Iowa PDL New Drug Review

Proprietary Name: Qfitlia®
Common Name: fitusiran injection, solution
PDL Category: Antihemophilic Agents

Pharmacology/Usage: Fitusiran, the active ingredient of Qfitlia®, is an antithrombin-directed double-stranded small interfering ribonucleic acid (siRNA), which is covalently linked to a ligand containing a triantennary N-acetyl galactosamine (GalNAc) moiety. It causes degradation of antithrombin (AT) messenger RNA (mRNA) through RNA interference, reducing plasma AT levels.

Indication: For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. It is not known if Qfitlia® can cause fetal harm when given to a pregnant woman or can affect reproduction capacity. Qfitlia® should be used during pregnancy only if the potential benefit justifies the potential risks, including those to the fetus. The safety and efficacy of use in the pediatric population below 12 years of age have not been established.

Dosage Form: Preservative-free solution in a single-dose for Injection:

- 50mg/0.5ml prefilled pen.
- 20mg/0.2ml vial.

If stored at room temperature, it is ready for use. If stored in the refrigerator, remove from the refrigerator and allow to reach room temperature for at least 30 minutes.

Recommended Dosage: For subcutaneous (SC) use only. Use is recommended under the supervision of a healthcare professional experienced in the treatment of hemophilia or bleeding disorders. Provide proper training to patients and/or caregivers on the preparation and administration of Qfitlia® prior to use. A patient may self-inject or the patient's caregiver may administer Qfitlia®. In pediatric patients 12 to 17 years of age, it is recommended that Qfitlia® be administered by or under the supervision of an adult. For injection into the thigh or abdomen, except for the 2 inches around the navel. A caregiver can also inject in the outer area of the patients upper arm.

Monitor antithrombin (AT) activity using an FDA-cleared test. Information on FDA-cleared tests for AT activity is available at http://www.fda.gov/CompanionDiagnositics. Measure AT activity prior to the start of Qfitlia®. Do not start Qfitlia® dosing if AT activity is <60%. After Qfitlia® is initiated, patients may continue their prior clotting factor concentrates (CFC) or bypassing agent (BPA) prophylaxis for the first 7 days of treatment. Discontinue CFC or BPA prophylaxis no later than 7 days after the initial dose of Qfitlia®.

The starting dose of Qfitlia® is 50mg once SC every 2 months. Adjust the dose and/or dosing interval, if needed, to maintain AT activity between 15-35%.

Regarding dosage modification, 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 should be considered. AT measurements should be restarted after a dose escalation.
- Refer to the prescribing information for additional information on dosage modification based on AT activity levels.

Once the patients target dose is identified based on AT activity 15-35%, measure AT activity annually. Additional AT measurements can be considered if bleeding control is not adequate.

After cessation of Qfitlia® dosing, routine AT monitoring is not needed unless the patient is bleeding and treatment with CFC/BPA is required. Based on data from the clinical studies, a majority of patients have AT activity >60% by 6 months after the last Qfitlia® dose, after which standard doses of CFC/BPA may be used.

Regarding breakthrough bleed management, if breakthrough bleeding requiring on-demand treatment with CFC or BPA occurs during the first 7 days after Qfitlia® initiation, manage the bleed using the patient's prior dosing regimen of CFC or BPA. If breakthrough bleeding occurs after 7 days from the first Qfitlia® dose, bleeds should be managed with a reduced dose and frequency of CFC/BPA to minimize the risk of thrombotic events. Initially, the weight-based dose of CFC/BPA should be reduced, and the dosing interval doubled compared to the standard dose. Refer to the prescribing information for reduced dosing information. If adequate hemostatic control is not achieved, higher doses may be used based on clinical judgement. Combination use of antifibrinolytics with CFC or BPA has not been studied.

In clinical studies, patients with hemophilia A or B with or without inhibitors have undergone both major (N=60) and minor (N=71) surgical procedures without discontinuing Qfitlia® prophylaxis. Utilize bleed management guidelines during the perioperative period for hemostatic management.

Serum transaminase elevations have been observed in the clinical studies. Avoid use of Qfitlia® in patients with established hepatic impairment.

Drug Interactions: Qfitlia® prophylaxis leads to increased thrombin generation with additive increase in peak thrombin when used concomitantly with clotting factor concentrates (CFC) or bypassing agents (BPAs).

Use of Qfitlia® in women using hormonal contraceptives may increase the risk of thrombotic events. Estrogen based hormonal contraceptives are an established risk factor for thrombosis in women with inherited AT deficiency. Advise patients using hormonal contraceptives to use an alternative non-hormonal contraception prior to starting treatment with and while receiving Qfitlia®.

Box Warning: Qfitlia® has a box warning regarding thrombotic events and acute and recurrent gallbladder disease.

