Neighborhood Health Plan OF RHODE ISLAND™
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Hemophilia Products – Factor VIII: Advate, Adynovate, Afstyla, Eloctate, Hemofil M, Koate/Koate DVI, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, Xyntha/Xyntha Solofuse, Jivi, Esperoct, Altuviiio (Intravenous)

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Scope: Medicaid, Commercial, Medicare-Medicaid Plan (MMP)

I. Length of Authorization

Unless otherwise specified*, the initial authorization will be provided for 3 months and may be renewed.

Note: The cumulative amount of medication the patient has on-hand will be taken into account for authorizations. Up to 5 'on-hand' doses for the treatment of acute bleeding episodes will be permitted at the time of the authorization request.

** Initial and renewal authorization periods may vary by specific covered indication*

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC unit]:

N/A

B. Max Units (per dose and over time) [HCPCS Unit]:

- Advate: 64,400 billable units per 28 day supply
- Adynovate: 46,000 billable units per 28 day supply
- Afstyla: 69,000 billable units per 28 day supply
- Eloctate: 74,750 billable units per 30 day supply
- Kogenate: 64,400 billable units per 28 day supply
- Kovaltry: 55,200 billable units per 28 day supply
- Novoeight: 69,000 billable units per 28 day supply
- Nuwiq: 64,4000 billable units per 28 day supply
- Hemofil M: 55,200 billable units per 28 day supply
- Koate DVI: 55,200 billable units per 28 day supply
- Recombinate: 64,400 billable units per 28 day supply
- Xyntha/Xyntha Solofuse: 41,400 billable units per 28 day supply
- Obizur: 115,000 billable units per 90 day supply

- Jivi: 41,400 billable units per 30 day supply
- Esperoct: 40,250 billable units per 28 day supply
- Altuviiio 23,000 billable units per 28 day supply

III. Initial Approval Criteria [1-14,15,16,21]

Hemophilia Management Program
Requirements for half-life study and inhibitor tests are a part of the hemophilia management program. This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide.

Coverage is provided in the following conditions:

MMP members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements

Advate, Eloctate **Φ**, Hemofil M, Koate/KoateDVI, Kogenate FS **Φ**, Novoeight, Recombinate, Xyntha/Xyntha Solofuse **Φ**, Nuwiq, Adynovate, Kovaltry, Afstyla, Jivi, Esperoct, Altuviiio

Hemophilia A (congenital factor VIII deficiency) †

- Diagnosis of congenital factor VIII deficiency has been confirmed by blood coagulation testing; **AND**
- If the request is for Jivi, patient must be at least 12 years of age; **AND**
- Will not be used for the treatment of von Willebrand's disease; **AND**
- Used as treatment in at least one of the following:
  - On demand and control and control of bleeding episodes; **OR**
  - Perioperative management *(*Authorizations valid for 1 month)*; **OR**
  - Routine prophylaxis; **AND**
    - Used to reduce the frequency of bleeding episodes; **OR**
    - Used to reduce the frequency of bleeding episodes and reduce the risk of joint damage in children without pre-existing joint damage (***Kogenate-FS ONLY***); **AND**
      - Used as primary prophylaxis in patients with severe Factor VIII deficiency (factor FVIII level of <1%); **OR**
      - Used as secondary prophylaxis in patients with at least TWO documented episodes of spontaneous bleeding into joints; OR
  - Patient was previously treated with valoctocogene roxaparvovec (Roctavian) and factor VIII activity levels decreased and/or bleeding was not controlled

Hemophilia Management Program
• If the request is for routine prophylaxis and the requested dose exceeds dosing limits under part II or if member BMI≥ 30, a half-life study should be performed to determine the appropriate dose and dosing interval. • If the request is for Eloctate, Adynovate, Jivi, Esperoct, or Altuviiio the following criteria should be met: o Patient is not a suitable candidate for a standard non- EHL factor VIII product. o A half-life study must be scheduled to determine the appropriate dose and dosing interval of the EHL product when initiated. o Prior to switching to Eloctate, Adynovate, Jivi, or Esperoct a half-life study should also be performed on current non-EHL factor VIII product to ensure that a clinical benefit will be achieved. • If the request exceeds any of the following dosing limits, documentation must be submitted specifying why the member is not a suitable candidate for Hemlibra and alternative EHL factor VIII products. – 50 IU/kg every 4 days (total weekly dose of 87.5 IU/kg) for Eloctate – 40 IU/kg twice weekly (total weekly dose of 80 IU/kg) for Adynovate – 60 IU/kg every 5 days (total weekly dose of 84 IU/kg) for Jivi – 50 IU/kg every 4 days (total weekly dose of 87.5 IU/kg) for Esperoct • For minimally treated patients (< 50 exposure days to factor products) previously receiving a different factor product, inhibitor testing is required at baseline, then at every comprehensive care visit (yearly for the mild and moderate patients, semi-annually for the severe patients)

A. Obizur [10]

Acquired Hemophilia A (acquired factor VIII deficiency) †

- Patient is at least 18 years of age; **AND**
- Diagnosis of acquired factor VIII deficiency has been confirmed by blood coagulation testing; **AND**
- Used as on-demand treatment and control of bleeding episodes; **AND**
- Is NOT being used for congenital Hemophilia A OR von Willebrand disease; **AND**
- Patient does not have baseline anti-porcine factor VIII inhibitor titer >20 Bethesda Units (BU)

Hemophilia Management Program
• For members with a BMI ≥ 30, a half-life study should be performed to determine the appropriate dose and dosing interval.

- For minimally treated patients (< 50 exposure days to factor products) previously receiving a different factor product, inhibitor testing is required at baseline, then at every comprehensive care visit (yearly for the mild and moderate patients, semi-annually for the severe patients)

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); **Φ** Orphan Drug

IV. Dispensing Requirements for Rendering Providers (Hemophilia Management Program)

- Prescriptions cannot be filled without an expressed need from the patient, caregiver or prescribing practitioner. Auto-filling is not allowed.
- Monthly, rendering provider must submit for authorization of dispensing quantity before delivering factor product. Information submitted must include:
  - Original prescription information, requested amount to be dispensed, vial sizes available to be ordered from the manufacturer, and patient clinical history (including patient product inventory and bleed history)
  - Factor dose should not exceed +1% of the prescribed dose and a maximum of three vials may be dispensed per dose. If unable to provide factor dosing within the required threshold, below the required threshold, the lowest possible dose able to be achieved above +1% should be dispensed. Prescribed dose should not be increased to meet assay management requirements.
- The cumulative amount of medication(s) the patient has on-hand should be taken into account when dispensing factor product. Patients should not have more than 5 extra doses on-hand for the treatment of acute bleeding episodes.
- Dispensing requirements for renderings providers are a part of the hemophilia management program. This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide.

