Mesh] OR "recombinant factor VIII SQ"[Supplementary Concept]) OR ("von Willebrand Factor"[Mesh] OR "factor VIII, von Willebrand factor drug combination"[Supplementary Concept])) OR ((("factor VIII, von Willebrand factor drug combination"[Supplementary Concept] OR "factor VIII, von Willebrand factor drug combination"[All Fields] OR "alphanate"[All Fields]) OR humatep[All Fields]) OR wilate[All Fields]))))

Table 1. PubMed Search Strategies

PubMed Translations

Hemofil "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "hemofil"[All Fields]
Monoclate "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "monoclate"[All Fields]
Adynovate "BAX 855"[Supplementary Concept] OR "BAX 855"[All Fields] OR "adynovate"[All Fields]
Eloctate "factor VIII-Fc fusion protein"[Supplementary Concept] OR "factor VIII-Fc fusion protein"[All Fields] OR "eloctate"[All Fields]
Kogenate "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kogenate"[All Fields]
Kovaltry "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kovaltry"[All Fields]
Recombinate "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "recombinate"[All Fields]
ReFacto "recombinant factor VIII SQ"[Supplementary Concept] OR "recombinant factor VIII SQ"[All Fields] OR "refacto"[All Fields]
Xyntha "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "xyntha"[All Fields]
alphanate "factor VIII, von Willebrand factor drug combination"[Supplementary Concept] OR "factor VIII, von Willebrand factor drug combination"[All Fields] OR "alphanate"[All Fields]
animals[mh] "animals"[MeSH Terms]
humans[mh] "humans"[MeSH Terms]

PubMed Randomized Controlled Trials (RCTs) Search (June 7th, 2018; 611 results returned)

- Employed the Cochrane RCT filter[34]

((((("factor VIII, von Willebrand factor drug combination"[Supplementary Concept] OR "factor VIII, von Willebrand factor drug combination"[All Fields] OR "alphanate"[All Fields]) OR humatep[All Fields] OR wilate[All Fields] OR vonvendi[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "recombinant factor VIII SQ"[Supplementary Concept]) OR ((((((((((((((((("antihemophilic factor"[Title/Abstract] OR "antihaemophilic factor"[Title/Abstract]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "hemofil"[All Fields])) OR koate[All Fields]) OR koatedvi[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "monoclate"[All Fields])) OR advate[All Fields]) OR ("BAX 855"[Supplementary Concept] OR "BAX 855"[All Fields] OR "adynovate"[All Fields])) OR afstyla[All Fields]) OR ("factor VIII-Fc fusion protein"[Supplementary Concept] OR "factor VIII-Fc fusion protein"[All Fields] OR "eloctate"[All Fields])) OR helixate[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kogenate"[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kovaltry"[All Fields])) OR novoeight[All Fields]) OR nuwiq[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "recombinate"[All Fields])) OR ("recombinant factor VIII SQ"[Supplementary Concept] OR "recombinant factor VIII SQ"[All Fields] OR "refacto"[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "xyntha"[All Fields]))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti]) NOT ("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms])))) OR (((((("factor VIII, von Willebrand factor drug combination"[Supplementary Concept] OR "factor VIII, von Willebrand factor drug combination"[All Fields] OR "alphanate"[All Fields]) OR humatep[All Fields] OR wilate[All Fields] OR vonvendi[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "recombinant factor VIII SQ"[Supplementary Concept]) OR ((((((((((((((((("antihemophilic factor"[Title/Abstract] OR "antihaemophilic factor"[Title/Abstract]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "hemofil"[All Fields]))

Table 1. PubMed Search Strategies

OR koate[All Fields]) OR koatedvi[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "monoclate"[All Fields])) OR advate[All Fields]) OR ("BAX 855"[Supplementary Concept] OR "BAX 855"[All Fields] OR "adynovate"[All Fields])) OR afstyla[All Fields]) OR ("factor VIII-Fc fusion protein"[Supplementary Concept] OR "factor VIII-Fc fusion protein"[All Fields] OR "eloctate"[All Fields])) OR helixate[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kogenate"[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kovaltry"[All Fields])) OR novoeight[All Fields]) OR nuwiq[All Fields]) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "recombinate"[All Fields])) OR ("recombinant factor VIII SQ"[Supplementary Concept] OR "recombinant factor VIII SQ"[All Fields] OR "refacto"[All Fields])) OR ("F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "xyntha"[All Fields]))) OR "Factor VIII"[Mesh]) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti]) NOT ("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms])))

