Hemlibra (emicizumab-kxwh) Medical Drug Criteria with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
3/1/2023

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Hemlibra® (emicizumab-Kxwh) Injection for subcutaneous use	• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with Hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Hemophilia A	Hemophilia A, also called Factor VIII deficiency or classic hemophilia, is a genetic disorder caused by missing or defective Factor VIII (FVIII), a clotting protein. Although it is passed down from parents to children, about 1/3 of cases found have no previous family history.(6) Treatment for hemophilia A is dependent on several factors and there is not a universal therapy that will work for all patients. Clinically the hallmark of bleeding in hemophilia is bleeding into the joints, muscles, and soft tissues. The severity and the risk of that bleeding can be correlated to the residual amount of factor activity that can be measured in the blood. Patients with severe disease have less than 1% residual activity, and often have zero. These are the patients who are at risk for spontaneous as well as traumatic bleeding. Having over 5% residual amount makes bleeding into the joints very unusual (although not inconceivable), and most bleeding is triggered only by trauma. Residual activity of 1-5% appears for the most part to prevent spontaneous bleeding, but patients can still be at risk for joint bleeds with even relatively minor trauma.(8) The main goal of any therapy is to completely prevent bleeding. The current World Hemophilia Federation Guidelines for the Management of Hemophilia state:(3) • Both virus-inactivated plasma-derived and recombinant clotting factor concentrates (CFCs), as well as other hemostasis products when appropriate can be used for treatment of bleeding and prophylaxis in people with hemophilia

	• Prophylaxis is the standard of care for people with severe hemophilia, and for some people with moderate hemophilia or for those with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding
	• Episodic CFC replacement should not be considered a long-term option for the management of hemophilia as it does not alter its natural history of spontaneous bleeding and related complications
	• Emerging therapies in development with alternative modes of delivery (e.g., subcutaneous injection) and novel targets may overcome the limitations of standard CFC replacement therapy (i.e., need for intravenous administration, short half-life, risk of inhibitor formation).
	• The development of gene therapies for hemophilia has advanced significantly, with product registration likely in the near future
	• Gene therapy should make it possible or some people with hemophilia to aspire to and attain much better health outcomes and quality of life than that attainable with currently available hemophilia therapies
	• Given the ongoing advances transforming the hemophilia treatment landscape, it is important to establish systems to constantly monitor developments in emerging and gene therapies for hemophilia and make them available as soon as possible following approval by regulatory authorities
	
	Approximately 1 in 5 people with hemophilia A will develop an antibody – called an inhibitor – to the clotting factor concentrate(s) used to treat or prevent their bleeding episodes. Developing an inhibitor is one of the most serious and costly medical complications of a bleeding disorder because it becomes more difficult to treat bleeds. Inhibitors most often appear in the first 50 exposure days of clotting factor concentrates.(7-8)
	
	All persons with hemophilia are at risk of developing an inhibitor. The cause of inhibitor formation is not known but multiple research studies have found some characteristics that possibly play a role in increasing the risk of inhibitor development and includes the following:(3,7)
	
	• Certain types of hemophilia gene mutations
	  ○ The nature of disease-causing variants in both F8 and F9 has been found to be the strongest risk factors for inhibitor development
	  ○ Null variants, i.e., variants which result in total absence of the protein (large deletions, duplications, insertions, inversions, nonsense mutations, and splice-site variants), have shown the strongest association with inhibitors as compared to other variants (small in-frame deletions, duplications, insertions, missense mutations
	• Number of times a patient has used clotting factor concentrates in their lifetime
	• Increased frequency and dose of treatment
	• Black race or Hispanic ethnicity
	• Family history of inhibitors
	
	A blood test measures if an inhibitor is present and the inhibitor titer. Inhibitor titers are measured in Nijmegen-Bethesda units (NBU) or Bethesda units (BU) depending on the specific assay used. Test results below 5.0 NBU/BU are considered low titer inhibitors, and test results of 5.0 NBU/BU or greater are considered high titers. People diagnosed with low titer inhibitors are more likely to have shorter and more successful inhibitor treatment than those with high titer inhibitors. For these reasons, it is

	important that people with hemophilia who use clotting factor concentrates get tested for inhibitors at least once a year.(7) The National Hemophilia Foundation classifies inhibitors as low responding and high responding in addition to low titer (less than 5 BU) and high titer (greater than or equal to 5 BU). In low responding inhibitors when the patient receives Factor VIII the inhibitor titer does not rise. These patients can be treated with higher doses of the CFC. If the inhibitor titer increases with CFC it is considered high- responding. For high responding inhibitors, the situation becomes much more complicated as even large doses of infused CFC are often rendered ineffectual by the sheer potency of the antibody response.(4) In the cases of high-responding inhibitors treatment is based on several components including the type of hemophilia and the nature of the bleed. During a life or limb-threatening bleeding episode, physicians can remove antibodies from the body using plasmapheresis. This is only a temporary solution however as within a few days the body will produce large amounts of new antibodies. For the person with a high responding inhibitor there are therapies that can effectively treat bleeds by circumventing the need to replace FVIII. These agents are commonly referred to as bypassing agents (BPAs) and include activated prothrombin complex concentrate (aPCC) and recombinant activated Factor VII concentrates. Hemlibra, a therapy that does not function by FVIII or Factor IX replacement, is a newer therapy that can be used for these patients.(4) If left unchecked, a persistent inhibitor will present a severe burden on patients and families, as the ongoing physical, emotional, and in many cases financial toll continue to intensify. Healthcare providers will often attempt to proactively stamp out an inhibitor through immune tolerance therapy (ITI). ITI is an approach to inhibitor eradication where the body's immune system begins to tolerate a therapy after daily doses of factor are administered over time. The majority of people who undergo ITI therapy will see an improvement within 12 months, but more difficult cases can take two years or longer.(9) There is a general consensus that failure of ITI is the inability to achieve successful tolerance within 2-3 years of initiation of an ITI regimen.(3) The World Hemophilia Federation similarly recommends that treatment of patients with inhibitors depends on several components including the titer of the inhibitor, records of clinical response to product, and site and nature of the bleed. Patients with a low responding inhibitor or those with a high responding inhibitor but low titer may be treated with factor product at a much higher dose. With an inhibitor level greater than or equal to 5 BU, the likelihood that specific factor replacement will be effective in overwhelming the inhibitor without ultra-high dose continuous infusion therapy and alternative agents, include bypassing agents such as recombinant factor VIIa and activated prothrombin complex concentrate (aPCC) is extremely low.(3) Emicizumab-kxwh is a recombinant, humanized, bispecific immunoglobulin G4 monoclonal antibody that substitutes for part of the cofactor function of activated factor VIII (FVIII) by bridging activated factor IX and Factor X. Emicizumab-kxwh is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages, newborn and older, with hemophilia A with

