CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761367Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761367
PDUFA Goal Date	October 13, 2024
Nexus TTT #	2023-5415
Reviewer Name	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	October 9, 2024
Subject	Evaluation of Need for a REMS
Established/Proper Name	Garadacimab-gxii
Trade Name	Andembry
Name of Applicant	CSL Behring LLC
Therapeutic Class	Activated Factor XII (FXIIa) inhibitor (monoclonal antibody)
Formulation(s)	Injection: 200 mg/1.2 mL available as a single-dose prefilled autoinjector or single-dose prefilled syringe with needle safety device
Dosing Regimen	Initial loading dose of 400 mg (two 200 mg injections) administered subcutaneously on the first day of treatment followed by a maintenance dose of 200 mg administered subcutaneously monthly

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Andembry (garadacimab) is necessary to ensure the benefits outweigh its risks. CSL Behring, LLC (hereafter referred to as the Applicant) submitted a Biologics Licensing Application (BLA) 761367 for garadacimab with the proposed indication for prophylaxis to prevent attacks of hereditary angioedema in adult and pediatric patients (aged 12 years and older). This application is under review in the Division of Pulmonology, Allergy, and Critical Care (DPACC). During the course of the review, the Agency revised the indication to the following: for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. The Applicant did not submit a REMS or risk management plan with this application.

The recommended regulatory action is a Complete Response due to deficiencies in facility inspection, microbiology, and product quality. None of the deficiencies are related to safety or efficacy. Based on the available clinical data, DRM and DPACC agree that a REMS is not needed to ensure the benefits of garadacimab outweigh its risks. The benefit of garadacimab for prophylaxis to prevent HAE attacks was demonstrated in a single, pivotal phase 3, double-blind, placebo-controlled trial which showed a statistically significant and clinically meaningful reduction in the monthly HAE attack rates compared to placebo. The Prescribing Information and Patient Package Insert will communicate the available safety data for prescribers and patients. Final labeling negotiations will not be complete until after the Applicant responds to the Complete Response. The likely prescribers for garadacimab are allergists and clinical immunologists who have experience with HAE and prescribing other similar therapies. The safety profile was similar to other products that act on the kallikrein-bradykinin pathway and there does not appear to be any new or unexpected serious risks. Based on the available safety and efficacy data, risk mitigation beyond labeling is not required.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Andembry (garadacimab) is necessary to ensure the benefits outweigh its risks. CSL Behring, LLC (hereafter referred to as the Applicant) submitted a Biologics Licensing Application (BLA) 761367 for garadacimab with the proposed indication for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients (aged 12 years and older).[1] This application is under review in the Division of Pulmonology, Allergy, and Critical Care (DPACC). The Applicant did not submit a REMS or risk management plan with this application.

2. Background

2.1. Product Information

Andembry (garadacimab-gxii, hereafter referred to as garadacimab), a new molecular entity[a], is an activated Factor XII inhibitor proposed to be indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients (aged 12 years and older).[1] Garadacimab is an inhibitor of activated Factor XII that binds to the catalytic domain of activated Factor XII (FXIIa βFXIIa) and inhibits its catalytic activity. Factor XII is the first factor activated in the contact activation pathway and initiates the inflammatory bradykinin-producing kallikrein-kinin system. The inhibition of FXIIa decreases the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks, thus reducing the cascade of events leading to an HAE attack.[2]

Garadacimab is proposed to be supplied as a 200 mg/1.2 mL solution for injection available in a single-dose prefilled autoinjector and a single-dose prefilled glass syringe with a needle safety device. The proposed dose is an initial loading dose of 400 mg (two 200 mg/1.2 mL injections administered subcutaneously) on the first day of treatment, followed by maintenance dose of 200 mg administered subcutaneously every month as chronic therapy.[2,b] Garadacimab will likely primarily be used in the outpatient setting and administered by the patient or a caregiver. Garadacimab is not currently approved in any other jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761367 relevant to this review:

- **04/30/2020:** Orphan drug designation granted for IND 139936 for the treatment of bradykinin-mediated angioedema.
- **12/14/2021:** Fast track designation granted for IND 139936 for hereditary angioedema.
- **06/29/2023:** BLA 761367 submission received.[3]
- **08/28/2023**: The Agency issued a Refuse to File Letter because the results of the Rabbit Pyrogen Test were not available for review.[4]
- **10/13/2023**: The Applicant resubmitted BLA 781367 for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients (aged 12 years and older).[1]
- **04/05/2024:** A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there were no major safety concerns identified to date that require a REMS.[5]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- **07/09/2024**: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed Applicant that there were no major safety concerns identified to date that require a REMS.[6]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hereditary angioedema (HAE) is a serious, rare, autosomal dominant genetic disorder characterized by intermittent, unpredictable attacks of angioedema, which most often affects the skin, upper respiratory tract, and gastrointestinal tract.[7] Symptoms and severity vary depending on the affected sites and may range from swelling of the affected tissues; nausea, vomiting, and abdominal pain; to life-threatening laryngeal edema that may cause fatal airway obstruction.[7,8,c] HAE is a rare disease; the exact prevalence for HAE is not known and estimates vary widely in the literature.[9] The prevalence of type I and II HAE is estimated to be 1 per 50,000 to 1 per 100,000, suggesting approximately 6,000 to 10,000 individuals with HAE in the United States.[8,10,d]

The pathophysiology of HAE typically involves excessive production of the vasoactive peptide bradykinin.[11] The majority of cases are caused by mutations of *SERPING1*, the gene for complement 1 esterase inhibitor (C1-INH), the major regulator of the contact activation pathway.[8,12,13] Mutations of the *SERPING1* gene cause a deficiency or dysfunction of C1-INH. This leads to the dysregulation of the contact system, a plasma protease cascade initiated by factor XII that activates both the procoagulant intrinsic coagulation pathway and proinflammatory kallikrein-kinin pathways. Due to the deficiency or dysfunction of C1-INH in patients with HAE, the kallikrein activity modulated by C1-INH continues uncontrolled, leading to overall excess bradykinin release. Bradykinin then increases vascular permeability that produces the characteristic swelling seen in acute HAE attacks.[8,12,13]

HAE with C1-INH deficiency or dysfunction can be further categorized into two types. Type I comprises approximately 85% of cases and is caused by low production of normal C1-INH protein. Type II makes up approximately 15% and is caused by normal production levels of dysfunctional C-INH. A third type, referred to as HAE with normal C1-INH (or previously Type III) has been identified but is thought to be caused by a different mutations, including a mutation in the coagulation factor XII gene (F12) gene, but this type is not yet well understood.[8,14] HAE with normal C1-INH is very rare (<1%) and occurs predominantly in females with normal levels and function of C1-INH.[8,14]

The majority of patients will experience their first HAE attack in childhood or adolescence and it is generally a lifelong condition.[7,12,15] Attack frequency typically worsens during puberty. The frequency of attacks varies and in untreated patients can range from weekly to 1-2 episodes per year.[7] The

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

attacks are self-limited and swelling will resolve without treatment in 2-5 days; however, laryngeal edema can cause fatal asphyxiation. Laryngeal attacks account for 0.9% of all attacks; however, more than 50% of patients have a laryngeal attack in their lifetime.[12] The attacks may be triggered by stress, trauma, surgery/procedures, infections, medications, hormonal changes, or have no identifiable trigger. Prior to the availability of treatments, up to one-third of patients died due to asphyxiation. Effective therapies have improved the prognosis; however, serious fatal attacks may still occur.[7] Due to the unpredictable nature and potential severity of HAE attacks, it has a high disease burden and a significant negative impact on patient's quality of life.[9]

3.2. Description of Current Treatment Options

There is no cure for HAE. According to guidelines published in 2020 by the United States Hereditary Angioedema Association Medical Advisory Board (US HAEA MAB), the core approach for managing HAE include availability of on-demand acute therapy for all patients, early treatment to prevent attack progression; treatment of attacks regardless of the site of swelling; and incorporation of an agent for long-term prophylaxis.[8] Approved on-demand therapies include the following: human plasma derived C1-INH, including Cinryze and Berinert; recombinant C1-INH including Ruconest, the bradykinin B2 receptor antagonist, Firazyr (icatibant); and the kallikrein inhibitor, Kalbitor (ecallantide[e]).

