Qfitlia™
(fitusiran)

Date of Origin: 05/11/2025 **Last Review Date: 02/11/2026** **Effective Date: 05/11/2025**

Dates Reviewed: 05/11/2025; 02/25/2026

Developed By: Medical Criteria Committee

I. Length of Authorization

A. Authorization is valid for 12 months and may be renewed.

II. Dosing Limits

A. Max Units (per dose and over time) [Medical Benefit]:
- 1,250 billable units every month

III. Initial Evaluation

A. **Fitusiran (Qfitlia)** may be considered medically necessary when the following criteria are met:
   a. Member is 12 years of age or older; **AND**
   b. Medication is prescribed by, or in consultation with, a hematologist; **AND**
   c. Medication will not be used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
   d. Fitusiran (Qfitlia) will be used as routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
   e. A diagnosis of one of the following:
      i. **Hemophilia A with inhibitors**; **AND**
         1. Clinical documentation confirming of a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units)]; **AND**
         2. Member has had two or more documented episodes of spontaneous bleeding; **AND**
         3. Clinical documentation of intolerance or contraindication to emicizumab-kxwh (Hemlibra); **OR**
      ii. **Hemophilia A without inhibitors**; **AND**
         1. Clinical documentation confirming that the member does not have a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units); **AND**
         2. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
            a. Member has had two or more documented episodes of spontaneous bleeding; **AND**
         3. Clinical documentation that prior prophylaxis with factor VIII (e.g., Advate, Eloctate, Nuwiq, etc.) was ineffective for prevention of bleeding episodes; **AND**
         4. Clinical documentation of intolerance or contraindication to emicizumab-kxwh (Hemlibra); **OR**
      iii. **Hemophilia B with inhibitors; AND**
         1. Clinical documentation confirming of a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units)]; **AND**
         2. Member has had two or more documented episodes of spontaneous bleeding; **OR**

a. Member has had an inadequate response to Immune Tolerance Induction (ITI); **OR**

iv. **Hemophilia B without inhibitors; AND**

1. Clinical documentation confirming that the member does not have a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units); **AND**
2. Member has moderate to severe hemophilia B (defined as factor IX level of less than or equal to 5%); **OR**
   a. Member has had two or more documented episode of spontaneous bleeding; **AND**
3. Clinical documentation that prior prophylaxis with factor IX (e.g., BeneFIX, Idelvion, etc.) was ineffective for the prevention of bleeding episodes

B. Fitusiran (Brand) is considered investigational when used for all other conditions, including but not limited to:
   a. Fitusiran (Qfitlia) used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
   b. Pediatric patients <12 years of age with hemophilia A or B
   c. Von Willebrand disease

IV. Renewal Evaluation

A. Member has exhibited improvement or stability of disease symptoms (e.g., decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline); **AND**
B. Medication will not be used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
C. Documentation of antithrombin (AT) lab value within the past three months; **AND**
   i. If member has been established on a dose of 10mg administered once every two months, most recent antithrombin (AT) is above 15%

V. Supporting Evidence

A. Fitusiran (Qfitlia) is a novel synthetic small interfering RNA (siRNA) FDA-approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent (≥12 years old) patients with hemophilia A or B with or without inhibitors. Fitusiran (Qfitlia) is a subcutaneous injection dosed monthly or every other month. Fitusiran (Qfitlia) targets the production of antithrombin (AT) which serves as up to 80% of the inhibitory component to thrombin formation. When antithrombin levels are reduced, the clotting cascade can continue to function leading to hemostasis.
B. The efficacy and safety of fitusiran (Qfitlia) has not been studied in a pediatric population less than 12 years of age. Current FDA approval is limited to those 12 years of age and older.
C. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX) are X-linked inherited coagulation factor deficiencies that result in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A and B. The severity of an individual's hemophilia is determined by the amount of clotting factor present. Plasma levels of FVIII or FIX < 40% are indicative of hemophilia; however, hemophilia A and B are classified moderate when factor levels are 1% to < 5%, and severe when factor levels are < 1%. Joint bleeds are the most frequent bleeding experienced by people with hemophilia of all severities (70-80%) which can lead to deformity, arthropathy, and irreversible joint damage leading to decreased mobility. Given the

complexities of diagnosis and treatment of hemophilia A and B, supervision of treatment by a hematologist is required.