	and without Factor VIII inhibitors. There is significant reduction in annualized bleeding rates at all doses for all age groups, with or without inhibitors.(10) The Future of Immunotolerance Treatment (FIT) Expert group was established to determine and recommend the best management options for patients with hemophilia A and inhibitors. This group concluded that despite the considerable success of emicizumab in the management of inhibitor patients, eradicating inhibitors is important. The availability of emicizumab and other non-factor therapies in the future might impact greatly on how ITI is undertaken. Theoretically, concomitant use of emicizumab and FVIII might allow emicizumab to effectively prevent bleeding with lower dose ITI regimens. But as there are no published data regarding the concomitant use of emicizumab and FVIII for ITI, the FIT Expert group encourages the undertaking of properly conducted prospective studies to explore these approaches further.(13) The FIT Expert group stratified patients into the following four groups based on historical pre-ITI peak titer to predict the potential success with ITI treatment:(13) • Patients with titer less than 25 BU have a very good prognosis • Patients with titer 25 to less than 200 BU have a good prognosis • Patients with titer 200 to less than 1000 BU have a poor prognosis • Patients with titer greater than or equal to 1000 BU have a very poor prognosis Factor VIII and emicizumab-kxwh are fundamentally different proteins and are regulated differently. These differences should also be a part of the discussion on treatment.(10) Some of the differences of Factor VIII and emicizumab are:(10) a. FVIIIa has multiple sites of interaction with FIXa, FX and the phospholipid surface, emicizumab has a single site b. FVIII needs to be activated (thrombin mediated), emicizumab does not c. FVIII binds to VWF, emicizumab does not d. FVIII binds to phospholipid surface, emicizumab does not - greater FVIII binding limits movement of the FX-activating complex more than emicizumab e. FVIIIa binds to surface on activated platelet, emicizumab most likely does not f. FVIII has a much higher binding affinity than emicizumab g. FVIIIa enhances FXa generation approximately 10 fold over emicizumab h. Emicizumab can bind both activated and non-activated forms of FIX and FX Based on the clinical trial data, The Medical and Scientific Advisory Council (MASAC) recommends the following for emicizumab therapy:(10) • Any person with hemophilia A with an inhibitor who has spontaneous or traumatic bleeding episodes, whether treated with episodic or prophylactic BPA, should be considered for emicizumab prophylaxis as first-line of therapy

	• Patients on BPA prophylaxis with few bleeding episodes could consider switching from BPA prophylaxis to emicizumab prophylaxis based on overall cost-effectiveness and simpler administration • Infants should be considered for prophylaxis with emicizumab at any time after birth given the increased risk of intracranial hemorrhage prior to initiation of FVIII prophylaxis • Prescribers should discuss use of emicizumab prophylactic therapy in patients with hemophilia A without inhibitors. Discussion should include an assessment of the risks and benefits of emicizumab compared to their existing therapy • For patients without inhibitors, FVIII prophylaxis continuation during the week after initiation of emicizumab is a common and reasonable approach. However, given that steady-state levels of emicizumab are not achieved until after four weekly doses of 3 mg/kg, it may be reasonable to continue FVIII prophylaxis in select individuals based on their bleeding history and physical activity level, until they are ready to start maintenance dosing The World Federation of Hemophilia Guidelines state that CFCs are the treatment of choice for people with hemophilia as they are very safe and effective for treating and preventing bleeds. These guidelines do have further clarification on emicizumab use. The guidelines state that patients with hemophilia with inhibitors emicizumab should be used for regular prophylaxis and patients with hemophilia A with no inhibitors emicizumab can be used for regular prophylaxis.(3) In 2020 The Institute for Clinical and Economic Review (ICER) reviewed prophylaxis with FVIII products and prophylaxis with emicizumab for patients without inhibitors. Their conclusions were there is high certainty that there is at least a comparable benefit of emicizumab compared with Factor VIII prophylaxis at the doses now typically used in the US and a moderate certainty of a small or substantial net health benefit. ICER rated emicizumab as comparable or better (C++) compared with FVIII prophylaxis.(11) In 2018 ICER reviewed emicizumab treatment for hemophilia patients with inhibitors. The conclusions of this report are for people ages 12 and older with hemophilia A with inhibitors who will not be treated with ITI or for whom ITI has been unsuccessful, the have high certainty that emicizumab provides a substantial net health benefit ("A") compared with no prophylaxis. Given the results of the trials and the reduced burden with emicizumab, for children younger than 12 they have high certainty that emicizumab provides at least a small net health benefit ("B+") compared with no prophylaxis, and in adults and children they have high certainty that emicizumab provides at least a small net health benefit ("B+") compared with prophylaxis with BPAs.(5) There is limited data on the concomitant use of emicizumab prophylaxis during ITI. There is a case series of children with hemophilia A and inhibitors who underwent ITI in combination with emicizumab prophylaxis (Atlanta Protocol), and a larger clinical trial of this protocol is underway [MOTIVATE study (NCT04023019)].(10) The MOTIVATE study is a non-interventional, multicenter, observational, international study in male persons with hemophilia A who have developed inhibitors to any replacement coagulation Factor VIII (FVIII product). The purpose of the study is to capture different approaches in the management and to evaluate the efficacy and safety of immune tolerance induction, including the combination of FVIII and emicizumab. Patients will be assigned to 1 of 3 groups based on the treatments they