PubMed Translations

hemofil "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "hemofil"[All Fields]
monoclate "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "monoclate"[All Fields]
adynovate "BAX 855"[Supplementary Concept] OR "BAX 855"[All Fields] OR "adynovate"[All Fields]
eloctate "factor VIII-Fc fusion protein"[Supplementary Concept] OR "factor VIII-Fc fusion protein"[All Fields] OR "eloctate"[All Fields]
kogenate "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kogenate"[All Fields]
kovaltry "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "kovaltry"[All Fields]
recombinate "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "recombinate"[All Fields]
refacto "recombinant factor VIII SQ"[Supplementary Concept] OR "recombinant factor VIII SQ"[All Fields] OR "refacto"[All Fields]
xyntha "F8 protein, human"[Supplementary Concept] OR "F8 protein, human"[All Fields] OR "xyntha"[All Fields]
clinical trials as topic[mesh:noexp] "clinical trials as topic"[MeSH Terms:noexp]
animals[mh] "animals"[MeSH Terms]
humans[mh] "humans"[MeSH Terms]

[a] McMaster Review Filter (maximized specificity) was defined as MEDLINE[Title/Abstract] OR (systematic[Title/Abstract] AND review[Title/Abstract]) OR meta analysis[Publication Type]

Table 2. EMBASE Search Strategies

Embase SR Search (June 5th, 2018; 243 results produced)