D. Typical hemophilia therapies include factor replacement with clotting factor concentrates (CFCs). For some patients treated with CFCs, neutralizing antibodies (i.e., inhibitors) develop in response to repeated exposure to exogenous factor products. Inhibitors are most commonly developed in patients with severe hemophilia A (30%). Incidence of inhibitor development in mild and moderate hemophilia A and hemophilia B populations are lower at 5% and 3% respectively. Inhibitors can significantly increase the cost of care and make bleeding episodes more difficult to treat as high doses of CFCs or bypassing agents are needed to circumvent inhibitors.
E. The World Federation of Hemophilia (WFH) guidelines recommend use of agents for both bleeding prophylaxis and control of acute breakthrough bleeds. Therapy recommendations are not sequential but rather cite the need for individualized care considering a patient's bleeding phenotype, joint status, pharmacokinetic profile, and preference. Medications include factor replacement with clotting factor concentrates (CFCs) (i.e., standard half-life (SHLs) for FVIII for hemophilia A and FIX for hemophilia B), long-acting CFCs (i.e., extended half-life (EHLs)), non-factor, and gene therapies. The frequency of injections varies but overall injection burden is high. The WFH split treatment recommendations for hemophilia A with inhibitors (HAwI) and hemophilia B with inhibitors (HBwI) based on whether the inhibitor is low-responding or high-responding. The WFH recommends FVIII concentrate for hemophilia A patients with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate) for those with high-responding inhibitors. Hemophilia B patients with low-responding FIX inhibitors, use of a FIX-containing product to treat acute bleeds is recommended. Whereas for those with high-responding FIX inhibitors, rFVIIa is preferred. Additionally, HAwI and HBwI patients may undergo immune tolerance induction (ITI) to eradicate the inhibitor and, thus, allow the patient to return to ordinary CFC replacement therapies. The basic approach used by ITI is to give large doses of FVIII for FIX, often daily, for months or years. The relative success rate of ITI can be low and is only guideline recommended for HAwI though it can be used in HBwI. For patients with hemophilia A who develop persistent low responding inhibitors, the WFH suggests that immune tolerance induction ITI be considered. Guidelines have not been updated to include fitusiran (Qfitlia).
F. There are varying severities of hemophilia A and B depending on the level of factor produced by the patient, these are divided into the following per the International Society on Thrombosis and Hemostasis (ISTH):
    a. Severe: <1% factor activity (<0.01 IU/mL)
    b. Moderate: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
    c. Mild: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)
E. There is a lack of strong scientific evidence from randomized controlled trials supporting the efficacy and safety of multiple agents for routine prophylaxis used in combination. Therefore, use of fitusiran (Qfitlia) in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.] is not allowable per policy. There is a lack of head-to-head trials showing superior safety or efficacy comparing fitusiran (Qfitlia) to other prophylactic agents for the treatment of hemophilia A or B. Given the known safety, established efficacy, and cost-effectiveness of these therapies, prior prophylaxis with emicizumab-kxwh (Hemlibra) remains the preferred specialty agents by this plan due to efficacy, safety, and cost. Fitusiran (Qfitlia) is specifically more costly than other agents, despite not having any evidence of improved clinical efficacy or safety.
F. Fitusiran (Qfitlia) was studied in three Phase 3 trials under the ATLAS clinical trial program (ATLAS-INH, ATLAS-A/B, and ATLAS-PPX) with a dose of 80mg administered monthly. After the completion