	receive and may switch to another group if their treatment is changed. The 3 groups are:(12) • ITI with Nuwiq, Octanate, or Wilate • ITI with Nuwiq, Octanate, or Wilate with emicizumab • Prophylaxis with emicizumab, aPCC, or recombinant FVIIIa without immune tolerance induction MASAC recommends that the pros and cons of the various approaches for patients with hemophilia A and inhibitors be part of a patient/clinician shared decision-making and ITI should remain an option for their care. MASAC also recommends that long term follow up and interventional trials that include the concomitant use of emicizumab with ITI should be encouraged. If ITI with concomitant emicizumab prophylaxis will be pursued MASAC provides the following recommendations:(10) • No more than 50-100 IU/kg per dose of CFCs be administered unless observation will occur within a clinical trial. This relates to the uncertainty as to any potential incremental risk of an elevated FVIII level, even transiently, in patients on emicizumab who may need treatment with a BPA for breakthrough bleeding during ITI • Data on the use of emicizumab prophylaxis with ITI should be conducted under a clinical trial or as part of existing databases collecting data on the natural history of emicizumab use within the US The World Federation of Hemophilia states that the availability of non-factor replacement therapies (e.g., emicizumab) that are effective in bleed prevention in patients with FVIII inhibitors has raised questions about whether such agents should be used before, during, after, or in place of ITI. This remains controversial, however, as there are insufficient data to resolve this question.(3)
Pain	People with bleeding disorders experience both acute and chronic pain associated with bleeding. Bleeding into soft tissues and joints, whether spontaneous or associated with trauma, often causes acute pain. Repeated bleeding events over time can lead to long-term changes in affected tissues, particularly joints. Chronic arthropathy causes disability and reduces quality of life due to chronic pain.(14) Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain in patients with bleeding disorders. Non-steroidal anti-inflammatory drugs (NSAIDs) should typically be avoided in patients with bleeding disorders, particularly higher doses over extended durations, due to risks of potential short-term interference with platelet function and of GI ulcer formation. Selective COX-2 inhibitors (e.g., celecoxib) appear to be associated with decreased risk of anti-platelet effects and ulcer formation when compared to NSAIDs and may be considered.(14)
Efficacy(1)	Hemlibra (emicizumab-kxwh) is a humanized monoclonal modified immunoglobulin G4(IgG4) antibody with a bispecific antibody structure binding factor IXa and factor X. Emicizumab-kxwh is produced in genetically engineered mammalian (Chinese hamster ovary) cells. Emicizumab bridges activated factor IX and factor X to restore the function of activated factor VIII.

	The efficacy of Hemlibra for routine prophylaxis in patients with hemophilia A with FVIII inhibitors was evaluated in three clinical trials [adult and adolescent studies (HAVEN 1 and HAVEN 4) and a pediatric study (HAVEN 2)]. The HAVEN 4 study included patients with and without inhibitors. The HAVEN 1 study was a randomized phase 3, multicenter, open label trial that enrolled 109 adult and adolescent males (ages 12-75 and weighing greater than 40kg) with hemophilia A with FVIII inhibitors who previously received either episodic (on-demand) or prophylactic treatment with bypassing agents (rFVIIa and/or aPCC). The patients were randomized into 4 arms. Patients who received on-demand treatment with bypassing agents prior to the study entry were randomized 2:1 into arms A and B respectively. Arm A patients received prophylactic emicizumab. The active comparator arm B patients did not receive emicizumab prophylaxis. Arm C was an experimental arm and enrolled patients who received prophylactic bypassing agents prior to the study entry. Arm D was for patients that used on-demand or prophylactic therapy with bypassing agents but were unable to enroll in arms A through C. After at least 24 weeks on-study, the patients in Arm B had the opportunity to switch to emicizumab prophylaxis. All Arms continued to receive episodic bypassing agent therapy to treat breakthrough bleeds. The primary outcome measure of the HAVEN 1 study was the Annualized Bleed Rate (ABR) for Treated Bleeds (Arms A and B). Secondary outcome measures included ABR for various other bleeds including all Bleeds (treated or untreated), all joint bleeds, targeted joint bleeds and spontaneous bleeds. The ABR for treated bleeds was 2.9 in the emicizumab group vs 23.3 in the no prophylaxis group resulting in 87% reduction in ABR (95%CI p less than 0.0001). Secondary outcomes had similar results (80-92% reduction all with 95%CI and p less than 0.0001). The HAVEN 2 trial was a non-randomized, single-arm, multicenter, open-label, in pediatric males (ages less than 12, or ages 12-17 weighing less than 40 kg) with hemophilia A with FVIII inhibitors. The patients received emicizumab 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter. The primary outcome measure was efficacy of weekly emicizumab prophylaxis, including the efficacy of weekly emicizumab compared with previous episodic (on-demand) and prophylactic bypassing agent, measured by ABR. An interim analysis of 23 patients was used for FDA approval in this population. The ABR for all treated bleeds was 0.2 (95% CI). The intra-patient analysis comparing emicizumab to previous therapy showed a 99% reduction in bleed rate (previous ABR while on bypassing agents was 17.2 and 0.2 after emicizumab prophylaxis) in the 13 patients in this group. Since the time from FDA approval to now, this study has expanded and currently has 3 arms. Arm A consists of patients using 1.5 mg/kg every week. Arm B consists of patients using 3 mg/kg every 2 weeks. Arm C consists of patients using 6mg/kg every 4 weeks. The HAVEN 4 study was a single-arm, multicenter, open-label, clinical trial in 41 adult and adolescent males with hemophilia A with or without Factor VIII inhibitors who previously received wither episodic (on demand) or prophylactic treatment with Factor VIII or with bypassing agents. Efficacy was evaluated in a subgroup of 36 patients with hemophilia A without Factor VIII inhibitors based on the bleed rate for bleeds requiring treatment with coagulation factors. The study also evaluated the efficacy of

Hemlibra prophylaxis on all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds. The results are shown in the table below.

Intra-Patient Comparison of Annualized Bleed Rate with Hemlibra Prophylaxis versus previous FVIII Prophylaxis

Endpoint	**Hemlibra** **1.5 mg/kg once every week (N=48)**	**Previous FVII (N=48)**
Median Observation Period (weeks)	33.7	30.1
Treated Bleeds		
ABR (95% CI)[a]	1.5 (1, 2.3)	4.8 (3.2,7.1)
% reduction (95% CI) p-value	68% (48.6%,80.5%) less than 0.0001	
% patients with 0 bleeds (95% CI)	54.2 (39.2,68.6)	39.6 (25.8,54.7
Median ABR (IQR)	0 (0,2.1)	1.8 (0,7.6)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

a - Based on negative binomial regression model

The efficacy of Hemlibra for routine prophylaxis in patients with hemophilia A without Factor VIII inhibitors was evaluated in two clinical trials [adult and adolescent studies HAVEN 3 and HAVEN 4)]. The HAVEN 4 trial included patients with and without inhibitors (see results above).