- Thrombotic Events:
    - Serious thrombotic events have occurred in Qfitlia®-treated patients with risk factors for thromboembolism including persistent antithrombin (AT) activity less than 15%, use of Qfitlia® 80mg once monthly, presence of indwelling venous catheters, and in the post-operative setting when bleed management guidelines were not followed.
    - Monitor AT activity using an FDA-cleared test and target AT activity 15-35% to reduce the risk of thrombosis. Monitor patients for signs and symptoms of thrombotic events. Interrupt Qfitlia® in patients with a thrombotic event and manage as clinically indicated.
- Acute and Recurrent Gallbladder Disease:
    - Acute and recurrent gallbladder disease, including cholelithiasis and cholecystitis have occurred in Qfitlia®-treated patients, some of whom required cholecystectomy or had complications (e.g., pancreatitis) related to gallbladder disease. Monitor patients for signs and symptoms of acute and recurrent gallbladder disease.
    - Consider interruption or discontinuation of Qfitlia® if gallbladder disease occurs. Consider alternative treatment for hemophilia in patients with a history of symptomatic gallbladder disease.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Qfitlia®). There was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included viral infection (29%), nasopharyngitis (26%), bacterial infection (11%), hepatic injury (8%), arthralgia (8%), prothrombin fragment 1.2 increased (7%), injection site reaction (6%), headache (5%), and cough (5%).

Serious thrombotic events have been reported in Qfitlia®-treated patients. Participants with established thrombophilia or a history of thrombosis were generally excluded from studies with Qfitlia®. The risk of thrombosis is greater in patients with persistent AT activity <15%, with comorbidities that predispose to thrombosis, when bleeding management guidelines are not followed in the post-operative setting, when there is an indwelling venous catheter, and with the use of 80mg once monthly dose. Monitor AT activity using an FDA-cleared test and target AT activity 15-35% to reduce the risk of thrombosis. Monitor patients for signs and symptoms of thrombotic events. Interrupt Qfitlia® prophylaxis in patients with a thrombotic event and manage as clinically indicated. Inform patients to monitor for and report signs and symptoms of thrombotic events. Consider the benefits and risks of resuming Qfitlia® prophylaxis following resolution of the thrombotic event.

Treatment with Qfitlia® is associated with an increased occurrence of acute and recurrent gallbladder disease, including cholelithiasis and cholecystitis. If gallbladder disease is suspected, appropriate imaging and clinical follow-up are indicated. Consider alternative treatment for hemophilia in patients with a history of symptomatic gallbladder disease. Consider interruption or discontinuation of Qfitlia® if gallbladder disease occurs.

In two randomized studies testing Qfitlia® 80mg QM, serum alanine transaminase (ALT) and aspartate transaminase (AST) elevations above 3 times the upper limit of normal (ULN) occurred in 32% of patients with hemophilia with inhibitors and 18% of patients with hemophilia without inhibitors compared to no events of AST or ALT elevation greater than 3 times the ULN in the control groups. Qfitlia® 80mg QM is not approved or recommended for use. Avoid use of Qfitlia® in patients with hepatic impairment. Obtain baseline liver tests, including AST, ALT, and total bilirubin prior to starting treatment, monthly for at least the first 6 months of Qfitlia® use, monthly for at least 6 months after a dose increase, and periodically thereafter as clinically indicated. Refer to the prescribing information for additional information.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Genzyme Corporation

Analysis: The efficacy and safety of Qfitlia® in adult and pediatric patients 12 years of age and older with hemophilia A or B with or without inhibitors were established in two clinical studies:

- Hemophilia A or B with Inhibitory Antibodies: ATLAS-INH.
- Hemophilia A or B without Inhibitory Antibodies: ATLAS-A/B.
- Patients in the above parent studies rolled over into the long-term extension study: ATLAS-OLE.

The two clinical studies (ATLAS-INH and A/B) tested an 80mg monthly fixed dose of Qfitlia®. Because of thrombotic events with this dose, the Qfitlia® AT-DR targeting AT activity of 15-35% was implemented in ATLAS-OLE. The AT-DR was started when studies ATLAS-INH and ATLAS-A/B were almost completed; thus, the efficacy of Qfitlia® AT-DR treatment was assessed by comparing the Qfitlia® AT-DR treatment data from the long-term extension study ATLAS-OLE to the control data from studies ATLAS-INH and ATLAS-A/B.

ATLAS-INH was a randomized, multicenter, open-label study that included adult and pediatric males aged ≥12 years (N=57) with hemophilia A or B with inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX), who previously received on-demand (episodic) treatment with BPAs for bleeding. Patients eligible were randomized to receive Qfitlia® prophylaxis at a fixed dose 80mg SC QM (N=38) or BPA on demand for treatment of breakthrough bleeding episodes (N=19) for 9 months. Note that the 80mg dose is not approved because of an increased risk of serious thrombotic events, gallbladder events, and hepatotoxicity. Of the 57 enrolled, all had inhibitors, 45 patients had Hemophilia A, 12 had hemophilia B, all were male, the mean age of patient was 28.4 years, and 10 (17.5%) were between 12-17 years of age. In addition, 68.4% were Asian.

