NEW DRUG APPROVAL

Brand Name	Altuviiio™
Generic Name	antihemophilic factor (recombinant)
Drug Manufacturer	Bioverativ Therapeutics Inc.

Indications for Use

Altuviiio™ [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl] is a recombinant DNA-derived, Factor VIII concentrate indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency) for:

- Routine prophylaxis to reduce the frequency of bleeding episodes.
- On-demand treatment & control of bleeding episodes.
- Perioperative management of bleeding.

Limitation of Use: Altuviiio™ is not indicated for the treatment of von Willebrand disease.

New Drug Approval

FDA approval date: February 23, 2023

Review designation: N/A

Type of review: Biologic License Application (BLA): 125771

Dispensing restriction: N/A

Therapeutic Class

Antihemophilic Agent

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hemophilia, which means love (philia) of blood (hemo), manifests with prolonged and excessive bleeding either spontaneously or after insignificant trauma. Hemophilia encompasses a group of inherited ailments that alter the body's normal blood coagulation. A hereditary hemorrhagic disorder resulting from congenital deficit or scarcity of factor VIII, hemophilia A, which is known as classical hemophilia, manifests as protracted and excessive bleeding either spontaneously or secondary to trauma.

Hemophilia A is a hereditary blood disorder, primarily affecting males, characterized by a deficiency of the blood clotting protein known as Factor VIII that results in abnormal bleeding. Babylonian Jews first described hemophilia more than 1700 years ago; the disease first drew widespread public attention when Queen Victoria transmitted it to several European royal families. Mutation of the *HEMA* gene on the X chromosome causes Hemophilia A. Normally, females have two X chromosomes, whereas males have one X and one Y chromosome. Since males have only a single copy of any gene located on the X chromosome, they cannot offset damage to that gene with an additional copy as can females. Consequently, X-linked disorders such as Hemophilia A are far more common in males. The *HEMA* gene codes for Factor VIII, which is synthesized mainly in the liver, and is one of many factors involved in blood coagulation; its loss alone is enough to cause Hemophilia A even if all the other coagulation factors are still present.

Epidemiology: Hemophilia A, the most common hereditary disorder of hemostasis, occurs in one out of 5000 males and accounts for 80% of hemophilia cases. Hemophilia A occurs in more than 400000 males worldwide, many of whom remain undiagnosed in the developing world.

Efficacy

The safety, efficacy, and pharmacokinetics of Altuviiio™ were evaluated in two multicentre, prospective, open-label clinical studies (one study in adults and adolescents ≥12 years of age and one pediatric study in children <12 years of age) in previously treated patients (PTPs) with severe hemophilia A (<1% endogenous Factor VIII activity or a documented genetic mutation consistent with severe hemophilia A).

All studies evaluated the efficacy of routine prophylaxis with a weekly dose of 50 IU/kg and determined hemostatic efficacy in the treatment of bleeding episodes and during perioperative management in subjects undergoing major or minor surgical procedures.

The completed adult and adolescent study enrolled a total of 159 PTPs (158 male and 1 female subjects) with severe hemophilia A. Subjects were aged 12 to 72 years and included 25 adolescent subjects aged 12 to 17 years. All 159 enrolled subjects received at least one dose of Altuviiio™ and were evaluable for efficacy. A total of 149 subjects (93.7%) completed the study.

The ongoing pediatric study enrolled 67 male PTPs <12 years of age with severe hemophilia A (31 subjects were 1 to 5 years of age and 36 were 6 to 11 years of age) at data cut-off. Of the 67enrolled subjects, all received at least 1 dose of Altuviiio™.

Routine Prophylaxis to Reduce Bleeding Episodes

Adult and Adolescent Study: The efficacy of weekly 50 IU/kg Altuviiio™ as routine prophylaxis was evaluated as estimated by the mean annualized bleed rate (ABR) and by comparing the ABR during on-study prophylaxis vs. the ABR during pre-study FVIII prophylaxis. A total of 133 adults and adolescents, who were on pre-study FVIII prophylaxis, were assigned to receive Altuviiio™ for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 52 weeks (Arm A). An additional 26 subjects, who were on pre-study episodic (on-demand) treatment with FVIII, received episodic (on-demand) treatment with Altuviiio™ at doses of 50 IU/kg IV for 26 weeks, followed by routine prophylaxis at a dose of 50 IU/kg IV once weekly for 26 weeks (Arm B). Overall, 115 subjects received at least a total number of 50 exposure days (EDs) in Arm A and 17 subjects completed at least 25 EDs of routine prophylaxis in Arm B.