The HAVEN 3 trial was a randomized, multicenter, open-label, clinical trial in 152 adult and adolescent males with hemophilia A without Factor VIII inhibitors, who previously received either episodic (on demand) or prophylactic treatment with Factor VIII. Efficacy was evaluated after a minimum of 24 weeks of follow-up based on the bleed rate for bleeds requiring treatment with coagulation factors. The results are shown in the table below.

Annualized Bleed Rate with Hemlibra Prophylaxis vs No Prophylaxis in Patients greater than or equal to 12 years of Age without Factor VIII Inhibitors

Endpoint	**Hemlibra** **1.5 mg/kg once every week (N = 36)**	**Hemlibra** **3 mg/kg once every two weeks (N = 35)**	**No P** **(N =**
Treated Bleeds			
ABR (95% CI)[a]	1.5 (0.9,2.5)	1.3 (0.8,2.3)	38.2
% reduction (95% CI)	96% (92.5%,98%)	97% (93.4, 98.3%)	-

	p-value	less than 0.0001	less than 0.0001	
	% of patients with 0 bleeds (95% CI)	55.6 (38.1, 72.1)	60 (42.1, 76.1)	0 (0,18.5)
	Median ABR (IQR)	0 (0,2.5)	0 (0,1.9)	40.4 (25.3
	All Bleeds			
	ABR (95% CI)[a]	2.5 (1.6,3.9)	2.6 (1.6,4.3)	47.6 (28.5
	%reduction (95%CI) p-value	95% (90.1%,97%) less than 0.0001	94% (89.7%,97%) less than 0.0001	-
	% of patients with 0 bleeds (95%CI)	50 (32.9,67.1)	40 (23.9,57.9)	0 (0,18.5)
	Median ABR (IQR)	0.6 (0,3.9)	1.6 (0,4)	46.9 (26.1
	Treated Spontaneous Bleeds			
	ABR (95% CI)[a]	1.0 (0.5,1.9)	0.3 (0.1,0.8)	15.6 (7.6,3
	% reduction (95% CI) p-value	94% (84.9%,97.5%) less than 0.0001	98% (94.4%,99.4%) less than 0.0001	-
	% patients with 0 bleeds (95% CI)	66.7 (49.0,81.4)	88.6 (73.3,96.8)	22.2 (6.4,4
	Median ABR (IQR)	0 (0,1.3)	0 (0,0)	10.8 (2.1,2
	Treated Joint Bleeds			
	ABR (95% CI)[a]	0.6 (0.3,1.4)	0.7 (0.3,1.6)	13 (5.2,32
	% reduction (95%CI) p-value	95% (85.7%,98.4%) less than 0.0001	95% (85.3%,98.2%) less than 0.0001	-
	% patients with 0 bleeds (95% CI)	69.4 (51.9,83.7)	77.1 (59.9,89.6)	27.8 (9.7,5
	Median ABR (IQR)	0 (0,1.4)	0 (0,0)	12.8 (0,39

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile
a - Based on negative binomial regression model

The efficacy of Hemlibra prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds. In patients of previous prophylactic factor VIII therapy Hemlibra efficacy was compared to prophylactic factor VIII therapy efficacy. The annualized bleed rate was 1.5 in the Hemlibra treated patients vs 4.8 in these patients previously treated with Factor VIII prophylaxis (95% CI) which was a 68% reduction (95% CI, p less than 0.0001).

Safety(1)	• Due to the increased coagulation potential with emicizumab, if the patient is using a bypassing agent as prophylactic use, it is recommended to discontinue prophylactic use of bypassing agents the day before starting emicizumab. On-demand use of bypassing agents can be continued with caution based on black box warning. • Hemlibra has no limitations of use but the prescribing information contains a black box warning concerning thrombotic microangiopathy and thromboembolism when given with activated prothrombin complex concentrate (aPCC). If these agents must be used together, the patient should be monitored for the development of thrombotic microangiopathy and/or thromboembolism. If one of these events occurs, aPCC therapy should be discontinued and Hemlibra therapy should be interrupted and the event managed as clinically indicated. Consider the benefits and risks of resuming Hemlibra prophylaxis following complete resolution of the event on a case-by-case basis. • Do not use different vials of different concentrations of Hemlibra when combining vials to administer prescribed dose. The 60 mg, 105 mg, and/or 150 mg vials are the same concentration (150 mg/mL) and may be combined

	for dosing. The 30 mg vials (30 mg/mL) should not be combined in a single injection with the 60 mg, 105 mg, and 150 mg vials. • Hemlibra has no FDA labeled contraindications.