ATLAS A/B was a randomized, multicenter, open-label study that included adult and pediatric males aged ≥12 years (N=120) with hemophilia A or B without inhibitory antibodies to FVIII or FIX, who previously received on-demand (episodic) treatment with CFC for bleeding. Patients eligible were randomized to receive Qfitlia® 80mg SC QM (N=80) or CFCs on-demand to treat breakthrough bleeding episodes (N=40) for 9 months. Note the 80mg dose of Qfitlia® is not approved because of an increased risk of serious thrombotic events, gallbladder events, and hepatotoxicity. Of the 120 enrolled, none had inhibitors, 93 patients had hemophilia A, 27 had hemophilia B, all were male, the mean age of patients was 33. 8 years and 14 patients (11.7%) were 12-17 years of age. In addition, 59.2% were Asian.

ATLAS-OLE enrolled 227 patients from the two clinical studies discussed above and from ATLAS-PPX (a crossover study in patients previously on CFC or BPA prophylaxis) and were treated with Qfitlia® in ATLAS-OLE. This multicenter, open-label extension study assessed the long-term safety and efficacy of Qfitlia® in adult and pediatric males aged ≥12 years with hemophilia A or B, with or without inhibitory antibodies to FVIII or FIX. Eligible patients initially received Qfitlia® 80mg SC QM. The study was amended to assess the safety and efficacy of the AT-DR. A total of 213 patients were subsequently transitioned to AT-DR targeting AT activity of 15-35%.

In the AT-DR, the Qfitlia® starting dose was 50mg Q2M, and dosing was individually adjusted based on AT activity level using the INNOVANCE antithrombin assay. The dose could be increased to 50mg QM or 80mg QM or decreased to 20mg Q2M or 20mg QM. Qfitlia® was discontinued if AT activity was <15% at the lowest dose. No patients required escalation to 80mg QM to achieve the target AT range. The dose required to maintain AT activity 15-35% in patients who initiated dosing on 50mg Q2M was: 50mg Q2M (35.8% of patients), 50mg QM (15.7% of patients), 20mg Q2M (30.9% of patients), or 20mg QM (2.9% of patients). A total of 14.7% of patients discontinued Qfitlia® due to more than one AT activity <15%

The efficacy of Qfitlia® AT-DR in ATLAS-OLE was assessed for a duration of 7 months (primary efficacy period) following a 6-month dose adjustment period. The median observed annualized bleeding rate for treated bleeds was 3.7 overall, 1.9 in inhibitor patients and 3.8 in non-inhibitor patients.

The efficacy results of Qfitlia® prophylaxis using AT-DR in ATLAS-OLE compared to on-demand BPA or CFC control data from studies ATLAS-INH and ATLAS-A/B with respect to rate of treated bleeds, treated spontaneous bleeds, and treated joint bleeds are presented in the table below, which was adapted from the prescribing information. The first table includes patients with inhibitors while the second table includes patients without inhibitors.

Endpoint in patients with inhibitors	Qfitlia® AT-DR (N=38)	On-Demand BPA (N=19)
All Treated Bleeds		
Annualized Bleed Rate (ABR)	5.1	19.1
% reduction; p-value	73%; p=0.0006	
Treated Spontaneous Bleeds		
ABR	3.1	17.1
% reduction; p-value	82%; p<0.0001	
Treated Joint Bleeds		
ABR	4.0	14.4
% reduction; p-value	73%; p=0.0001	

Endpoint in patients without inhibitors	Qfitlia® AT-DR (N=80)	On-Demand CFC (N=40)
All treated Bleeds		
Annualized Bleed Rate (ABR)	9.0	31.4
% reduction; p-value	71%; p<0.0001	
Treated Spontaneous Bleeds		
ABR	5.4	21.0
% reduction; p-value	74%; p<0.0001	
Treated Joint Bleeds		
ABR	6.2	21.6
% reduction; p-value	71%; p<0.0001	

Place in Therapy: Qfitlia® is an antithrombin-directed small interfering ribonucleic acid indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors. It is for subcutaneous use only. It has a box warning regarding thrombotic events and acute and recurrent gallbladder disease. The efficacy of Qfitlia® prophylaxis using AT-DR in ATLAS-OLE compared to on-demand BPA or CFC control data from studies ATLAS-INH and ATLAS-A/B were reported. The ABR for all treated bleeds in patients with inhibitors for Qfitlia® AT-DR as compared with on-demand BPA was significantly in favor of Qfitlia® (p=0.0006). The ABR for all treated bleeds in patients without inhibitors for Qfitlia® AT-DR vs on-demand CFC was significantly in favor of Qfitlia® (p<0.0001).

Summary

There is some evidence to suggest that Qfitlia® may be more effective than on-demand BPA and on-demand CFC for ABR; however, there is no evidence to suggest that it is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Qfitlia® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**

References

[1] Qfitlia [package insert]. Cambridge, MA: Genzyme Corp; 2025.

Prepared By: Iowa Medicaid Date: 06/23/2025