V. Renewal Criteria [1-14,15,16,21]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: anaphylaxis and hypersensitivity reactions (e.g., angioedema, chest tightness, dyspnea, wheezing, urticaria, pruritus, hypotension, etc.), thromboembolic events (thromboembolism, pulmonary embolism), development of neutralizing antibodies (inhibitors), etc.; **AND**
- Any increases in dose must be supported by an acceptable clinical rationale (i.e., weight gain, half-life study results, increase in breakthrough bleeding when patient is fully adherent to therapy, etc.); **AND**
- The cumulative amount of medication(s) the patient has on-hand will be taken into account when authorizing. The authorization will allow up to 5 doses on-hand for the treatment of acute bleeding episodes as needed for the duration of the authorization; **AND**

- Renewals will be approved for a 6-month authorization period

Perioperative management of bleeding

- Coverage may NOT be renewed

Routine prophylaxis to prevent or reduce the frequency of bleeding episode

- Renewals will be approved for a 12-month authorization period; **AND**
- Patient has demonstrated a beneficial response to therapy (i.e., the frequency of bleeding episodes has decreased from pre-treatment baseline)

VI. Dosage/Administration[1-16]

Advate

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Circulating Factor VIII required (% of normal) (20-40%) = 10-20 IU/ kg -Repeat every 12-24 hours as needed (every 8 to 24 hours for patients under age of 6). Continue until the bleeding episode is resolved (approximately 1 to 3 days). Moderate Circulating Factor VIII required (% of normal) (30-60%) = 15-30 IU/ kg - Repeat every 12-24 hours as needed (every 8 to 24 hours for patients under age of 6). Continue until the bleeding episode is resolved (approximately 3 days or more). Major Circulating Factor VIII required (% of normal) (60-100%) = 30-50 IU/ kg - Repeat every 8-24 hours as needed (every 6 to 12 hours for patients under age of 6). Continue until the bleeding episode is resolved.
Routine prophylaxis Congenital Hemophilia A	For prophylaxis regimen to prevent or reduce frequency of bleeding episodes, dose between 20 to 40 IU per kg every other day (3 to 4 times weekly). Alternatively, an every third day dosing regimen targeted to maintain FVIII trough levels ≥ 1% may be employed. Adjust dose based on the patient's clinical response.

Indication	Dose
Perioperative management Congenital Hemophilia A	Dose (IU/kg) = desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Circulating Factor VIII required (% of normal) (60-100%) = 30-50 IU/ kg –Single dose within one hour of the operation. Repeat after 12- 24 hours for optional additional dosing as needed to control bleeding. Major Circulating Factor VIII required (% of normal) (80-120%) = Preoperative: 40-60 IU/ kg to achieve 100% activity. Followed by a repeat dose every 8-24 hours (every 6 to 24 hours for patients under age of 6). Postoperatively until healing is complete.

Adynovate

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU) = Body Weight (kg) x Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Target Factor VIII level (IU/dL or % of normal) (20-40%) = 10-20 IU/kg -Repeat every 12-24 hours until the bleeding episode is resolved Moderate Target Factor VIII level (IU/dL or % of normal) (30-60%) = 15-30 IU/kg - Repeat every 12-24 hours until the bleeding episode is resolved Major Target Factor VIII level (IU/dL or % of normal) (60-100%) = 30-50 IU/kg - Repeat every 8-24 hours until the bleeding episode is resolved.
Perioperative management Congenital Hemophilia A	Dose (IU) = Body Weight (kg) × Desired factor VIII Rise (IU/dL or % of Normal) × 0.5 (IU/kg per IU/dL) Minor Target Factor VIII required (% of normal) (60-100%) = 30-50 IU/ kg –Single dose within one hour of the operation. Repeat after 24 hours, if necessary, single dose or repeat as needed until bleeding is resolved. Major Target Factor VIII required (% of normal) (80-120%) (pre- and post- operative) = 40-60 IU/ kg within 1 hour of the operation to achieve 100% activity. Repeat dose every 8-24 hours (every 6 to 24 hours for patients under age of 12) to maintain FVIII activity within the target range and continue until adequate wound healing.
Routine prophylaxis Congenital Hemophilia A	Administer 40-50 IU per kg body weight 2 times per week in children and adults (12 years and older). Administer 55 IU per kg body weight 2 times per week in children (<12 years) with a maximum of 70 IU per kg. Adjust the dose based on the patient's clinical response.

Afstyla

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU) = Body Weight (kg) x Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Target Factor VIII level (IU/dL or % of normal) 20-40% -Repeat every 12-24 hours until the bleeding episode is resolved Moderate Target Factor VIII level (IU/dL or % of normal) 30-60%- Repeat every 12-24 hours until the bleeding episode is resolved Major Target Factor VIII level (IU/dL or % of normal) 60-100%- Repeat every 8-24 hours until the bleeding episode is resolved.
Perioperative management Congenital Hemophilia A	Minor Target Factor VIII level (IU/dL or % of normal) 30-60%- Repeat every 24 hours, for at least one day, until the bleeding episode is resolved. Major Target Factor VIII level (IU/dL or % of normal) 80-100%- Repeat every 8-24 hours until adequate wound healing, then continue for at least another 7 days to maintain a Factor VIII activity of 30-60% (IU/dL).
Routine prophylaxis Congenital Hemophilia A	Adults and adolescents *(≥12yrs old)*: Administer 20-50 IU per kg body weight 2 to 3 times per week. Adjust the dose based on the patient's clinical response. Children *(<12 yrs old):* Administer 30-50 IU per kg body weight 2 to 3 times per week. Adjust the dose based on the patient's clinical response.

Altuviiio

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Minor/Moderate Single dose of 50 IU/kg. For minor and moderate bleeding episodes occurring within 2 to 3 days after a prophylactic dose, a lower dose of 30 IU/kg dose may be used. Additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered. Major

	Single dose of 50 IU/kg. Additional doses of 30 or 50 IU/kg every 2 to 3 days can be considered. *Note: For resumption of prophylaxis (if applicable) after treatment of a bleed, it is recommended to allow an interval of at least 72 hours between the last 50 IU/kg dose for treatment of a bleed and resuming prophylaxis dosing. Thereafter, prophylaxis can be continued as usual on the patient's regular schedule.*
Perioperative management Congenital Hemophilia A	Minor Single dose of 50 IU/kg. An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered. Major Single dose of 50 IU/kg. Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered as clinically needed for perioperative management.
Routine prophylaxis Congenital Hemophilia A	The recommended dosing for routine prophylaxis for adults and children is 50 IU/kg of Altuviiio administered once weekly.
– For the dose of 50 IU/kg, the expected in vivo peak increase in Factor VIII level expressed as IU/dL (or % of normal) is estimated using the following formula: – Estimated Increment of Factor VIII (IU/dL or % of normal) = 50 IU/kg x 2 (IU/dL per IU/kg) – To achieve a specific target Factor VIII activity level, use the following formula: Dosage (IU) = Body Weight (kg) x Desired Factor VIII Increase (IU/dL or % normal) x 0.5 (IU/kg per IU/dL).	