REFERENCES

Number	Reference
1	Hemlibra prescribing information. Gentech Inc. June 2022.
2	~~National Hemophilia Foundation. Steps for Living. The Basics of Bleeding Disorders/Treatment Basics/Treatment Logs. Accessed at: https://stepsforliving.hemophilia.org/basics-of-bleeding-disorders/treatment-basics/treatment-logs.~~ Reference not used
3	Srivastave A, Santagostino E, Dougall A, et al. World Federation of Hemophilia Guidelines for the Management of Hemophilia. 3rd edition. August 2020.
4	National Hemophilia Foundation Bleeding Disorders A-Z Overview Inhibitors Treatment for Inhibitors. https://www.hemophilia.org/bleeding-disorders-a-z/overview/inhibitors/treatment-for-inhibitors
5	Institute for Clinical and Economic Review. Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value. April 2018
6	National Hemophilia Foundation. Bleeding Disorders A-Z/ Types/ Hemophilia A. Accessed at https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a
7	CDC Centers for Disease Control and Prevention. Inhibitors and Hemophilia. Accessed at https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html
8	National Hemophilia Foundation. One Size Does Not Fit All: Individualized Therapy. Dr Steven Pipe. September 2016. Accessed at https://www.hemophilia.org/educational-programs/education/online-education/one-size-does-not-fit-all-individualized-therapy
9	National Hemophilia Foundation. Bleeding Disorders A-Z/ Overview/ Inhibitors/ Immune Tolerance. Accessed at https://www.hemophilia.org/bleeding-disorders-a-z/overview/inhibitors/immune-tolerance
10	Medical and Scientific Advisory Council (MASAC) MASAC Document 258 – Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors. March 2020
11	Institute for Clinical and Economic Review. Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value. November 2020
12	Clinicaltrials.gov. NCT04023019. Treatment of Hemophilia A Patients With FVIII Inhibitors (MOTIVATE). Accessed at: https://clinicaltrials.gov/ct2/show/NCT04023019?term=NCT04023019&draw=2&rank=1
13	Carcao M, Escuriola-Ettingshausen C, Santagostino E, et al. The changing face of immune tolerance induction in haemophilia A with the advent of emicizumab. Haemophilia Volume 25, Issue 4. April 2019
14	James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Advances 12 January 2021. Volume 5, Number 1. 280-300.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Preferred Status	Effective Date
J7170	Hemlibra	emicizumab-kxwh subcutaneous soln	105 MG/0.7ML ; 150 MG/ML ; 30 MG/ML ; 60 MG/0.4ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Days Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date
Hemlibra	Emicizumab-kxwh Subcutaneous Soln 105 MG/0.7ML (150 MG/ML)	105 MG/0.7 ML	0.0		0		Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			
Hemlibra	Emicizumab-kxwh Subcutaneous Soln 150 MG/ML	150 MG/ML	0.0		0		Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			
Hemlibra	Emicizumab-kxwh Subcutaneous Soln 30 MG/ML	30 MG/ML	0.0		0		Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			
Hemlibra	Emicizumab-kxwh Subcutaneous Soln 60 MG/0.4ML (150 MG/ML)	60 MG/0.4 ML	0.0		0		Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities			

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Days Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date
							chart for guidance			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Hemlibra	emicizumab-kxwh subcutaneous soln	105 MG/0.7ML ; 150 MG/ML ; 30 MG/ML ; 60 MG/0.4ML	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Hemlibra	Emicizumab-kxwh Subcutaneous Soln 105 MG/0.7ML (150 MG/ML)	105 MG/0.7ML	Commercial ; HIM ; ResultsRx
Hemlibra	Emicizumab-kxwh Subcutaneous Soln 150 MG/ML	150 MG/ML	Commercial ; HIM ; ResultsRx
Hemlibra	Emicizumab-kxwh Subcutaneous Soln 30 MG/ML	30 MG/ML	Commercial ; HIM ; ResultsRx
Hemlibra	Emicizumab-kxwh Subcutaneous Soln 60 MG/0.4ML (150 MG/ML)	60 MG/0.4ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Hemlibra (emicizumab-kxwh) 1. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent within the past 90 days (starting on samples is not approvable) AND is at risk if therapy is changed **OR** B. The patient has a diagnosis of hemophilia A with or without inhibitors **AND** 2. The requested agent will be used as prophylaxis to prevent or reduce the frequency of bleeding episodes **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. Beyond the first week of starting the requested agent, the patient will NOT be using the requested agent in combination with a Factor VIIa product (e.g., NovoSeven RT), a Factor VIII product (e.g., Advate, Adynovate, Eloctate, Nuwiq, Recombinate, Xyntha), or a bypassing agent (e.g., Feiba, NovoSeven) used for prophylaxis treatment or immune

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	tolerance therapy (ITT) (immune tolerance induction [ITI]) (on-demand treatment is acceptable to continue) **AND** 5. If the patient is receiving Feiba [activated prothrombin complex concentrate (aPCC)] for breakthrough bleeds, BOTH of the following: A. The patient will be monitored for thrombotic microangiopathy and thromboembolism **AND** B. The prescriber has counseled the patient on the maximum dosages of Feiba to be used (i.e., no more than 100 u/kg/24 hours) **AND** 6. ONE of the following: A. The patient will NOT be using the requested agent in combination with a nonsteroidal anti-inflammatory agent (NSAID) (e.g., aspirin, ibuprofen) other than cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib) NOTE: for the purposes of this criteria COX-2 inhibitors will be accepted for concomitant use **OR** B. The prescriber has provided information in support of using an NSAID for this patient **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. The requested quantity (dose) is within the FDA labeled dosing based on the patient's weight and dosing interval **Length of Approval:** 1 month for induction therapy 6 months for maintenance therapy (or remainder of 6 months if requesting induction therapy and maintenance therapy) NOTE: Quantity Limit applies, please see Quantity Limit criteria section below. **Renewal Evaluation** **Target Agent(s**) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. ONE of the following: A. The patient has shown clinical benefit since starting the requested agent (i.e., less breakthrough bleeds as reported in the treatment log and/or chart notes) (medical records including treatment log and/or chart notes required) **OR** B. The prescriber has provided information supporting the continued use of the requested agent (medical record required) **AND** 3. If the patient is receiving Feiba [activated prothrombin complex concentrate (aPCC)] for breakthrough bleeds, the patient will be monitored for thrombotic microangiopathy and thromboembolism **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient will NOT be using the requested agent in combination with a Factor VIIa product (e.g., NovoSeven RT), a Factor VIII product (e.g., Advate, Adynovate, Eloctate, Nuwiq, Recombinate, Xyntha), or a bypassing agent (e.g., Feiba, NovoSeven) used for prophylaxis treatment or immune tolerance therapy (ITT) (immune tolerance induction [ITI]) (on-demand treatment is acceptable to continue) **AND** 6. ONE of the following: A. The patient will NOT be using the requested agent in combination with a nonsteroidal anti-inflammatory agent (NSAID) (e.g., aspirin, ibuprofen) other than cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib) NOTE: for the purposes of this criteria COX-2 inhibitors will be accepted for concomitant use **OR** B. The prescriber has provided information in support of using an NSAID for this patient **AND**