The aim of preventative treatment is to minimize the number and severity of HAE attacks. FDA-approved treatments to prevent HAE attacks in the United States consist of C1-INH (Cinryze and Haegarda), monoclonal antibody kallikrein inhibitor (Takhzyro [lanadelumab]), a small molecule plasma kallikrein inhibitor (Orladeyo [erotralstat]), and attenuated androgen (danazol). Refer to Section 10.2, Appendix 1 for a table summarizing the currently approved options to prevent HAE attacks. None of the products approved to prevent HAE attacks were approved with a REMS. Limitations in current therapies relate to tolerability, side effects, and route of administration. C1-INH therapies have a short half-life, making it necessary to administer either intravenously or subcutaneously every three to four days. Takhzyro (lanadelumab) is available as a subcutaneous injection and has a longer duration of action allowing less frequent dosing (every 2 weeks). In 2020, Orladeyo (berotralstat), the first oral option for prophylaxis was approved; however, higher doses may increase the risk of QTc prolongation. Androgens are associated with side effects that limit tolerability and are considered second-line. Despite the availability of long-term prophylaxis, most patients still experience breakthrough attacks. There is an unmet need for additional options that are effective, safe, and with improved ease of administration (routes and dosing intervals).

[e]Due to the risk of anaphylaxis, Kalbitor was approved with a REMS consisting of a communication plan and timetable for submission of assessments on December 1, 2009. This REMS was eliminated on April 10, 2013 as the communication plan was complete and the REMS met its goals.

4. Benefit Assessment

The pivotal trial supporting the efficacy of garadacimab as prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and adolescent patients 12 years of age and older was CSL312_3001 (National Clinical Trial [NCT] 04656418; hereafter referred to as Trial 3001).

Trial 3001 was a multicenter, double-blind, randomized, placebo-controlled, parallel-arm study. The trial consisted of a screening period (up to 1 month), a run-in period (up to 2 months) to confirm baseline attack rate, a treatment period (6 months), and a follow up period (2 months). Subjects who completed the treatment period were eligible to roll into a phase 3b open-label extension trial (CSL312_3002).

Eligible subjects for Trial 3001 were 12 years or older with a clinically confirmed C1-INH HAE Type I or Type II diagnosis. Subjects with Type III HAE were excluded). Subjects needed to have experienced 3 or greater HAE attacks during the 3 months prior to screening to be enrolled and enter the run-in period. During the run-in period, subjects needed to experience at least an average of 1 HAE attack per month (at least 2 HAE attacks). Sixty-four subjects were randomized (3:2) to garadacimab 200 mg monthly after an initial 400 mg loading dose (N=39) or placebo (N=25) for 6 months.[f] Subjects were required to discontinue other prophylactic HAE medications prior to entering the study. All patients were allowed to use on-demand medications for the treatment of HAE attacks during the trial.

The primary efficacy endpoint was the time normalized number of HAE attacks per month compared to placebo during the treatment period. The review team concluded that this was a well-established and clinically meaningful endpoint that has served as the basis of approval for this indication for other products.[10] Secondary endpoints included the percent reduction in the time-normalized number of HAE attacks per month compared to placebo, the time-normalized number of HAE attacks requiring on-demand therapy per month, and the time-normalized number of moderate or severe HAE attacks per month.

The study population was primarily female (59.4%), White (85.9%) with an average age of 41.2 years (range 12 to 69 years; N=6 <17 years). The majority of subjects had Type I HAE (87.5%), 59.4% of subjects had a history of laryngeal attacks, and 32.8% were on prior prophylaxis. There was a statistically significant reduction in the least squares (LS) mean HAE attack rate per month in the garadacimab arm compared to placebo (see Table 1).