Eloctate

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor and Moderate Circulating Factor VIII required (% of normal) (40-60%) = 20-30 IU/ kg -Repeat every 24-48 hours as needed (every 12 to 24 hours for patients under age of 6). Continue until the bleeding episode is resolved. Major Circulating Factor VIII required (% of normal) (80-100%) = 40-50 IU/ kg - Repeat every 12-24 hours as needed (every 8 to 24 hours for patients under age of 6). Continue until the bleeding episode is resolved (approximately 7-10 days).
Routine prophylaxis Congenital Hemophilia A	Adults and adolescents ≥ 6: The recommended starting regimen is 50 IU/kg administered every 4 days. The regimen may be adjusted based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals. Children < 6 years of age: The recommended starting regimen is 50 IU/kg administered twice weekly. The regimen may be adjusted based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals. More frequent or higher doses up to 80 IU/kg may be required.

Indication	Dose
Perioperative management Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Circulating Factor VIII required (% of normal) (50-80%) = 25-40 IU/ kg -Repeat every 24 hours as needed (every 12 to 24 hours for patients under age of 6). Continue at least 1 day until healing is achieved. Major Circulating Factor VIII required (% of normal) (80-120%) = Preoperative: 40-60 IU/ kg – Followed by a repeat dose of 40-50 IU/kg after 8-24 hours (6 to 24 hours for patients under age of 6). Continue every 24 hours until adequate wound healing; then continue therapy for at least 7 days to maintain FVII activity within the target range.

Esperoct

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	One IU of Factor VIII activity corresponds to the quantity of Factor VIII in one milliliter of normal human plasma. The calculation of the required dosage of Factor VIII is based on the empirical finding that one IU of Factor VIII per kg body weight raises the plasma Factor VIII activity by two IU/dL. *To achieve a specific target Factor VIII activity level, use the following formula: Dosage (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 ;* ***OR***

Type of bleeding	Adolescents/Adults ≥12 years Dose (IU/kg)	Children <12 years Dose (IU/kg)	Additional doses
Minor Early hemarthrosis, mild muscle bleeding, or oral bleeding	40	65	One dose should be sufficient
Moderate More extensive hemarthrosis, muscle bleeding, or hematoma	40	65	An additional dose may be administered after 24 hours
Major Life- or limb-threatening hemorrhages, gastro- intestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, fractures	50	65	Additional dose(s) may be administered approximately every 24 hours

Routine prophylaxis Congenital Hemophilia A	– Adults and adolescents (≥ 12 years): The recommended starting dose is 50 IU per kg body weight every 4 days. This regimen may be individually adjusted to less or more frequent dosing based on bleeding episodes. – Children (< 12 years): A dose of 65 IU per kg body weight twice weekly. This regimen may be individually adjusted to less or more frequent dosing based on bleeding episodes.

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td>Perioperative management Congenital Hemophilia A</td><td>To achieve a specific target Factor VIII activity level, use the following formula: Dosage (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 ; OR
<table>
<tr><th>Type of surgery</th><th>Adolescents/Adults ≥12 years Dose (IU/kg)</th><th>Children <12 years Dose (IU/kg)</th><th>Additional doses</th></tr>
<tr><td>Minor
Including tooth extraction</td><td>50</td><td>65</td><td>Additional dose(s) can be given after 24 hours if necessary</td></tr>
<tr><td>Major
Intracranial, intra-abdominal, intrathoracic, or joint replacement surgery</td><td>50</td><td>65</td><td>Additional doses can be given every 24 hours for the first week and then approximately every 48 hours until wound healing has occurred</td></tr>
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Hemofil M

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) <u>Early hemarthrosis or muscle bleed or oral bleed</u> Circulating Factor VIII required (% of normal) (20-40%) = Begin infusion every 12 to 24 hours for one-three days until the bleeding episode as indicated by pain is resolved or healing is achieved. <u>More extensive hemarthrosis, muscle bleed, or hematoma</u> Circulating Factor VIII required (% of normal) (30-60%) = Repeat every 12-24 hours for usually three days or more until pain and disability are resolved. <u>Life threatening bleeds such as head injury, throat bleed, severe abdominal pain</u> Circulating Factor VIII Required (% of normal) (60-100%) = Repeat every 8-24 hours until the bleeding threat is resolved.
Perioperative management Congenital Hemophilia A	<u>Minor</u> Circulating Factor VIII required (% of normal) (60-80%) A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases. <u>Major</u> Circulating Factor VIII required (% of normal) (80-100% pre- and post-operative): Repeat dose every 8-24 hours depending on state of healing.

Jivi

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x reciprocal of expected recovery (or observed recovery, if available) (e.g., 0.5 for a recovery of 2 IU/dL per IU/kg) <u>Minor</u> Circulating Factor VIII required (% of normal) (20-40%) – 10-20IU/kg repeat dose every 24-48 hours until bleed resolves <u>Moderate</u>

Indication	Dose
	Circulating Factor VIII required (% of normal) (30-60%) – 15-30IU/kg repeat dose every 24-48 hours until bleed resolves Major Circulating Factor VIII Required (% of normal) (60-100%) – 30-50IU/kg repeat dose every 8-24 hours until bleed resolves
Perioperative management Congenital Hemophilia A	Minor Circulating Factor VIII required (% of normal) (30-60%) – 15-30IU/kg repeat dose every 24 hours for at least 1 day until healing is achieved Major Circulating Factor VIII required (% of normal) (80-100%) – 40-50IU/kg repeat dose every 12-24 hours until adequate wound healing is complete, then continue therapy for at least another 7 days to maintain Factor VIII activity of 30–60% (IU/dL)
Routine prophylaxis Congenital Hemophilia A	The recommended initial regimen is 30–40 IU/kg twice weekly. Based on the bleeding episodes, the regimen may be adjusted to 45–60 IU/kg every 5 days or may be further individually adjusted to less or more frequent dosing.

Koate/Koate DVI

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Circulating Factor VIII required (% of normal) (30%) = 15 IU/kg repeat dose every 12 hours until hemorrhage stops and healing has been achieved. Moderate Circulating Factor VIII required (% of normal) (50%) = 25 IU/kg repeat dose every 12 hours until healing has been achieved. Major Circulating Factor VIII Required (% of normal) (80-100%) = Initial: 40-50 IU/kg. Maintenance dose 25 IU/kg. Repeat every 12 hours for at least 3 – 5 days until healing has been achieved for up to 10 days.
Routine prophylaxis Hemophilia A §	25-40 IU/kg three times weekly or 15-30 IU/kg three times weekly. Adjust dosing regimen based on individual response.
Perioperative management Congenital Hemophilia A	Prior to surgery Circulating Factor VIII Required (% of normal) (80-100%) = 40-50 IU/kg for one dose prior to surgery.

	After surgery Circulating Factor VIII Required (% of normal) (60-100%) = 30-50 IU/kg repeat dose every 12 hours for the next 7 – 10 days or until healing has been achieved.