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	7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. The requested quantity (dose) is within the FDA labeled dosing based on the patient's weight and dosing interval **Length of Approval:** 12 months NOTE: Quantity Limit applies, please see Quantity Limit criteria section below.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Quantity Limit for Target Agent(s)** will be approved when ONE of the following is met: 1. The patient is requesting induction therapy only **OR** 2. The patient is requesting induction therapy and maintenance therapy and the requested quantity (dose) for maintenance therapy does not exceed the program quantity limit (see Hemlibra Weight-Based Approvable Quantities chart) **OR** 3. The patient is requesting maintenance therapy only and the requested quantity (dose) does not exceed the program quantity limit (see the Hemlibra Weight-Based Approvable Quantities chart) **Length of Approval:** 1 month for induction therapy 6 months for maintenance therapy (or remainder of 6 months if requesting induction therapy and maintenance therapy) **Renewal Evaluation** **Quantity Limit for the Target Agent(s)** will be approved when the requested quantity (dose) for maintenance therapy does not exceed the program quantity limit (see the Hemlibra Weight-Based Approvable Quantities chart) **Length of Approval:** 12 months **Hemlibra Weight-Based Approvable Quantities (maintenance dosing)**

Weight (kg)	Dosing Schedule	30 mg/1 mL vials	60 mg/0.7 mL vials	105 mg/0.7 mL vials	150 mg/0.7 mL vials
less than or equal to 5 kg	1.5 mg/kg every week	4 mL (4 vials)/28 days	0	0	0
less than or equal to 5 kg	3 mg/kg every 2 weeks	2 mL (2 vials)/28 days	0	0	0
less than or equal to 5	6 mg/kg every 4 weeks	1 mL	0	0	0

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		(1 vial)/28 days			
greater than 5 and less than or equal to 10 kg	1.5 mg/kg every week	4 mL (4 vials)/28 days	0	0	0
greater than 5 and less than or equal to 10 kg	3 mg/kg every 2 weeks	2 mL (2 vials)/28 days	0	0	0
greater than 5 and less than or equal to 10 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	0	0
greater than 10 and less than or equal to 15 kg	1.5 mg/kg every week	4 mL (4 vials)/28 days	0	0	0
greater than 10 and less than or equal to 15 kg	3mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	0	0
greater than 10 and less than or equal to 15 kg	6 mg/kg every 4 weeks	1 mL (1 vial)/28 days	0.4 mL (1 vial)/28 days	0	0
greater than 15 and less than or equal to 20 kg	1.5 mg/kg every week	4 mL (4 vials)/28 days	0	0	0
greater than 15 and less than or equal to 20 kg	3 mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	0	0
greater than 15 and less than or equal to 20 kg	6 mg/kg every 4 weeks	0	0.8 mL (2 vials)/28 days	0	0
greater than 20	1.5 mg/kg	0	1.6 mL	0	0

Module	Clinical Criteria for Approval					
	and less than or equal to 25 kg	every week		(4 vials)/28 days		
	greater than 20 and less than or equal to 25 kg	3 mg/kg every 2 weeks	2 mL (2 vials)/28 days	0.8 mL (2 vials)/28 days	0	0
	greater than 20 and less than or equal to 25 kg	6 mg/kg every 4 weeks	0	0	0	mL (1 vial)/28 days
	greater than 25 and less than or equal to 30 kg	1.5 mg/kg once every week	0	1.6 mL (4 vials)/28 days	0	0
	greater than 25 and less than or equal to 30 kg	3mg/kg every 2 weeks	2 mL (2 vials)/28 days	0.8 mL (2 vials)/28 days	0	0
	greater than 25 and less than or equal to 30 kg	6 mg/kg every 4 weeks	0	1.2 mL (3 vials)/28 days	0	0
	greater than 30 and less than or equal to 35 kg	1.5 mg/kg once every week	0	1.6 mL (4 vials)/28 days	0	0
	greater than 30 and less than or equal to 35 kg	3mg/kg every 2 weeks	0	0	1.4 mL (2 vials)/28 days	0
	greater than 30 and less than or equal to 35 kg	6 mg/kg every 4 weeks	0	0	1.4 mL (2 vials)/28 days	0
	greater than 35 and less than or equal to 40 kg	1.5 mg/kg once every week	0	1.6 mL (4 vials)/28 days	0	0

Module	Clinical Criteria for Approval					
	greater than 35 and less than or equal to 40 kg	3 mg/kg every 2 weeks	0	1.6 mL (4 vials)/28 days	0	0
	greater than 35 and less than or equal to 40 kg	6 mg/kg every 4 weeks	0	1.6 mL (4 vials)/28 days	0	0
	greater than 40 and less than or equal to 45 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	0	0
	greater than 40 and less than or equal to 45 kg	3 mg/kg every 2 weeks	2 mL (2 vials)/28 days	0	1.4 mL (2 vials)/28 days	0
	greater than 40 and less than or equal to 45 kg	6 mg/kg every 4 weeks	0	0.8 mL (2 vials)/28 days	0	1 mL (1 vial)/28 days
	greater than 45 and less than or equal to 50 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	0	0
	greater than 45 and less than or equal to 50 kg	3 mg/kg every 2 weeks	0	0	0	2 mL (2 vials)/28 days
	greater than 45 and less than or equal to 50 kg	6 mg/kg every 4 weeks	0	0	0	2 mL (2 vials)/28 days
	greater than 50 and less than or equal to 55 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	0	0
	greater than 50 and less than or	3 mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	1.4 mL (2 vials)/28 days	0

Module	Clinical Criteria for Approval					
	equal to 55 kg					
	greater than 50 and less than or equal to 55 kg	6 mg/kg every 4 weeks	0	0.8 mL (2 vials)/28 days	1.4 mL (2 vials)/28 days	0
	greater than 55 and less than or equal to 60 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	0	0
	greater than 55 and less than or equal to 60 kg	3 mg/kg every 2 weeks	0	2.4 mL (6 vials)/28 days	0	0
	greater than 55 and less than or equal to 60 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	0	2 mL (2 vials)/28 days
	greater than 60 and less than or equal to 65 kg	1.5 mg/kg once every week	0	0	2.8 mL (4 vials)/28 days	0
	greater than 60 and less than or equal to 65 kg	3 mg/kg every 2 weeks	2 mL (2 vials)/28 days	0.8 mL (2 vials)/28 days	1.4 mL (2 vials)/28 days	0
	greater than 60 and less than or equal to 65 kg	6 mg/kg every 4 weeks	0	1.6 mL (4 vials)/28 days	0	1 mL (1 vial)/28 days
	greater than 65 and less than or equal to 70 kg	1.5 mg/kg once every week	0	0	2.8 mL (4 vials)/28 days	0
	greater than 65 and less than or equal to 70 kg	3 mg/kg every 2 weeks	0	0	2.8 mL (4 vials)/28 days	0
	greater than 65 and less	6 mg/kg every 4 weeks	0	0.8 mL (2 vials)/28 days	0	2 mL (2 vials)/28 days