#8	#6 AND #7	**243 [Systematic Reviews set]**
#7	('systematic review'/de OR 'meta analysis'/mj OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR ((systematic NEAR/2 review):ti,ab)) NOT ('conference abstract'/it OR 'conference paper'/it OR (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de)))) AND [english]/lim	222,792
#6	#1 OR #2 OR #3 OR #5	38,169
#5	'blood clotting factor 8'/de OR 'anti hemophilia factor':ti,ab,de,mn,tn OR 'antihaemophilic factor':ti,ab,de,mn,tn OR 'antihaemophilic factor a':ti,ab,de,mn,tn OR 'antihaemophilic factor viii':ti,ab,de,mn,tn OR 'antihaemophilic globulin':ti,ab,de,mn,tn OR 'antihaemophilic globulin a':ti,ab,de,mn,tn OR 'antihemofilic factor a':ti,ab,de,mn,tn OR 'antihemofilic globulin':ti,ab,de,mn,tn OR 'antihemophilia a factor':ti,ab,de,mn,tn OR 'antihemophilia factor':ti,ab,de,mn,tn OR 'antihemophilia globulin':ti,ab,de,mn,tn OR 'antihemophilic factor':ti,ab,de,mn,tn OR 'antihemophilic factor a':ti,ab,de,mn,tn OR 'antihemophilic factor viii':ti,ab,de,mn,tn OR 'antihemophilic globulin':ti,ab,de,mn,tn OR 'antihemophilic globulin a':ti,ab,de,mn,tn OR 'blood clotting factor viii':ti,ab,de,mn,tn OR 'blood coagulation factor 8':ti,ab,de,mn,tn OR 'blood coagulation factor viii':ti,ab,de,mn,tn OR 'blood factor viii':ti,ab,de,mn,tn OR 'bovine blood clotting factor 8':ti,ab,de,mn,tn OR 'clotting factor 8':ti,ab,de,mn,tn OR 'clotting factor 8 variant':ti,ab,de,mn,tn OR 'clotting factor viii':ti,ab,de,mn,tn OR 'coagulation factor viii':ti,ab,de,mn,tn OR 'coagulation globulin':ti,ab,de,mn,tn OR 'factor 8':ti,ab,de,mn,tn OR 'factor viii':ti,ab,de,mn,tn OR factorate:ti,ab,de,mn,tn OR ((globulin NEAR/1 antihaemophilic):ti,ab,de,mn,tn) OR 'globulin, antihemophilic':ti,ab,de,mn,tn OR humafac:ti,ab,de,mn,tn OR 'thrombocyte co factor 1 c':ti,ab,de,mn,tn OR 'thrombocyte co factor 1c':ti,ab,de,mn,tn	37,960
#4	#1 OR #2 OR #3	6,955
#3	'blood clotting factor 8 plus von willebrand factor'/de OR alphanate:ti,ab,de,mn,tn OR koate:ti,ab,de,mn,tn OR 'koate dvi':ti,ab,de,mn,tn OR koatedvi:ti,ab,de,mn,tn OR biostate:ti,ab,de,mn,tn OR 'blood clotting factor 8 von willebrand factor':ti,ab,de,mn,tn OR 'coagulation factor viii plus von willebrand factor':ti,ab,de,mn,tn OR fandhi:ti,ab,de,mn,tn OR fanhdi:ti,ab,de,mn,tn OR haemate:ti,ab,de,mn,tn OR 'haemate hs':ti,ab,de,mn,tn OR 'haemate p':ti,ab,de,mn,tn OR 'hemate p':ti,ab,de,mn,tn OR 'humate hs':ti,ab,de,mn,tn OR 'humate p':ti,ab,de,mn,tn OR immunate:ti,ab,de,mn,tn OR optivate:ti,ab,de,mn,tn OR talate:ti,ab,de,mn,tn OR 'von willebrand factor plus blood clotting factor 8':ti,ab,de,mn,tn OR 'von willebrand factor plus coagulation factor viii':ti,ab,de,mn,tn OR voncento:ti,ab,de,mn,tn OR wilate:ti,ab,de,mn,tn OR wilstart:ti,ab,de,mn,tn	1,101
#2	'recombinant blood clotting factor 8'/de OR adynovate:ti,ab,de,mn,tn OR 'kogenate fs':ti,ab,de,mn,tn OR advate:ti,ab,de,mn,tn OR adynovi:ti,ab,de,mn,tn OR afstyla:ti,ab,de,mn,tn OR 'bax 855':ti,ab,de,mn,tn OR bax855:ti,ab,de,mn,tn OR 'bay 94 9027':ti,ab,de,mn,tn OR 'bay 94-9027':ti,ab,de,mn,tn OR 'bay w 6240':ti,ab,de,mn,tn OR 'bay w6240':ti,ab,de,mn,tn OR 'bay94 9027':ti,ab,de,mn,tn OR 'beroctocog alfa':ti,ab,de,mn,tn OR 'beroctocog alpha':ti,ab,de,mn,tn OR bioclate:ti,ab,de,mn,tn OR 'csl 627':ti,ab,de,mn,tn OR csl627:ti,ab,de,mn,tn OR 'damoctocog alfa':ti,ab,de,mn,tn OR 'damoctocog alfa pegol':ti,ab,de,mn,tn OR 'damoctocog alpha':ti,ab,de,mn,tn OR 'damoctocog alpha pegol':ti,ab,de,mn,tn OR 'efmoroctocog alfa':ti,ab,de,mn,tn OR 'efmoroctocog alpha':ti,ab,de,mn,tn OR elocta:ti,ab,de,mn,tn OR eloctate:ti,ab,de,mn,tn OR 'green eight':ti,ab,de,mn,tn OR helixate:ti,ab,de,mn,tn OR 'helixate fs':ti,ab,de,mn,tn OR 'helixate nexgen':ti,ab,de,mn,tn OR helixatenexgen:ti,ab,de,mn,tn OR iblias:ti,ab,de,mn,tn OR kogenate:ti,ab,de,mn,tn OR kogenatebayer:ti,ab,de,mn,tn OR kovaltry:ti,ab,de,mn,tn OR 'lonoctocog alfa':ti,ab,de,mn,tn OR 'lonoctocog alpha':ti,ab,de,mn,tn OR 'moroctocog alfa':ti,ab,de,mn,tn OR 'moroctocog alpha':ti,ab,de,mn,tn OR novoeight:ti,ab,de,mn,tn OR nuwiq:ti,ab,de,mn,tn OR obizur:ti,ab,de,mn,tn OR 'octocog alfa':ti,ab,de,mn,tn OR 'octocog alpha':ti,ab,de,mn,tn OR 'recombinant antihaemophilic factor':ti,ab,de,mn,tn OR 'recombinant antihemophilic factor':ti,ab,de,mn,tn OR 'recombinant coagulation factor viii':ti,ab,de,mn,tn OR	