Kogenate FS

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Circulating Factor VIII required (% of normal) (20-40%) = 10-20 IU/ kg - Repeat dose if there is evidence of further bleeding and continue until the bleeding episode is resolved. Moderate Circulating Factor VIII required (% of normal) (30-60%) = 15-30 IU/ kg - Repeat every 12-24 hours as needed. Continue until the bleeding episode is resolved. Major Circulating Factor VIII Required (% of normal) (80-100%) = Initial: 40-50 IU/ kg; Repeat 20-25 IU/kg every 8-12 hours until the bleeding episode is resolved.
Routine prophylaxis Congenital Hemophilia A	Routine Prophylaxis in Adults 25 units per kg of body weight three times per week. Routine Prophylaxis in Children 25 IU/kg of body weight every other day.
Perioperative management Congenital Hemophilia A	Minor Circulating Factor VIII required (% of normal) (30-60%) = 15-30 IU/ kg – Repeat every 12- 24 hours until bleeding is resolved. Major Circulating Factor VIII required (% of normal) (100%) = Preoperative: 50 IU/ kg to achieve 100% activity. Followed by a repeat dose every 6-12 hours to keep FVIII activity in desired range. Continue until healing is complete.

Kovaltry

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	• Required dose (IU) = body weight (kg) x desired Factor VIII rise (% of normal or IU/dL) x reciprocal of expected/observed recovery (e.g., 0.5 for a recovery of 2 IU/dL per IU/kg) • Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg) Minor (Early hemarthrosis, minor muscle, oral bleeds) Factor VIII level required (IU/dL or % of normal): 20-40 – repeat every 12-24 hours at least 1 day, until bleeding episode as indicated by pain is resolved or healing is achieved. Moderate

Indication	Dose
	(More extensive hemarthrosis, muscle bleeding, or hematoma) Factor VIII level required (IU/dL or % of normal): 30-60 – repeat every 12-24 hours for 3 to 4 days or more until pain and acute disability are resolved. Major (Intracranial, intra-abdominal or intrathoracic hemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath, life or limb threatening hemorrhage) Factor VIII level required (IU/dL or % of normal): 60-100 – repeat every 8-24 hours until bleeding is resolved.
Routine prophylaxis Congenital Hemophilia A	Individualize the patient's dose based on clinical response: • Adults and adolescents: 20 to 40 IU of KOVALTRY per kg of body weight two or three times per week. • Children ≤12 years old: 25 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirements.
Perioperative management Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor (Such as tooth extraction) Factor VIII level required (IU/dL or % of normal): 30-60 (pre- and post-operative) – repeat every 24 hours at least 1 day until healing is achieved. Major (Such as intracranial, intraabdominal, intrathoracic, or joint replacement surgery) Factor VIII level required (IU/dL or % of normal): 80-100 – repeat every 8-24 hours until adequate wound healing is complete, then continue therapy for at least another 7 days to maintain Factor VIII activity of 30-60% (IU/dL).

Novoeight

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Circulating Factor VIII required (% of normal) (20-40%), every 12 – 24 hours for at least 1 day until the bleeding episode is resolved. Moderate Circulating Factor VIII required (% of normal) (30-60%), every 12 – 24 hours until pain and acute disability are resolved, approximately 3-4 days. Major Circulating Factor VIII Required (% of normal) (60-100%), every 8 – 24 hours until resolution of bleed, approximately 7-10 days.

Perioperative management Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Circulating Factor VIII required (% of normal) (30-60%), every 24 hours for at least 1 day until healing is achieved. Major Circulating Factor VIII required (% of normal) (80-100%) every 8 – 24 hours until adequate wound healing, then continue therapy for at least 7 days to maintain a factor VIII activity of 30 – 60% (IU/dL).
Routine prophylaxis Hemophilia A	Adults and adolescents (≥12 yrs): 20-50 IU/kg three times weekly OR 20-40 IU/kg every other day Children (<12 yrs): 25-60 IU/kg three times weekly OR 25-50 IU/kg every other day

NUWIQ

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL) Expected Factor VIII rise (% of normal) = 2 x administered IU/body weight (kg) Minor Required peak post-infusion Factor VIII activity (% of normal or IU/dL): 20-40 every 12 – 24 hours for at least 1 day until the bleeding episode is resolved Moderate to Major Required peak post-infusion Factor VIII activity (% of normal or IU/dL): 30-60 every 12 – 24 hours for 3-4 days or more until the bleeding episode is resolved Life-threatening Required peak post-infusion Factor VIII activity (% of normal or IU/dL): 60-100 every 8 – 24 hours bleeding risk is resolved
Routine prophylaxis Congenital Hemophilia A	Dose Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL) Expected Factor VIII rise (% of normal) = 2 x administered IU/body weight (kg) Adolescents (12-17 years) and adults 30 – 40 IU/kg every other day Children (2-11 years) 30 – 50 IU/kg every other day or three times per week
Perioperative management Congenital Hemophilia A	Dose Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)

Indication	Dose
	Expected Factor VIII rise (% of normal) = 2 x administered IU/body weight (kg) Minor Required peak post-infusion Factor VIII activity (% of normal or IU/dL): 30-60 (pre- and post-operative) every 24 hours for at least 1 day until healing is achieved Major Required peak post-infusion Factor VIII activity (% of normal or IU/dL): 80-100 (pre- and post-operative) every 8 - 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain Factor VIII activity of 30% to 60% (IU/dL)

Obizur

Indication	Dose
On-demand treatment and control of bleeding episodes Acquired Hemophilia A	Minor and Moderate Loading dose: 200IU/kg; Maintenance dose: Titrate to maintain recommended FVIII trough levels at 50-100 IU/dL every 4 to 12 hours Major Loading dose: 200 IU/kg; Maintenance dose: Titrate to maintain recommended FVIII trough levels at 100-200 (to treat an acute bleed), then 50-100 IU/dL (after acute bleed is controlled) every 4 to 12 hours

Recombinate

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Early hemarthrosis or muscle bleed or oral bleed Circulating Factor VIII required (% of normal) (20-40%) - Begin infusion every 12 to 24 hours for one-three days until the bleeding episode as indicated by pain is resolved or healing is achieved. More extensive hemarthrosis, muscle bleed, or hematoma Circulating Factor VIII required (% of normal) (30-60%) - Repeat every 12-24 hours for usually three days or more until pain and disability are resolved. Life threatening bleeds such as head injury, throat bleed, severe abdominal pain Circulating Factor VIII Required (% of normal) (60-100%) - Repeat every 8-24 hours until the bleeding threat is resolved.
Routine prophylaxis Hemophilia A §	25-40 IU/kg three times weekly or 15-30 IU/kg three times weekly. Adjust dosing regimen based on individual response.

Indication	Dose
Perioperative management Congenital Hemophilia A	Minor Circulating Factor VIII required (% of normal) (60-80%) - A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases. Major Circulating Factor VIII required (% of normal) (80-100% pre- and post-operative) - Repeat dose every 8-24 hours depending on state of healing.