The ABR in subjects evaluable for efficacy with at least 26 weeks of exposure are summarized in Table 1. Routine prophylaxis resulted in a mean ABR (95% CI) of 0.7 (0.5, 1.0), a median (Q1, Q3) ABR of 0 (0, 1.0), and a median (Q1, Q3) annualized joint bleeding rate of 0 (0, 1.0).

Table 1: Summary of Annualized Bleeding Rate (ABR) with Altuviiio™ Prophylaxis, Altuviiio™ Ondemand Treatment, and After Switch to Altuviiio™ Prophylaxis in Patients ≥12 Years of Age

Endpoint*	Arm A Prophylaxis†	Arm B On-demand‡	Arm B Prophylaxis‡
	N = 128	N = 26	N = 26
Treated bleeds			
Mean ABR (95% CI) §	0.7 (0.5, 1.0)	21.4 (18.8, 24.4)	0.7 (0.3, 1.5)
Median ABR (Q1, Q3)	0 (0, 1.0)	21.1 (15.1, 27.1)	0 (0, 0)

Table 1: Summary of Annualized Bleeding Rate (ABR) with Altuviiio™ Prophylaxis, Altuviiio™ Ondemand Treatment, and After Switch to Altuviiio™ Prophylaxis in Patients ≥12 Years of Age			
Endpoint*	**Arm A Prophylaxis†**	**Arm B On-demand‡**	**Arm B Prophylaxis‡**
subjects with zero bleeds, n (%)	82 (64.1)	0	20 (76.9)
Treated spontaneous bleeds			
Mean ABR (95% CI) §	0.3 (0.2, 0.4)	15.8 (12.3, 20.4)	0.4 (0.2, 1.2)
Median ABR (Q1, Q3)	0 (0, 0)	16.7 (8.6, 23.8)	0 (0, 0)
% Subjects with zero bleeds, n (%)	103 (80.5)	1 (3.8)	22 (84.6)
Treated joint bleeds			
Mean ABR (95% CI) §	0.5 (0.4, 0.7)	17.5 (14.9, 20.5)	0.6 (0.3, 1.5)
Median ABR (Q1, Q3)	0 (0, 1.0)	18.4 (10.8, 23.9)	0 (0, 0)
% Subjects with zero bleeds, n (%)	92 (71.9)	0	21 (80.8)
All Bleeds (treated and untreated) *			
Mean ABR (95% CI) §	1.1 (0.8, 1.5)	22.2 (19.4, 25.4)	0.9 (0.4, 1.8)
Median ABR (Q1, Q3)	0 (0, 1.2)	21.1 (16.8, 27.1)	0 (0. 1.9)
% Subjects with zero bleeds, n (%)	71 (55.5)	0	19 (73.1)

ABR = annualized bleed rate; CI = confidence interval; Q1= 25th percentile, Q3=75th percentile.

* Reflects all bleeds reported by patients including those where no Altuviiio™ was administered.
† Subjects assigned to receive Altuviiio™ prophylaxis for 52 weeks.
‡ Subjects assigned to receive Altuviiio™ for 26 weeks.
§ Based on negative binomial model.

An intra-subject comparison (N = 78) between mean ABR during on-study prophylaxis with Altuviiio™ and that during pre-study FVIII prophylaxis yielded a 77% reduction in treated bleeds (95% CI: 58%, 87%).

All subjects with target joints at baseline (defined as ≥3 spontaneous bleeding episodes in a major joint which occurred in a consecutive 6-month period) achieved resolution of all target joints (45/45, 100%) with 12 months of prophylactic treatment with Altuviiio™ (defined as ≤2 bleeding episodes in the target joint in 12 months).