Table 2. EMBASE Search Strategies

	'recombinant factor viii':ti,ab,de,mn,tn OR recombinate:ti,ab,de,mn,tn OR refacto:ti,ab,de,mn,tn OR 'refacto af':ti,ab,de,mn,tn OR 'rurioctocog alfa':ti,ab,de,mn,tn OR 'rurioctocog alfa pegol':ti,ab,de,mn,tn OR 'rurioctocog alpha':ti,ab,de,mn,tn OR 'rurioctocog alpha pegol':ti,ab,de,mn,tn OR 'simoctocog alfa':ti,ab,de,mn,tn OR 'simoctocog alpha':ti,ab,de,mn,tn OR 'susoctocog alfa':ti,ab,de,mn,tn OR 'susoctocog alpha':ti,ab,de,mn,tn OR 'turoctocog alfa':ti,ab,de,mn,tn OR 'turoctocog alfa pegol':ti,ab,de,mn,tn OR 'turoctocog alpha':ti,ab,de,mn,tn OR 'turoctocog alpha pegol':ti,ab,de,mn,tn OR vihuma:ti,ab,de,mn,tn OR xyntha:ti,ab,de,mn,tn OR ((human NEAR/2 ('coagulation factor viii' OR 'blood clotting factor 8') NEAR/4 recombinant):ti,ab,de,mn,tn)	4,061
#1	'blood clotting factor 8 concentrate'/de OR aafact:ti,ab,de,mn,tn OR alphanate:ti,ab,de,mn,tn OR amofil:ti,ab,de,mn,tn OR 'bayer koate-hp':ti,ab,de,mn,tn OR beriate:ti,ab,de,mn,tn OR 'beriate hs':ti,ab,de,mn,tn OR 'beriate p':ti,ab,de,mn,tn OR 'blood clotting factor viii concentrate':ti,ab,de,mn,tn OR 'connaught factor 8':ti,ab,de,mn,tn OR 'connaught factor viii':ti,ab,de,mn,tn OR cryobulin:ti,ab,de,mn,tn OR 'cutter factor 8':ti,ab,de,mn,tn OR 'cutter factor viii':ti,ab,de,mn,tn OR 'cutter koate-hp':ti,ab,de,mn,tn OR emoclot:ti,ab,de,mn,tn OR 'emoclot di':ti,ab,de,mn,tn OR 'emoclot octa':ti,ab,de,mn,tn OR factane:ti,ab,de,mn,tn OR 'factor 8 concentrate':ti,ab,de,mn,tn OR 'factor viii concentrate':ti,ab,de,mn,tn OR haemoctin:ti,ab,de,mn,tn OR 'haemoctin sdh':ti,ab,de,mn,tn OR 'haemosolvate factor viii':ti,ab,de,mn,tn OR hemofil:ti,ab,de,mn,tn OR 'hemofil m':ti,ab,de,mn,tn OR 'hemofil t':ti,ab,de,mn,tn OR hemophil:ti,ab,de,mn,tn OR 'hp 250':ti,ab,de,mn,tn OR humaclot:ti,ab,de,mn,tn OR 'humafactor 8':ti,ab,de,mn,tn OR 'hyate c':ti,ab,de,mn,tn OR klott:ti,ab,de,mn,tn OR koate:ti,ab,de,mn,tn OR 'koate hs':ti,ab,de,mn,tn OR 'koate ht':ti,ab,de,mn,tn OR 'koate r':ti,ab,de,mn,tn OR 'koate dvi':ti,ab,de,mn,tn OR 'koate hp':ti,ab,de,mn,tn OR kryobulin:ti,ab,de,mn,tn OR 'kryobulin tim 3':ti,ab,de,mn,tn OR 'kryobulin tim3':ti,ab,de,mn,tn OR 'monarc m':ti,ab,de,mn,tn OR monoclate:ti,ab,de,mn,tn OR 'monoclate p':ti,ab,de,mn,tn OR nordiocto:ti,ab,de,mn,tn OR 'octa v.i.':ti,ab,de,mn,tn OR octafil:ti,ab,de,mn,tn OR octanate:ti,ab,de,mn,tn OR 'octanate lv':ti,ab,de,mn,tn OR octavi:ti,ab,de,mn,tn OR octobulin:ti,ab,de,mn,tn OR octonativ:ti,ab,de,mn,tn OR 'octonativ m':ti,ab,de,mn,tn OR omrixate:ti,ab,de,mn,tn OR profilate:ti,ab,de,mn,tn OR 'profilate osd':ti,ab,de,mn,tn OR 'profilate sd':ti,ab,de,mn,tn OR replenate:ti,ab,de,mn,tn	3,303