of these parent studies, patients were rolled over into the long-term extension study (ATLAS-OLE) whose revised AT-based dosing regimen (AT-DR) (50mg Q2M) is to inform the labeled indication. ATLAS-OLE consisted of 227 PwHA/B with and without inhibitors. Participants averaged 30.7 years of age (range 13-72), hemophilia A (76.7%), hemophilia B (23.3%) and 12% were from North America. The primary efficacy outcome was long-term safety and efficacy as measured by an estimated mean ABR. An integrated analysis was completed to compare the fitusiran (Qfitlia) revised AT-DR as compared to comparative therapy arms in the parent trials.

G. Results of ATLAS-OLE showed fitusiran (Qfitlia) was able to significantly reduce the estimated ABR as compared to bypassing agents (BPA) on-demand, CFC on-demand, and BPA prophylaxis therapies. When compared to CFC prophylaxis however, fitusiran (Qfitlia) was non-inferior to CFC prophylaxis (p=0.61). The observed median ABR (IQR) among all patients within the ATLAS-OLE primary efficacy period was 3.7 (0.0 to 7.5), 1.9 (0.0 to 5.6) in patients with inhibitors, and 3.8 (0.0 to 11.2) in patients without inhibitors. Lastly, 31.5% of patients were able to achieve zero bleeds while 47.2% were able to achieve one bleed event or less on prophylaxis therapy with fitusiran (Qfitlia). A total of 78% participants were maintained on Q2M regimens, of which 38% required zero dose adjustments and 56% required one dose adjustment to achieve AT 15–35%.
H. Secondary endpoints, including those measuring patient reported outcomes, were not assessed as a part of the ATLAS-OLE trial. Data from the parent trials demonstrated reductions in the Haem-A-QoL transformed total and physical scores though results meeting minimal clinically important differences were mixed. There are remaining limitations and unknowns specifically in regard to the small sample size of the trial, open-label trial design, lack of long term safety data with the AT-DR, lack of statistically significant QoL measures in certain treatment populations (Fitusiran versus prophylaxis (BPA/CFC) for the treatment of hemophilia A or B) and lack of comparative efficacy data to other hemophilia products of special interest (Hemlibra). Given the combination of data and reduction in mean ABR across trial populations the level of evidence is considered moderate.
I. Fitusiran (Qfitlia) was not directly compared with prophylaxis with emicizumab-kxwh (Hemlibra) therapy for the treatment of hemophilia A. Balancing long-term safety data, efficacy, and costs of alternative therapies compared to fitusiran (Qfitlia), treatment with emicizumab-kxwh (Hemlibra), when applicable, is required.
J. When antithrombin levels are reduced, the clotting cascade can continue to function leading to hemostasis. It is hypothesized that an antithrombin level of less than 25% may lead to a desirable reduction in annualized bleed rate. The mechanism of fitusiran (Qfitlia) blocks the production of antithrombin to rebalance hemostasis. In clinical trials vascular thrombotic events did occur in five individuals. Individuals with thrombotic events had lower levels of AT (<10%). Therefore, under amended protocol for ATDR it's recommended to discontinue fitusiran (Qfitlia) if AT is measured at <15% on two repeated measurements.
K. Per the FDA label, AT activity is to be measured using an FDA-cleared test at Weeks 4 (Month 1), 12 (Month 3), 20 (Month 5), and 24 (Month 6) following the starting dose and after any dose modification. If any AT activity is 35% after 6 months, or if the patient has not achieved satisfactory bleed control, dose escalation should be considered. AT measurements should be restarted after a dose escalation.