Xyntha/Xyntha Solofuse

Indication	Dose
On-demand treatment and control of bleeding episodes Congenital Hemophilia A	Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Minor Circulating Factor VIII required (% of normal) (20-40%) - Repeat dose every 12- 24 hours for least 1 day, depending upon the severity of the bleeding episode. Moderate Circulating Factor VIII required (% of normal) (30-60%) - Repeat every 12-24 hours as needed. Continue for 3-4 days or until adequate local hemostasis is achieved. Major Circulating Factor VIII Required (% of normal) (60-100%) - Repeat every 8-24 hours until bleeding is resolved.
Perioperative management Congenital Hemophilia A	Minor Circulating Factor VIII required (% of normal) (30-60%) - Repeat every 12- 24 hours. Continue for 3-4 days or until adequate local hemostasis is achieved. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient. Major Circulating Factor VIII required (% of normal) (60-100%) - Repeat every 8-24 hours. Continue until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved.
Routine prophylaxis Hemophilia A	– Adults and adolescents (≥12 years): The recommended starting regimen is 30 IU/kg of Xyntha administered 3 times weekly. – Children (<12 years): The recommended starting regimen is 25 IU/kg of Xyntha administered every other day. More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group. Note: Adjust the dosing regimen (dose or frequency) based on the patient's clinical response.

§ Utrecht and/or Malmö protocols used as basis for dosing

VII. Summary of Evidence

Adynovate, Jivi, Advate, Afstyla, Kovalty, Kogenate, Novoeight, Nuwiq, Hemofil M, Xyntha, Esperoct, Altuviiio, and Eloctate are antihemophilic factor indicated for use in on-demand treatment, perioperative management and routine prophylaxis in patients with Hemophilia A. The safety, efficacy, and PK of Adynovate were evaluated in a multicenter, open-label, prospective, non-randomized, two-arm clinical trial that compared the efficacy of a twice weekly prophylactic treatment regimen to on-demand treatment and determined hemostatic efficacy in the treatment of bleeding episodes. A total of 137 male patients with severe hemophilia A received at least one infusion with Adynovate. The safety and efficacy of Eloctate was evaluated in two multi-center, prospective, open label clinical trials and is being evaluated in an ongoing extension study. The adult and adolescent study compared the efficacy of each of two prophylactic treatment regimens (individualized and fixed weekly) to episodic (on-demand) treatment; determined hemostatic efficacy in the treatment of bleeding episodes; and determined hemostatic efficacy during perioperative management in subjects undergoing major surgical procedures. The study enrolled a total of 165 previously treated male patients with severe Hemophilia A. The efficacy of Jivi for on-demand treatment, perioperative management of bleeding and routine prophylaxis in male subjects with severe hemophilia A were evaluated in one international clinical study in subjects ≥ 12 years. A multinational, open-label, uncontrolled, partially randomized study in adolescent and adult previously treated patients consisted of three parts. Part A of the study evaluated the PK (single dose of 60 IU/kg), safety and efficacy of Jivi for on-demand treatment and routine prophylaxis A total of 134 patients received at least one infusion of Jivi. Despite all three having their separate clinical trials, each were rated based on a four-point rating scale of excellent, good, moderate or poor/no response. The homeostatic efficacy in treatment of bleeds was rated excellent or good in 95.3%, 78.1% and 73.3% of Adynovate, Eloctate and Jivi first injections, respectively. In evaluation of perioperative management, overall hemostatic efficacy was rated excellent or good across all three medications. When assessing efficacy for routine prophylaxis, Jivi revealed the annualized bleeding rates was significantly reduced by 88.2% in the 5-day arm ($p<0.0001$) compared to the on-demand treatment. There was no significant difference in ABRs between the twice weekly and extended interval treatment arms. Among the subjects in every 5-day arm, 19 out of 43 (44%) experienced no bleeding episodes during weeks 10–36. In the Eloctate trial, the analysis of ABR revealed a 92% reduction ($p<0.001$) for subjects in the individualized prophylaxis arm and a 76% reduction ($p<0.001$) for subjects in the weekly prophylaxis arm compared to the episodic (on-demand) arm. Among the subjects on individualized prophylaxis, 53 out of 117 (45%) experienced no bleeding episodes, while 4 out of 23 (17%) subjects on weekly prophylaxis had no bleeding episodes. The Adynovate clinical trial showed significant reduction ($p < 0.0001$) in ABR for subjects in the prophylaxis arm compared to the on-demand arm. During prophylaxis, the majority of bleeding episodes (95%) were of minor/moderate severity. In the prophylaxis arm, 45 out of 120 subjects (38%) experienced no bleeding episodes, and 68 out of 120 subjects (57%) had no joint bleeding episodes. Adverse reactions include headache, rash, fever, urticaria, malaise, arthralgia and myalgia.

In a double-blinded, randomized, cross-over study evaluating Advate, 111 previously treated patients (PTPs) with moderate to severe hemophilia A participated. The study, which included 103 Caucasian, 7 Black, and 1 Asian subjects aged 10 and older, assessed pharmacokinetics, safety, immunogenicity, and hemostatic efficacy. Out of 510 bleeding episodes, 86% were rated as excellent or good, with 81% of episodes managed with a single infusion. The study also documented that the rate of new bleeding episodes during the prophylactic regimen was evaluated in 107 subjects, totaling 274 new episodes. In a study involving 73 patients with severe hemophilia A (FVIII ≤ 2%), aged 12 to 59 years, Kogenate FS was administered over a period of up to 54 months. These patients had previously been

treated with other recombinant or plasma-derived factor VIII products. Throughout the study, a total of 5,684 bleeding episodes were treated, with 92.7% of these episodes managed using one (79.7%) or two (13.0%) infusions. The treatment approach included both on-demand and prophylactic regimens, with prophylaxis comprising 76% of all infusions. This prophylaxis was typically administered 2-3 times per week. Regarding surgical interventions, 30 patients underwent a total of 41 procedures during the study. These surgeries included both minor and major types, with 16 minor and 25 major procedures performed. The efficacy of hemostasis was assessed by comparing the estimated blood loss to that of non-hemophilic patients undergoing similar procedures. The results were positive, with hemostasis rated as satisfactory ("excellent" or "good") in all cases.

Kogenate FS was also evaluated in pediatric PUPs and MTPs with severe hemophilia A. This study involved 37 PUPs and 24 MTPs who were treated with a total of 9,419 infusions of Kogenate FS. The follow-up duration for these patients extended up to 3.1 years. During this period, 1,047 bleeding episodes were treated, with 73% of these managed with a single infusion and 15% with two infusions. The study also included 27 surgical procedures performed in 22 patients. Similar to the PTP studies, the efficacy of hemostasis was evaluated based on the estimated blood loss and rated as satisfactory ("excellent" or "good") in all cases. An ongoing, multicenter, open-label, randomized clinical study is examining the effect of routine prophylaxis with Kogenate FS versus on-demand use in adults and adolescents. This study includes 84 PTPs with severe hemophilia A (FVIII < 1 IU/dL) aged 15 to 50 years. Patients were randomized to receive prophylaxis (25 IU/kg three times a week) or on-demand treatment. The study allows for escalation of the prophylaxis dose by 5 IU/kg/infusion after years 1 and 2, up to a maximum of 35 IU/kg/infusion. The study, with a median follow-up period of 1.4 years, found that patients on prophylaxis experienced significantly fewer bleeds compared to those on on-demand treatment ($p<0.0001$). Specifically, the mean annualized bleed rate was 37 in the on-demand group versus 2 in the prophylaxis group. Most bleeding occurred in joints, with the median joint bleed rate being 24 in the on-demand group versus zero in the prophylaxis group. Among prophylaxis patients, 52% experienced no bleeding, and 29% experienced only 1-2 bleeds during the follow-up period. The mean number of infusions per week for prophylaxis patients was 2.8, with a median dose of 26 IU/kg per infusion.