Table 2. EMBASE Search Strategies

Embase RCT Search (June 11th, 2018; 396 results produced)		
#9	#8 NOT #6	**396 [RCTs** not SRs]
#8	#4 AND #7	403
#7	('clinical study'/mj OR 'clinical trial'/mj OR 'controlled clinical trial'/mj OR 'controlled study'/mj OR 'major clinical study'/mj OR 'randomized controlled trial'/mj OR 'control group'/mj OR (((clinical OR comparative OR efficacy OR effectiveness OR randomi* OR controlled OR multicentre OR multicenter OR 'multi centre' OR 'multi center') NEAR/3 (study OR trial)):ab) OR placebo:ab,ti OR controlled:ti OR trial:ti OR multicent*:ti OR 'multi cent*':ti OR study:ti OR randomly:ab OR 'head to head':ti,ab) NOT ('conference abstract'/it OR 'conference paper'/it OR (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de)))) AND [english]/lim	1,567,975
#6	#4 AND #5	69
#5	('systematic review'/de OR 'meta analysis'/mj OR metaanaly*:ti OR 'meta analy*':ti OR ((systematic NEAR/2 review):ti)) NOT ('conference abstract'/it OR 'conference paper'/it OR (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de)))) AND [english]/lim	182,097
#4	#1 OR #2 OR #3	6268
#3	'blood clotting factor 8 plus von willebrand factor'/de OR alphante:ti,ab,de,mn,tn OR 'humate p':ti,ab,de,mn,tn OR koate:ti,ab,de,mn,tn OR 'koate dvi':ti,ab,de,mn,tn OR koatedvi:ti,ab,de,mn,tn OR vonvendi:ti,ab,de,mn,tn OR wilate:ti,ab,de,mn,tn	824
#2	'recombinant blood clotting factor 8'/de OR advate:ti,ab,de,mn,tn OR adynovate:ti,ab,de,mn,tn OR afstyla:ti,ab,de,mn,tn OR eloctate:ti,ab,de,mn,tn OR 'helixate fs':ti,ab,de,mn,tn OR 'kogenate fs':ti,ab,de,mn,tn OR kovaltry:ti,ab,de,mn,tn OR novoeight:ti,ab,de,mn,tn OR nuwiq:ti,ab,de,mn,tn OR recombinate:ti,ab,de,mn,tn OR refacto:ti,ab,de,mn,tn OR xyntha:ti,ab,de,mn,tn	3892
#1	'blood clotting factor 8 concentrate'/de OR 'hemofil m':ti,ab,de,mn,tn OR 'monoclate p':ti,ab,de,mn,tn	2748