Investigational or Not Medically Necessary Uses

I. Fitusiran (Qfitlia) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:

A. Fitusiran (Qfitlia) used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
B. Pediatric patients <12 years of age with hemophilia A or B
C. Von Willebrand disease

VI. Dosage/Administration

Indication	Dose
Routine Prophylaxis in Congenital Hemophilia A or Hemophilia B	The starting dose is 50 mg once subcutaneously every two months. Adjust the dose and/or dosing interval, if needed, to maintain AT activity between 15-35%. Measure AT activity using an FDA-cleared test at Weeks 4 (Month 1), 12 (Month 3), 20 (Month 5) and 24 (Month 6) following the starting dose and after any dose modification. If any AT activity is <15%, a dose reduction is required. The lower dose should be initiated 3 months after the prior dose. AT measurements should be restarted after a dose reduction. If AT activity is >35% after 6 months, or if the patient has not achieved satisfactory bleed control, dose escalation to 50 mg monthly should be considered. AT measurements should be restarted after a dose escalation.
1 unit = 0.04 mg	

Dose Modification Based on Antithrombin Activity Levels

Last Dosage Administered	Antithrombin Activity Level	Dose Modification	Quantity Limit
50mg every 2 months	Less than 15%	20mg every 2 months	0.2mL/56 days
	15% to 35%	Continue current dosage	0.5mL/56 days
	Greater than 35% after 6 months	50mg every month	0.5mL/28 days
20mg every 2 months	Less than 15%	10mg every 2 months	0.2mL/56 days
	15% to 35%	Continue current dosage	0.2mL/56 days
	Greater than 35% after 6 months	20mg every month	0.2mL/28 days
10mg every 2 months	Less than 15%	Discontinue fitusiran (Qfitlia)	N/A
	15% to 35%	Continue current dosage	0.2mL/56 days
	Greater than 35% after 6 months	10mg every month	0.2mL/28 days

VII. Billing Code/Availability Information

- Jcode:
  - J7174 – injection, Qfitlia, fitusiran, 0.04mg; 1 billable unit = 0.4 mg

- NDC:
  - Qfitlia, fitusiran 50mg/0.5 mL prefilled pen: 58468-0348-1
  - Qfitlia, fitusiran 20mg/0.2 mL single dose vial: 58468-0347-1

VII. References

1. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Hemophilia. 2020: 26(Suppl 6): 1-158.
2. Young G, Srivastava A, Kavakli K, Ross C, Sathar J, You CW, Tran H, Sun J, Wu R, Poloskey S, Qiu Z, Kichou S, Andersson S, Mei B, Rangarajan S. Efficacy and safety of fitusiran prophylaxis in people with hemophilia A or hemophilia B with inhibitors (ATLAS-INH): a multicentre, open-label, randomised phase 3 trial. Lancet. 2023 Apr 29;401(10386):1427-1437.
3. Kenet G, Nolan B, Zulfikar B, Antmen B, Kampmann P, Matsushita T, You CW, Vilchevska K, Bagot CN, Sharif A, Peyvandi F, Young G, Negrier C, Chi J, Kittner B, Sussebach C, Shammas F, Mei B, Andersson S, Kavakli K. Fitusiran prophylaxis in people with hemophilia A or B who switched from prior BPA/CFC prophylaxis: the ATLAS-PPX trial. Blood. 2024 May 30;143(22):2256-2269.
4. Srivastava A, Rangarajan S, Kavakli K, Klamroth R, Kenet G, Khoo L, You CW, Xu W, Malan N, Frenzel L, Bagot CN, Stasyshyn O, Chang CY, Poloskey S, Qiu Z, Andersson S, Mei B, Pipe SW. Fitusiran prophylaxis in people with severe hemophilia A or hemophilia B without inhibitors (ATLAS-A/B): a multicentre, open-label, randomised, phase 3 trial. Lancet Haematol. 2023 May;10(5):e322-e332.
5. Fitusiran unapproved product dossier. Sanofi. March 18, 2024.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D66	Hemophilia A (congenital factor VIII deficiency) with or without FVIII inhibitors
D67	Hemophilia B (congenital factor IX deficiency) with or without FIX inhibitors