The safety and efficacy of Afstyla were evaluated in an open-label, multicenter, crossover study involving 175 previously treated male subjects with severe hemophilia A (endogenous Factor VIII activity <1%). The participants, aged 12 to 65 years, included 14 adolescents (ages 12 to 17). Out of the 175 subjects enrolled, 174 received at least one dose of Afstyla, and 173 (99%) were evaluable for efficacy. The study saw 161 subjects (92.5%) complete the trial. Among them, 120 (69.0%) were treated for at least 50 exposure days (EDs), with 52 (29.9%) receiving treatment for at least 100 EDs. In total, 14,592 injections were administered, with a median of 67.0 injections per subject (range 1 to 395). In this study, a total of 848 bleeding episodes were treated with Afstyla, and 835 of these episodes were assessed for efficacy by the investigator. The majority of bleeding episodes occurred in joints. The median dose per injection for managing a bleeding episode was 31.7 IU/kg (range 6 to 84 IU/kg). Notably, 686 (81%) of the bleeding episodes were controlled with a single injection of Afstyla, and 107 (13%) required two injections. Only 55 (6%) episodes necessitated three or more injections. The hemostatic efficacy rating for 94% of the bleeding episodes was categorized as either excellent or good. In the adult/adolescent study evaluating Afstyla, prophylactic regimens were individualized based on the subjects' previous Factor VIII treatment history and their bleeding phenotype. Among the 146 subjects on prophylaxis, 54% received Afstyla three times a week, 32% received it twice a week, 6% were on an every-other-day regimen, and 8% followed other dosing schedules. The annualized bleeding rate (ABR) was similar between subjects on the three times weekly regimen (median ABR of 1.53) and those on the twice weekly regimen (median ABR of 0.00). Likewise, the annualized spontaneous bleeding rate (AsBR) was

comparable, with both regimens showing a median AsBR of 0.0. The proportion of subjects requiring dose adjustments was also similar between the two regimens, with 34.2% (27 subjects) in the three times weekly group and 27.7% (13 subjects) in the twice weekly group. For those on the three times weekly regimen, the median prescribed dose was 30 IU/kg (ranging from 12 to 50 IU/kg). In contrast, the median prescribed dose for the twice weekly regimen was slightly higher at 35 IU/kg (ranging from 17 to 50 IU/kg). When comparing prophylaxis to on-demand treatment, the ABR during prophylaxis (median of 1.14) was significantly lower ($p < 0.0001$) than the ABR observed with on-demand treatment (median of 19.64). Notably, 63 of the 146 subjects (43%) experienced no bleeding episodes while on prophylaxis. There were no reports of severe or life-threatening bleeds, such as intracranial hemorrhage, among subjects receiving prophylactic treatment with Afstyla. In the adult/adolescent study of Afstyla, a total of 13 subjects underwent 16 surgical procedures. Hemostatic efficacy was evaluated by investigators for these procedures, with 15 out of 16 surgeries rated as excellent and 1 rated as good. This high level of efficacy indicates that Afstyla effectively managed bleeding during the perioperative period. The median factor consumption for managing bleeding pre- and intra-operatively was 89.4 IU/kg, with a range from 40.5 to 108.6 IU/kg. This suggests that the dosing of Afstyla was adequate for maintaining hemostasis during surgical interventions.

The safety and efficacy of Kovaltry were assessed across three major international clinical studies focusing on on-demand treatment, perioperative management of bleeding, and routine prophylaxis in patients with severe hemophilia A (Factor VIII activity <1%). All studies included immunocompetent subjects with severe hemophilia A and no history of Factor VIII inhibitors. Trial 1: This multi-center, open-label, cross-over, uncontrolled study involved adolescent, and adult previously treated patients (PTPs) aged 12 to 65 years with at least 150 exposure days (EDs). It evaluated the pharmacokinetics, efficacy, and safety of Kovaltry for routine prophylaxis and perioperative management of bleeding. The prophylactic regimen consisted of 20 to 50 IU/kg administered two or three times per week, with dosing frequency determined by the investigator based on individual patient needs. The primary efficacy variable was the annualized bleeding rate (ABR). Trial 2: This multi-center, open-label, cross-over, uncontrolled randomized study also involved adolescent and adult PTPs (ages 12 to 65 years) with at least 150 EDs. It aimed to demonstrate the superiority of prophylaxis over on-demand treatment with Kovaltry over a one-year period. Prophylaxis regimens were either 20 to 30 IU/kg administered twice per week or 30 to 40 IU/kg administered three times per week. Randomization determined treatment groups, and the primary efficacy measure was the ABR. Trial 3: This multi-center, open-label, uncontrolled study was conducted in two parts. Part A focused on previously treated patients (PTPs) aged 12 years or younger with at least 50 EDs. Part B included previously untreated patients (PUPs) and minimally treated patients (MTPs) under 6 years of age with three or fewer EDs. The study evaluated the pharmacokinetics, efficacy, and safety of Kovaltry for routine prophylaxis and perioperative management of bleeding. The primary efficacy endpoint in Part A was the annualized number of total bleeds during prophylaxis occurring within 48 hours after the previous prophylaxis infusion, with additional analysis of ABR during prophylaxis independent of infusion timing. Prophylactic regimens in Part A ranged from 25 to 50 IU/kg administered two to three times per week or every other day, as adapted by the investigator based on patient needs. Across all studies, treatment of breakthrough bleeds and perioperative management were administered at the investigator's discretion, following standard care protocols.

In four multi-center, open-label, non-controlled trials evaluating Novoeight, a total of 3,153 bleeding episodes in 260 subjects were treated. The majority of these bleeds (90%) were classified as mild to moderate in severity, with 54% being spontaneous and 67% localized in joints. An efficacy assessment was conducted for 3,153 of these bleeds, using a four-point scale: excellent, good, moderate, or none. The hemostatic response was rated as "excellent" or