Pediatric Study

The efficacy of weekly 50 IU/kg Altuviiio™ as routine prophylaxis in children <12 years was evaluated as estimated by the mean annualized bleed rate (ABR). At the time of the interim analysis, a total of 67 children (31 children <6 years of age and 36 children 6 to <12 years of age) were enrolled to receive Altuviiio™ for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 52 weeks. In subjects with at least 26 weeks of exposure (N=23), routine prophylaxis resulted in a mean ABR (95% CI) of 0.5 (0.2, 1.3) and a median (Q1, Q3) ABR of 0 (0, 1.3) for treated bleeds. For all bleeds (treated and non-treated), the mean ABR (95% CI) was 3.6 (1.6, 8.4) and the median (Q1, Q3) ABR was 0 (0, 4.5).

Efficacy in Control of Bleeding

In the adult and adolescent study, a total of 362 bleeding episodes were treated with Altuviiio™, most occurring during on-demand treatment in Arm B. Majority of bleeding episodes were localized in joints. Response to the first injection was assessed by subjects at least 8 hours after treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Bleeding was resolved with a single 50 IU/kg injection of Altuviiio™in 96.7% of bleeding episodes. The median (Q1; Q3) total dose to treat a bleeding episode was 50.9 IU/kg (50.0; 51.9). Control of bleeding episodes was similar across the treatment arms.

Perioperative Management of Bleeding

Perioperative hemostasis was assessed in 13 major surgeries in 12 subjects (11 adults and 1 child). Of the 13 major surgeries, 12 surgeries required a single pre-operative dose to maintain hemostasis during surgery; for 1 major surgery during routine prophylaxis no pre-operative loading dose was administered on the day of/or before surgery. The median dose per preoperative injection was 49.96 IU/kg (range 12.7 - 61.9).

The clinical evaluation of hemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or poor/none. The hemostatic effect of Altuviiio™ was rated as “excellent” in 13 of 13 surgeries (100%). No surgery had an outcome rated as “poor/none” or “missing.”

Types of major surgeries assessed include major orthopedic procedures such as joint arthroplasties (joint replacements of knee, hip, and elbow), joint revisions and ankle fusion. Other major surgeries included molar extractions and rhinoplasty/mentoplasty.

Perioperative hemostasis was assessed in 22 minor surgeries in 19 subjects (12 adults and 7 children). The hemostatic response was evaluated by the investigator/surgeon in 15 of these minor surgeries; an excellent response was reported in all (100%).

Most common adverse reaction (incidence >10%) are headache and arthralgia.

Safety

ADVERSE EVENTS

The safety of Altuviiio™ has been evaluated in 159 previously treated patients (PTPs) (134 adults and 25 adolescents) with severe Hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe Hemophilia A) who received at least one dose of Altuviiio™ for either routine prophylaxis, on-demand treatment of bleeding episodes or perioperative management. A total of 152 (96%) subjects achieved at least 25 exposure days and 115 (72%) subjects achieved at least 50 exposure days with a median of 53.0 (range 2-63) for both exposure days and injections per subject. Overall exposure was monitored for a total of 151.5 subject-years. Adverse drug reactions (ADRs) (summarized in Table 2) were reported in 57 (36%) of the 159 subjects treated with routine prophylaxis or on-demand therapy. There were no age-specific differences in ADRs observed between adolescent and adult subjects. In the study, no inhibitors were detected and no ADRs of anaphylaxis were reported.

Table 2: Adverse Drug Reactions with Frequency of ≥3% Reported for Altuviiio™

MedDRA System Organ Class	Adverse Drug Reactions	Number of Subjects n (%) (N = 159)
Nervous system disorders	Headache*	33 (21)
Musculoskeletal and connective tissue disorders		
	Arthralgia	26 (16)
	Back pain	9 (6)

* Includes preferred terms of headache (32 subjects) and migraine (1 subject).

In the ongoing pediatric study, the safety of Altuviiio™ was evaluated in 67 male PTPs <12 years of age with severe hemophilia A who received at least one dose of Altuviiio™. At the time of the interim analysis, a total of 23 (34%) subjects achieved at least 25 exposure days with a median of 14.0 (range 1-46) for both exposure days and injections per subject.