Module	Clinical Criteria for Approval					
	than or equal to 70 kg					
	greater than 70 and less than or equal to 75 kg	1.5 mg/kg once every week	0	3.2 mL (8 vials)/28 days	0	0
	greater than 70 and less than or equal to 75 kg	3 mg/kg every 2 weeks	0	1.6mL (4 vials)/28 days	1.4 mL (2 vials)/28 days	0
	greater than 70 and less than or equal to 75 kg	6 mg/kg every 4 weeks	0	0	0	3 mL (3 vials)/28 days
	greater than 75 and less than or equal to 80 kg	1.5 mg/kg once every week	0	3.2 mL (8 vials)/28 days	0	0
	greater than 75 and less than or equal to 80 kg	3 mg/kg every 2 weeks	0	3.2 mL (8 vials)/28 days	0	0
	greater than 75 and less than or equal to 80 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	2.8 mL (4 vials)/28 days	0
	greater than 80 and less than or equal to 85 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	0	2.8 mL (4 vials)/28 days	0
	greater than 80 and less than or equal to 85 kg	3 mg/kg every 2 weeks	0	0	1.4 mL (2 vials)/28 days	2 mL (2 vials)/28 days
	greater than 80 and less than or equal to 85 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days		3 mL (3 vials)/28 days

Module	Clinical Criteria for Approval					
	greater than 85 and less than or equal to 90 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	0	2.8 mL (4 vials)/28 days	0
	greater than 85 and less than or equal to 90 kg	3 mg/kg every 2 weeks	0	1.6 mL (4 vials)/28 days	0	2 mL (2 vials)/28 days
	greater than 85 and less than or equal to 90 kg	6 mg/kg every 4 weeks	0	0.8 mL (2 vials)/28 days	2.8 mL (4 vials)/28 days	0
	greater than 90 and less than or equal to 95 kg	1.5 mg/kg once every week	0	0	0	4 mL (4 vials)/28 days
	greater than 90 and less than or equal to 95 kg	3 mg/kg every 2 weeks	0	2.4 mL (6 vials)/28 days	1.4 mL (2 vials)/28 days	0
	greater than 90 and less than or equal to 95 kg	6 mg/kg every 4 weeks	0	0	2.8 mL (4 vials)/28 days	1 mL (1 vial)/28 days
	greater than 95 and less than or equal to 100 kg	1.5 mg/kg once every week	0	0	0	4 mL (4 vials)/28 days
	greater than 95 and less than or equal to 100 kg	3 mg/kg every 2 weeks	0	0	0	4 mL (4 vials)/28 days
	greater than 95 and less than or equal to 100 kg	6 mg/kg every 4 weeks	0	0	0	4 mL (4 vials)/28 days
	greater than 100 and less than or	1.5 mg/kg once every week	0	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0

Module	Clinical Criteria for Approval					
	equal to105 kg					
	greater than 100 and less than or equal to 105 kg	3 mg/kg every 2 weeks	0	0	4.2 mL (6 vials)/28 days	0
	greater than 100 and less than or equal to 105 kg	6 mg/kg every 4 weeks	0	0	4.2 mL (6 vials)/28 days	0
	greater than 105 and less than or equal to 110 kg	1.5 mg/kg once every week	0	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0
	greater than 105 and less than or equal to 110 kg	3 mg/kg every 2 weeks	0	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0
	greater than 105 and less than or equal to 110 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	0	4 mL (4 vials)/28 days
	greater than 110 and less than or equal to 115 kg	1.5 mg/kg once every week	0	4.8 mL (12 vials)/28 days	0	0
	greater than 110 and less than or equal to 115 kg	3 mg/kg every 2 weeks	0	3.2 mL (8 vials)/28 days	1.4 mL (2 vials)/28 days	0
	greater than 110 and less than or equal to 115 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	4.2 mL (6 vials)/28 days	0
	greater than 115 and less than or equal to 120 kg	1.5 mg/kg once every week	0	4.8 mL (12 vials)/28 days	0	0
	greater than 115 and ≤less	3 mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	0	4 mL (4 vials)/28 days

Module	Clinical Criteria for Approval					
	than or equal to120 kg					
	greater than 115 and less than or equal to 120 kg	6 mg/kg every 4 weeks	0	0.8 mL (2 vials)/28 days	0	4 mL (4 vials)/28 days
	greater than 120 and less than or equal to 125 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0
	greater than 120 and less than or equal to 125 kg	3 mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	4.2 mL (6 vials)/28 days	0
	greater than 120 and less than or equal to 125 kg	6 mg/kg every 4 weeks	0	0	0	5 mL (5 vials)/28 days
	greater than 125 and less than or equal to130 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0
	greater than 125 and less than or equal to 130 kg	3 mg/kg every 2 weeks	0	3.2 mL (8 vials)/28 days	0	2 mL (2 vials)/28 days
	greater than 125 and less than or equal to 130 kg	6 mg/kg every 4 weeks	0	1.2 mL (3 vials)/28 days	0	4 mL (4 vials)/28 days
	greater than 130 and less than or equal to 135 kg	1.5 mg/kg once every week	0	0	5.6 mL (8 vials)/28 days	0
	greater than 130 and less than or equal to 135 kg	3 mg/kg every 2 weeks	0	0	1.4 mL (2 vials)/28 days	4 mL (4 vials)/28 days

Module	Clinical Criteria for Approval					
	greater than 130 and less than or equal to 135 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	0	5 mL (5 vials)/28 days
	greater than 135 and less than or equal to 140 kg	1.5 mg/kg once every week	0	0	5.6 mL (8 vials)/28 days	0
	greater than 135 and less than or equal to 140 kg	3 mg/kg every 2 weeks	0	1.6 mL (4 vials)/28 days	0	4 mL (4 vials)/28 days
	greater than 135 and less than or equal to 140 kg	6 mg/kg every 4 weeks	0	0	5.6 mL (8 vials)/28 days	0
	greater than 140 and less than or equal to 145 kg	1.5 mg/kg once every week	0	3.2 mL (8 vials)/28 days	2.8 mL (4 vials)/28 days	0
	greater than 140 and less than or equal to 145 kg	3 mg/kg every 2 weeks	0	1.6 mL (4 vials)/28 days	4.2 mL (6 vials)/28 days	0
	greater than 140 and less than or equal to 145 kg	6 mg/kg every 4 weeks	0	0.8 mL (2 vials)/28 days		5 mL (5 vials)/28 days
	greater than 145 and less than or equal to 150 kg	1.5 mg/kg once every week	0	3.2 mL (8 vials)/28 days	2.8 mL (4 vials)/28 days	0
	greater than 145 and less than or equal to 150 kg	3 mg/kg every 2 weeks	0	0	0	6 mL (6 vials)/28 days
	greater than 145 and less than or	6 mg/kg every 4 weeks	0	0	0	6 mL (6 vials)/28 days