"good" for 2,809 bleeds (89%), indicating a successful treatment outcome. Conversely, 274 bleeds (9%) were rated as moderate, 25 bleeds (0.8%) had no response, and the response was unknown for 45 bleeds (1%). A significant majority (89%) of the bleeding episodes were resolved with one or two injections of Novoeight. In the subset of 238 previously treated patients (PTPs) who experienced 2,793 bleeds, 2,492 bleeds (89%) were rated as having an excellent or good response to Novoeight. Of these bleeds, 2,504 (90%) were resolved with one or two injections. The remaining cases showed similar patterns with the majority being of mild/moderate severity. For the 59 previously untreated patients (PUPs) who experienced 360 bleeds, 317 (88%) were rated as excellent or good. Of these bleeds, 290 (81%) were managed with one or two injections of Novoeight. The bleeds in PUPs were predominantly mild/moderate, with subcutaneous bleeds being the most frequent. In the routine prophylaxis trials, 150 adult/adolescent subjects and 63 pediatric subjects received Novoeight. The adult/adolescent trial lasted 6 months, and the pediatric trial lasted 4 months. These subjects were treated with Novoeight every other day or three times weekly, based on the dose levels specified. An extension trial of up to 6 years included 188 of these subjects, along with 18 additional subjects from an on-demand sub-trial and a pharmacokinetic trial. In the trial involving previously untreated patients, 56 subjects under the age of 6 received Novoeight for routine prophylaxis. The median annualized bleeding rate (ABR) for these patients was 2.9 (interquartile range [IQR] 5.4), with a mean ABR of 4.4 (95% confidence interval [CI]: 3.3 to 5.8). A total of 30 surgeries were performed in 25 previously treated subjects aged 8 to 58 years. Among these, 26 were major surgeries (including 20 orthopedic, 5 non-orthopedic, and 1 circumcision), and 4 were minor (including 2 dental procedures, 1 circumcision, and 1 port-a-cath insertion). The quality of hemostasis during and after surgery was rated as "excellent" or "good" in all cases by the investigator.
The efficacy of Nuwiq for on-demand treatment and control of bleeding episodes was evaluated in a total of 1,124 bleeding episodes across 69 subjects, including 35 adults, 2 adolescents, and 32 children. Treatment responses were assessed using a four-point ordinal scale: excellent, good, moderate, or none. In the study focused exclusively on on-demand treatment, which accounted for 986 of the treated episodes, 65% of the bleeding episodes were spontaneous, 35% were traumatic, and 0.3% were due to other causes. The mean dose per injection used to treat these bleeding episodes was 32 IU/kg. Hemostatic efficacy was rated as excellent or good for 94% of the bleeding episodes, while 6% were rated as moderate. For breakthrough bleeding episodes experienced during routine prophylaxis, the mean dose per injection was 33.3 IU/kg for adults (15 patients with 30 bleeding episodes) and 45 IU/kg for pediatric patients (32 patients with 108 bleeding episodes). The median number of injections required to treat a bleeding episode was 1. Efficacy was rated as excellent or good for 100% of the bleeding episodes in adults and 82% in pediatric patients. Nuwiq's efficacy in perioperative management was assessed across a total of 33 surgical procedures involving 19 patients. Among these, 20 procedures were classified as minor (performed in 7 patients) and 13 as major (performed in 12 patients). Pre-operative dosing of Nuwiq ranged from 35 IU/kg to 50 IU/kg per infusion. The number of infusions administered varied from 1 to 5 for minor surgeries and from 4 to 35 for major surgeries; one major surgery required an additional Nuwiq injection during the procedure. For major surgeries, efficacy was rated as excellent in 9 cases (69%), good in 3 cases (23%), and moderate in 1 case (8%). All minor surgeries were rated as having excellent efficacy.
During the original safety and efficacy study of Recombinate, none of the 69 subjects who were inhibitor-negative at the start of the study developed inhibitors. In a separate cohort of previously untreated patients (PUPs), 73 subjects with severe hemophilia A (Factor VIII levels ≤2%) were administered Recombinate. These patients received a median of 100 days of treatment (range 3 to 821 days) and were subsequently tested for inhibitor development. Among these 73 PUPs, 23 individuals (32%) developed a detectable inhibitor, with the median time to detection

being 10 days (range 3 to 69 days). Of these 23 individuals, 8 subjects (11%) had inhibitor titers greater than 10 Bethesda Units (B.U.).

Koate is a human plasma-derived antihemophilic factor indicated for the control and prevention of bleeding episodes or to perform emergency and elective surgery in patients with hemophilia A. The efficacy of Koate for treating bleeding episodes was evaluated through a two-stage clinical trial. Stage I: This was a randomized, single-blind, single-dose, crossover, and pharmacokinetic (PK) study. In this stage, 19 subjects were randomly assigned to receive a single dose of 50 IU/kg of either heated Koate or unheated Koate to compare their pharmacokinetic profiles. Stage II: This stage involved a 6-month open-label safety study conducted across two hemophilia centers. In this phase, 19 subjects were treated with Koate, focusing on both on-demand treatment and control of bleeding episodes. Common adverse events include hypersensitivity reactions, intravascular hemolysis and CJD.

Xyntha was assessed in five completed clinical studies involving a total of 178 subjects, which included four studies specifically focusing on adult and pediatric previously treated patients (PTPs). The safety and efficacy of Xyntha were examined in two pivotal studies. In the first study, which involved 94 subjects, Xyntha was evaluated for routine prophylaxis and on-demand treatment in PTPs with severe to moderately severe hemophilia A (with Factor VIII activity in plasma ≤2%). These subjects received a total of 6,775 infusions of Xyntha. The second study, involving 30 subjects, focused on surgical prophylaxis in PTPs who required elective major surgery and were expected to receive Xyntha replacement therapy for at least six days post-surgery. A total of 1,161 infusions were administered in this study, although one subject only received Xyntha for a pre-surgery pharmacokinetic assessment and did not undergo surgery. Among the 72 pediatric PTPs studied (comprising 46 subjects under 6 years of age, including 4 infants aged 0 to <2 years; 4 subjects aged 6 to <12 years; and 22 adolescents aged 12 to <17 years), a total of 13,109 infusions of Xyntha were administered, with a median dose of 28 IU/kg per infusion (ranging from 6 to 108 IU/kg). The most common adverse reactions in both adult and pediatric PTPs were headache (24%), arthralgia (23%), pyrexia (23%), and cough (12%). Other adverse reactions reported in at least 5% of subjects included diarrhea (8%), vomiting (8%), and asthenia (6%).

Obizur, Antihemophilic Factor (Recombinant), Porcine Sequence, is an antihemophilic factor indicated for the on-demand treatment and control of bleeding episodes in adults with acquired hemophilia A. In a study of Obizur for treating serious bleeding episodes in patients with acquired hemophilia A, all 28 evaluable subjects responded positively to treatment within 24 hours. Positive responses were observed in 95% at 8 hours and 100% at 16 hours. Overall, 86% of subjects experienced successful treatment, with 94% success among those receiving Obizur as first-line therapy. Among those who had prior anti-hemorrhagic treatments, 73% achieved success. The median dose per infusion for initial bleeding episodes was 133 units/kg, with a median of 3 infusions (200 units/kg each) in the first 24 hours. For extended treatment, a median of 10.5 infusions (100 units/kg each) were given over a median of 6 days.