Appendix B: Excluded Studies

Wrong Study Design

1. Aledort LM, Navickis RJ, Wilkes MM. Can B-domain deletion alter the immunogenicity of recombinant factor VIII? A meta-analysis of prospective clinical studies. Journal of thrombosis and haemostasis : JTH. 2011;9(11):2180-2192.
2. Ar MC, Baslar Z, Soysal T. Personalized prophylaxis in people with hemophilia A: challenges and achievements. Expert review of hematology. 2016;9(12):1203-1208.
3. Arkin S, Rose E, Forster A, Aledort LM. Clinical efficacy of recombinant factor VIII. The rFactor VIII Clinical Trial Group. Seminars in hematology. 1991;28(2 Suppl 1):47-51.
4. Batlle J, López-Fernández MF, Fraga EL, Trillo AR, Pérez-Rodríguez MA. Von Willebrand factor/factor VIII concentrates in the treatment of von Willebrand disease. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2009;20(2):89-100.
5. Briët E, Rosendaal FR. Inhibitors in hemophilia A: are some products safer? Seminars in hematology. 1994;31(2 Suppl 4):11-15.
6. Briët E, Rosendaal FR, Kreuz W, et al. High titer inhibitors in severe haemophilia A. A meta-analysis based on eight long-term follow-up studies concerning inhibitors associated with crude or intermediate purity factor VIII products. Thrombosis and haemostasis. 1994;72(1):162-164.
7. Collins P, Chalmers E, Chowdary P, et al. The use of enhanced half-life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO. Haemophilia : the official journal of the World Federation of Hemophilia. 2016;22(4):487-498.
8. Ettingshausen CE, Kreuz W. Recombinant vs. plasma-derived products, especially those with intact VWF, regarding inhibitor development. Haemophilia. 2006;12(SUPPL. 6):102-106.
9. Franchini M. Plasma-derived versus recombinant Factor VIII concentrates for the treatment of haemophilia A: Recombinant is better. Blood Transfusion. 2010;8(4):292-296.
10. Franchini M, Makris M, Santagostino E, Coppola A, Mannucci PM. Non-thrombotic-, non-inhibitor-associated adverse reactions to coagulation factor concentrates for treatment of patients with hemophilia and von Willebrand's disease: a systematic review of prospective studies. Haemophilia : the official journal of the World Federation of Hemophilia. 2012;18(3):e164-172.
11. Franchini M, Mannucci PM. The safety of pharmacologic options for the treatment of persons with hemophilia. Expert Opinion on Drug Safety. 2016;15(10):1391-1400.
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Wrong Intervention

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Wrong Comparator

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Wrong Outcome

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Wrong Indication

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Appendix C: Comparative Pharmacokinetic Studies

Table 1. Head-to-head Pharmacokinetic Studies

Study Reference	Study Design	Interventions	Testing/Model	Pharmacokinetic Results
Shah, 2017[58]	Phase I, single-dose, open-label, randomized, crossover study in adult patients with severe hemophilia A	BAY 81-8973 (Kovaltry) vs. rAHF-PFM (Advate)	- Population PK model based on one-stage and chromogenic assays	• A single infusion of Kovaltry significantly improved AUC, half-life, mean residence time, and lower clearance vs. a single infusion of Advate • Half-life comparison (hours): o 4.5 (Kovaltry) vs. 11.7 (Advate) with one-stage assay o 13.9 (Kovaltry) vs. 12.0 (Advate) with chromogenic assay
Klamroth, 2016[69]	PK investigation in adult patients with severe hemophilia A as part of an ongoing phase I/III clinical study within the AFFINITY clinical trial program.	Octocog alfa (Advate) vs. rFVIII-single chain (Afstyla)	- One-stage clotting - Chromogenic substrate assays	• Compared to Advate, rFVIII-single chain displayed: o longer mean half-life (14.5 vs. 13.3 hours) o < mean clearance o > residence time o > mean AUC_{inf}
Shah, 2015[57]	LEOPOLD clinical trial Part A (phase 1 study to evaluate PK) in patients with severe hemophilia A (>12-65 years)	BAY 81-8973 (Kovaltry) vs. rFVIII-FS (Kogenate FS)	- One-stage and chromogenic assays for FVIII measurements	• Kovaltry PK profile is non-inferior to Kogenate FS. • AUC, half-life and MRT_{IV} were significantly higher with Kovaltry vs. rFVIII o Half-life comparison (hours): 13.4 (Kovaltry) vs. 12.2 (Kogenate) with one-stage assay and 13.8 (Kovaltry) vs. 12.0 (Kogenate) with chromogenic assay • Clearance was lower with Kovaltry vs. rFVIII
Mahlangu, 2014[70]	Phase 3 open-label, multicenter, partially randomized study of rFVIIIFc in	rFVIIIFc (Eloctate) vs. rFVIII (Advate)	- One-stage clotting assay and 2-stage chromogenic assay	• The terminal half-life of rFVIIIFc (19.0 hours) was extended 1.5-fold vs. rFVIII (12.4 hours; $p < .001$) • Clearance was significantly lower for rFVIIIFc vs. rFVIII ($p < .001$) • "rFVIIIFc was developed to reduce prophylactic injection frequency"