Adverse drug reactions, headache, were reported in 1 (1%) of subjects. In the study, no inhibitors were detected and no ADRs of anaphylaxis were reported.

Thromboembolic events occurred in 1% (3/206) of subjects in the long-term safety extension study; these three subjects had pre-existing risk factors.

Immunogenicity: All subjects were monitored for neutralizing antibodies (inhibitors) to Factor VIII in the clinical program. No subjects developed neutralizing antibodies to Factor VIII.

WARNINGS & PRECAUTIONS

Hypersensitivity Reactions: Allergic-type hypersensitivity reactions, including anaphylaxis, may occur with Altuviiio™. Allergic-type hypersensitivity reactions were not reported in the clinical trials. Inform patients of signs of hypersensitivity reactions that may progress to anaphylaxis (including hives, shortness of breath, chest tightness, wheezing, hypotension and itching). Advise patients to discontinue use of Altuviiio™ if hypersensitivity symptoms occur and contact a physician and/or seek immediate emergency care.

Neutralizing Antibodies: Formation of neutralizing antibodies (inhibitors) to Factor VIII are possible following administration of Altuviiio™. Neutralizing antibodies were not reported in the clinical trials. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If the patient's plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after Altuviiio™ administration, the presence of an inhibitor (neutralizing antibodies) should be suspected, and appropriate testing performed.

Monitoring Laboratory Tests: If assessment of plasma Factor VIII activity is needed, it is recommended to use a validated onestage clotting assay. The Altuviiio™ Factor VIII activity level is overestimated by the chromogenic assay and a specific ellagic acid based aPTT reagent in one-stage clotting assay by approximately 2.5-fold. If these assays are used, divide the result by 2.5 to approximate the patient's Altuviiio™ Factor VIII activity level. Use of a reference laboratory is recommended when a qualified one-stage clotting assay or chromogenic assay is not available locally.

Monitor for the development of Factor VIII inhibitors. If bleeding is not controlled with Altuviiio™ and the expected factor VIII activity plasma levels are not attained, perform an assay to determine if Factor VIII inhibitors are present (use Bethesda Units to titer inhibitors).

CONTRAINDICATIONS

Altuviiio™ is contraindicated in patients who have had severe hypersensitivity reactions, including anaphylaxis, to the product or its excipients.

Clinical Pharmacology

MECHANISMS OF ACTION

Altuviiio™ [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl] temporarily replaces the missing coagulation factor VIII needed for effective hemostasis. Altuviiio™ has demonstrated 3- to 4-fold prolonged half-life relative to other standard and extended half-life FVIII products.

Mechanism of Half-life Extension

Altuviiio™ is a recombinant FVIII analogue fusion protein that is independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII-VWF interactions. The D'D3 domain of VWF is the region that interacts with FVIII. Appending the D'D3 domain of VWF to a recombinant FVIII-Fc fusion protein provides protection and stability to FVIII, and prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII half-life imposed by VWF clearance. The Fc region of human immunoglobulin G1 (IgG1) binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by recycling them back into circulation, thus prolonging the plasma half-life of the fusion protein. Altuviiio™ contains 2 XTEN polypeptides, which alter the hydrodynamic radius of the fusion protein, thus reducing rates of clearance and degradation, and improving pharmacokinetic properties. In Altuviiio™, the natural FVIII B domain (except 5 amino acids) is replaced with the first XTEN, inserted in between FVIII N745 and E1649 amino acid residues; and the second XTEN is inserted in between the D'D3 domain and Fc.

Dose & Administration

ADULTS

- For routine prophylaxis: 50 IU/kg once weekly.
- For on-demand treatment and control of bleeding episodes and perioperative management: 50 IU/kg.
- Estimated Increment of Factor VIII (IU/dL or % of normal) = 50 IU/kg x 2 (IU/dL per IU/kg.)

PEDIATRICS

Refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

For injection: nominally 250, 500, 750, 1000, 2000, 3000, or 4000 IU, lyophilized powder in single-dose vials for reconstitution.