The safety and efficacy of Esperoct were assessed in five multinational, open-label trials involving male subjects with severe hemophilia A. One of these trials included a partial randomization to compare two prophylaxis regimens. All participants were previously treated, having received Factor VIII products for ≥150 exposure days (adolescents and adults) or ≥50 exposure days (pediatric subjects). Key exclusions included known hypersensitivity to trial products and a history of Factor VIII inhibitors or current inhibitor levels ≥0.6 Bethesda units. In the adolescent/adult trial, 186 subjects (161 adults and 25 adolescents) participated. During the Main Phase, 175 subjects followed a prophylaxis regimen of 50 IU/kg every 4 days, while 12 adults were treated on-demand. Thirteen (7%) of the prophylaxis group adjusted their dosing to every 3-4 days for convenience. Of the participants, 165 (91%) completed the Main Phase.

The safety, efficacy, and pharmacokinetics of Altuviiio were assessed in two multicenter, open-label studies: one involving adults and adolescents ≥12 years of age, and the other in pediatric patients <12 years of age, both with severe hemophilia A. The adult and adolescent study included 159 participants (158 male, 1 female), aged 12 to 72 years, with 25 adolescents aged 12 to 17. All subjects received at least one dose of Altuviiiio, and 149 (93.7%) completed the study. The pediatric study enrolled 74 male participants <12 years of age (38 aged 1 to 5 years and 36 aged 6 to 11 years). All enrolled subjects received at least one dose, with 72 subjects evaluable for efficacy. Both studies evaluated routine prophylaxis with a weekly dose of 50 IU/kg, as well as the treatment of bleeding episodes and perioperative management in subjects undergoing major or minor surgeries.

VIII. Billing Code/Availability Information

HCPCS code & NDC:

Drug	Manufacturer	J-Code	1 Billable Unit Equiv.	Vial Size	NDC
Advate	Baxalta US Inc	J7192	1 IU	250 units	00944-3051-02
				500 units	00944-3052-02
				1000 units	00944-3053-02
				1500 units	00944-3054-02
				2000 units	00944-3045-10
				3000 units	00944-3046-10
				4000 units	0944-3047-10
Kogenate FS	Bayer HealthCare LLC	J7192	1 IU	250 units	00026-3782-25
				500 units	00026-3783-35
				1000 units	00026-3785-55
				2000 units	00026-3786-65
				3000 units	00026-3787-75
Recombinate	Baxalta US Inc	J7192	1 IU	220-400 units	00944-2841-10
				401-800 units	00944-2842-10
				801-1240 units	00944-2843-10
				1241-1800 units	00944-2844-10
				1801-2400 units	00944-2845-10
Kovaltry	Bayer HealthCare LLC	J7211	1 IU	250 units	00026-3821-25
				500 units	00026-3822-25
				1000 units	00026-3824-25
				2000 units	00026-3826-50
				3000 units	00026-3828-50
Eloctate	Bioverativ Therapeutics Inc	J7205	1 IU	250 units	71104-0801-01
				500 units	71104 -0802-01
				750 units	71104 -0803-01
				1000 units	71104 -0804-01
				1500 units	71104 -0805-01
				2000 units	71104 -0806-01
				3000 units	71104 -0807-01
				4000 units	71104 -0808-01

				5000 units	71104 -0809-01
				6000 units	71104 -0810-01
Koate/Koate-DVI	Grifols Therapeutics Inc	J7190	1 IU	250 units	76125-0250-20 76125-0253-25
				500 units	76125-0667-30 76125-0662-50
				1000 units	76125-0672-50 76125-0674-10
Hemofil M	Takeda Pharmaceuticals USA, Inc	J7190	1 IU	250 units	00944-3940-02
				500 units	00944-3942-02
				1700 units	00944-3946-02
				1000 units	00944-3944-02
Novoeight	Novo Nordisk, Inc.	J7182	1 IU	250 units	00169-7825-01
				500 units	00169-7850-01
				1000 units	00169-7810-01
				1500 units	00169-7815-01
				2000 units	00169-7820-01
				3000 units	00169-7830-01
Nuwiq	Octapharma AB	J7209	1 IU	250 units 68982-0140-01	68982-0140-01
				500 units	68982-0142-01
				1000 units	68982-0144-01
				2000 units	68982-0146-01
				2500 units	68982-0148-01
				3000 units	68982-0148-01
				4000 units	68982-0150-01
Obizur	Baxalta US Inc	J7188	1 IU	500 units	00944-5001-xx
Xyntha/Xyntha Solofuse	Wyeth Pharmeuticals LLC	J7185	1 IU	250 units	58394-0012-01/ 58394-0022-03
				500 units	58394-0013-01/ 58394-0023-03
				1000 units	58394-0014-01/ 58394-0024-03
				2000 units	58394-0015-01/ 58394-0025-03
				3000 units	58394-0016-03
Afstyla	CSL Behring, LLC	J7210	1 IU	250 units	69911-0474-02
				500 units	69911-0475-02
				1000 units	69911-0476-02
				1500 units	69911-0480-02
				2000 units	69911-0477-02
				2500 units	69911-0481-02
				3000 units	69911-0478-02
Adynovate	Baxalta US Inc	J7207	1 IU	250 units	00944-4622-01
				500 units	00944-4623-01
				750 units	00944-4626-01

				1000 units	00944-4624-01
				1500 units	00944-4627-01
				2000 units	00944-4625-01
				3000 units	00944-4628-01
Jivi	Bayer	J7208	1 IU	500 units	00026-3942-25
				1000 units	00026-3944-25
				2000 units	00026-3946-25
				3000 units	00026-3948-25
Esperoct	Novo Nordisk	J7204)	1 IU	500 units	00169-8500-01
				1000 units	00169-8100-01
				1500 units	00169-8150-01
				2000 units	00169-8200-01
				3000 units	00169-8300-01
Altuviiio	Bioverativ Therapeutics Inc.	J7214	N/A	250 units	71104-0978-01
				500 units	71104-0979-01
				750 units	71104-0980-01
				1000 units	71104-0981-01
				2000 units	71104-0982-01
				3000 units	71104-0983-01
				4000 units	71104-0984-01

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Appendix 1 – Covered Diagnosis Codes

Obizur

ICD-10	ICD-10 Description
D68.311	Acquired hemophilia

Advate, Eloctate, Esperoct, Hemofil M, Koate-DVI, Kogenate FS, Recombinate, Xyntha/ Xyntha Solofuse, Novoeight. NUWIQ, Adynovate, Kovaltry, Afstyla, and Jivi

ICD-10	ICD-10 Description
D66	Hereditary factor VIII deficiency

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following

link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes		
Jurisdiction	**NCD/LCA/LCD Document (s)**	**Contractor**
N	A56482	First Coast Service Options, Inc.
J, M	A56065	Palmetto GBA
H, L	A56433	Novitas Solutions, Inc.

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Policy Rationale: Advate, Adynovate, Afstyla, Eloctate, Hemofil M, Koate/Koate DVI, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, Xyntha/Xyntha Solofuse, Jivi, Esperoct, and Altuviiio were reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Advate, Adynovate, Afstyla, Eloctate, Hemofil M, Koate/Koate DVI, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, Xyntha/Xyntha Solofuse, Jivi, Esperoct, or Altuviiio to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature.

Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For INTEGRITY (Medicare-Medicaid Plan) members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.