Table 1. Head-to-head Pharmacokinetic Studies

Study Reference	Study Design	Interventions	Testing/Model	Pharmacokinetic Results
	patients with severe hemophilia A (≥12 years). A subgroup compared rFVIII and rFVIIIFc PK			
Martinowitz 2011[71]	Open-label, first human dose, PK, safety, single-dose study in adolescent and adult patients with severe hemophilia A	N8 (Novoeight) vs. Advate	- One-stage APTT-based assay	• "N8 was **bioequivalent** to Advate" (primary and secondary endpoints were within the BE window of 0.8–1.25). AUC and half-life were comparable between groups
Recht, 2009[72]	Randomized, double-blind, crossover study to assess PK-equivalence of BDDrFVIII and FLrFVIII in at least 24 patients with severe haemophilia A	Moroctocog alfa (BDDrFVIII or Xyntha) vs. FLrFVIII (Advate)	- One-stage clotting assay	• "BDDrFVIII was **PK-equivalen**t to a full length rFVIII" (results of main parameters [AUC, K-value] were within the BE interval of 80%-125%). Half-life was not measured for PK-equivalence
Tarantino, 2004[73]	Randomized, double-blinded, crossover PK study in severe or moderately severe hemophilia A patients (≥10 years)	rAHF-PFM (Advate) vs. rAHF (R-FVIII or Recombinate)	- One-stage clotting assay and the chromogenic assay	• "rAHFPFM is bioequivalent to R-FVIII based on AUC and adjusted recovery" • Mean half-lives were similar between groups
White, 1997[74]	Phase I study (comparative in vivo pharmacokinetic half-life and recovery studies of	Hemofil M (pdFVIII) vs. Recombinate (rFVIII)	- Method of Lee, Poon and Kingdon to determine half-lives (two-phase linear regression approach)	• Similar mean in vivo half-lives between groups (14.7 hours)

Table 1. Head-to-head Pharmacokinetic Studies

Study Reference	Study Design	Interventions	Testing/Model	Pharmacokinetic Results
	pdFVIII vs. rFVIII) in moderate to severe hemophilia A patients		- One-stage APTT-based assay	
Morfini, 1992[75]	Cross-over evaluation of PK properties in patients with hemophilia A patients (6-62 years)	Recombinate vs. Hemofil M	- One-stage method - Model-dependent and model-independent approaches	• Recombinate displayed a significantly lower clearance, volume of distribution, and higher in vivo recovery, but a similar half-life to Hemofil M
Morfini, 1991[76]	Cross-over, single-dose, PK study in patients with severe hemophilia A patients	Hemofil M vs. Monoclate-P	- Compartmental and non-compartmental methods	• Similar clearance, mean residence time, half-life, and volume of distribution between products

Abbreviations: APTT, activated partial thromboplastin time; AUC, area under the curve; BDDrFVIII; B-domain deleted recombinant factor VIII; BE, bioequivalence; FLrFVIII, full-length recombinant factor VIII; MRT_{IV}; mean residence time after intravenous injection; pdFVIII, plasma-derived factor VIII; PK, pharmacokinetic; rAHF-PFM; recombinant antihemophilic factor plasma/albumin free method; rFVIII, recombinant factor VIII; R-FVIII, Recombinate rAHF; rFVIIIFc, recombinant FVIII Fc fusion protein; rFVIII-FS, sucrose-formulated recombinant FVIII

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