Module	Clinical Criteria for Approval					
	equal to 150 kg					
	greater than 150 and less than or equal to 155 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	0	5.6 mL (8 vials)/28 days	0
	greater than 150 and less than or equal to 155 kg	3 mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	1.4 mL (2 vials)/28 days	4 mL (4 vials)/28 days
	greater than 150 and less than or equal to 155 kg	6 mg/kg every 4 weeks	1 mL (1 vial)/28 days	0	0	6 mL (6 vials)/28 days
	greater than 155 and less than or equal to 160 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	0	5.6 mL (8 vials)/28 days	0
	greater than 155 and less than or equal to 160 kg	3 mg/kg every 2 weeks	2 mL (2 vials)/28 days	0	0	6 mL (6 vials)/28 days
	greater than 155 and less than or equal to 160 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	0	6 mL (6 vials)/28 days
	greater than 160 and less than or equal to 165 kg	1.5 mg/kg once every week	0	0	2.8 mL (4 vials)/28 days	4 mL (4 vials)/28 days
	greater than 160 and less than or equal to 165 kg	3 mg/kg every 2 weeks	0	2.4 mL (6 vials)/28 days	4.2 mL (6 vials)/28 days	0
	greater than 160 and less than or equal to 165 kg	6 mg/kg every 4 weeks	1 mL (1 vial)/28 days	0	1.4 mL (2 vials)/28 days	5 mL (5 vials)/28 days
	greater than 165 and less	1.5 mg/kg once	0	0	2.8 mL (4 vials)/28 days	4 mL (4 vials)/28 days

Module	Clinical Criteria for Approval					
	than or equal to 170 kg	every week				
	greater than 165 and less than or equal to 170 kg	3 mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	0	6 mL (6 vials)/28 days
	greater than 165 and less than or equal to 170 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	1.4 mL (2 vials)/28 days	5 mL (5 vials)/28 days
	greater than 170 and less than or equal to 175 kg	1.5 mg/kg once every week	0	2.4 mL (4 vials)/28 days	5.6 mL (8 vials)/28 days	0
	greater than 170 and less than or equal to 175 kg	3 mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	4.2 mL (6 vials)/28 days	2 mL (2 vials)/28 days
	greater than 170 and less than or equal to 175 kg	6 mg/kg every 4 weeks	0	0	0	7 mL (7 vials)/28 days
	greater than 175 and less than or equal to 180 kg	1.5 mg/kg once every week	0	2.4 mL (4 vials)/28 days	5.6 mL (8 vials)/28 days	0
	greater than 175 and less than or equal to 180 kg	3 mg/kg every 2 weeks	2 mL (2 vials)/28 days	0	2.8 mL (4 vials)/28 days	4 mL (4 vials)/28 days
	greater than 175 and less than or equal to 180 kg	6 mg/kg every 4 weeks	1 mL (1 vial)/28 days	0	0	7 mL (7 vials)/28 days
	greater than 180 and less than or equal to 185 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	0	2.8mL (4 vials)/28 days	4 mL (4 vials)/28 days

Module	Clinical Criteria for Approval					
	greater than 180 and less than or equal to 185 kg	3 mg/kg every 2 weeks	0	0	1.4 mL (2 vials)/28 days	6 mL (6 vials)/28 days
	greater than 180 and less than or equal to 185 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	0	7 mL (7 vials)/28 days
	greater than 185 and less than or equal to 190 kg	1.5 mg/kg once every week	4 mL (4 vials)/28 days	0	2.8mL (4 vials)/28 days	4 mL (4 vials)/28 days
	greater than 185 and less than or equal to 190 kg	3 mg/kg every 2 weeks	0	0.8 mL (2 vials)/28 days	2.8 mL (4 vials)/28 days	4 mL (4 vials)/28 days
	greater than 185 and less than or equal to 190 kg	6 mg/kg every 4 weeks	1 mL (1 vial)/28 days	0	1.4 mL (2 vials)/28 days	6 mL (6 vials)/28 days
	greater than 190 and less than or equal to 195 kg	1.5 mg/kg once every week	0	0	0	8 mL (8 vials)/28 days
	greater than 190 and less than or equal to 195 kg	3 mg/kg every 2 weeks	2 mL (2 vials)/28 days	0	1.4 mL (2 vials)/28 days	6mL (6 vials)/28 days
	greater than 190 and less than or equal to 195 kg	6 mg/kg every 4 weeks	0	0.4 mL (1 vial)/28 days	1.4 mL (2 vials)/28 days	6 mL (6 vials)/28 days
	greater than 195 and less than or equal to 200 kg	1.5 mg/kg once every week	0	0	0	8 mL (8 vials)/28 days
	greater than 195 and less than or	3 mg/kg every 2 weeks	0	0	0	8 mL (8 vials)/28 days

Module	Clinical Criteria for Approval
	<table><tr><td>equal to 200 kg</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>greater than 195 and less than or equal to 200 kg</td><td>6 mg/kg every 4 weeks</td><td>0</td><td>0</td><td>0</td><td>8 mL (8 vials)/28 days</td></tr><tr><td>greater than 200 kg</td><td colspan="5">Approve quantity requested if appropriate for patient weight and dosing interval</td></tr><tr><td colspan="6"></td></tr><tr><td colspan="6">The 60 mg, 105 mg and/or 150 mg vials are the same concentration (150 mg/mL) and may be combined for dosing</td></tr><tr><td colspan="6">The 30 mg vials (30mg/mL) should NOT be combined in the same injection with the 60 mg, 105 mg, or 150 mg vials and should be given as a separate injection</td></tr></table>