[f] A total of 65 subjects were randomized, however, one subject was randomized to placebo in error and did not receive study treatment. The ITT and safety populations were comprised of 64 participants (39 on garadacimab and 25 on placebo). The PP population was comprised of 63 participants (39 on garadacimab and 24 on placebo), where one participant on placebo had a major protocol deviation (missed visit and then withdrew consent)

Table 1. Primary Efficacy Results (ITT population) for Monthly HAE Attack Rate in Trial 3001[2]

	Garadacimab (N=39)	Placebo (N=25)
Monthly HAE attack rate		
LS mean (95% CI)	0.22 (0.11, 0.47)	2.07 (1.49, 2.87)
Percent reduction relative to placebo (95% CI)	89.2 (75.6, 95.2)	
P-value	<0.001	

CI=confidence interval; HAE=hereditary angioedema; ITT=intent-to-treat; LS=least squares

The secondary endpoints also demonstrated benefit for garadacimab. There was a 91.2% reduction with garadacimab relative to placebo in the monthly rate of HAE attacks requiring on-demand therapy and a 93.6% reduction with garadacimab relative to placebo in the monthly rate of moderate or severe HAE attacks.[2] The proportion of patients with a ≥50%, ≥70%, ≥90%, and 100% reduction in the monthly HAE attack rate during treatment compared to the 2-month period prior to treatment was 95%, 92%, 74%, and 62% on garadacimab and 33%, 17%, 8%, and 0% on placebo, respectively.[2]

The review team concluded that substantial evidence of efficacy was demonstrated for garadacimab in adults and adolescents 12 years of age and older with Type I or Type II HAE based on a single, adequate and well-controlled trial (Trial 3001). The review team concluded data from Trial 3001 demonstrated a statistically significant and clinically meaningful reduction in the monthly HAE attack rates compared to placebo.[10,g] In addition, garadacimab also demonstrated benefit in clinically meaningful pre-specified secondary endpoints including reductions in the number of moderate to severe attacks and the number of monthly HAE attacks requiring acute on-demand treatment. Confirmatory evidence was based on mechanistic data which included the well-established pathophysiology of HAE across all age groups and the mechanism of action of garadacimab. The review team recommends approval of garadacimab for the prophylaxis of HAE attacks in adults and adolescents 12 years of age and older based on the data available.[10,h]

5. Risk Assessment & Safe-Use Conditions

The safety population is comprised of subjects with HAE in the placebo-controlled pivotal phase 3 study (Trial 3001) and CSL312_3002 (NCT04739059; hereafter referred to as Trial 3002), an open-label study evaluating the long-term safety and efficacy of once monthly garadacimab Additional supportive data

[g] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[h] The review team concluded that although adolescents were included in the pivotal trial (n=6), the efficacy and safety of adolescent patients 12 to <18 years was primarily based on extrapolation from adults and matching pharmacokinetic exposure.

from Trial CSL312_2001 (NCT03712228; hereafter referred to as Trial 2001), a phase 2, multicenter, randomized, placebo-controlled, parallel arm, dose ranging study was reviewed.[10,16]

The safety population included 161 adult and adolescent subjects aged 12 years and older with HAE from the pivotal study and the open label study who received at least one dose of garadacimab 200 mg subcutaneously. Among the 161 subjects, 77% were exposed for at least one year. The median duration of treatment was 14 months.[2]

The most common adverse events in Trial 3001 with incidence ≥7% and occurred more frequently than placebo included nasopharyngitis (n=8; 20.5%) and abdominal pain (n=3; 7.7%). [2,10]

There were no deaths reported in the clinical trials.[10,16] In Trial 3001, there was one subject in the garadacimab-treated group with a serious adverse event[i] of laryngeal attack requiring hospitalization.[j] The review team commented that many patients continue to experience HAE attacks despite prophylaxis therapy and the event is likely due to the underlying condition rather than an adverse reaction related to garadacimab treatment.[10] There were no treatment-emergent adverse events that led to treatment discontinuation in Trial 3001.[10,16] In the open-label extension, Trial 3002, there were three SAEs reported (HAE attack [n=1]; COVID-19 infections [n=2]); however, the review team concluded these were unlikely to be related to garadacimab treatment.[10] There were three adverse events that led to treatment discontinuation (pregnancy [n=1]; mood swing [n=1], and injection site reaction [n=1]).[10]

Factor XII is the first component of the intrinsic coagulation pathway and is typically activated on contact with substances that reflect tissue injury or damage. Inhibition of Factor XII by garadacimab has the potential to cause abnormal coagulation. Therefore, bleeding events and thrombolic events were pre-specified adverse events of special interest and actively monitored in Trial 3001 and 3002. These trials excluded subjects with clinically significant bleeding due to coagulopathy or thrombotic disorders.[16] There were no serious or life-threatening bleeding or thromboembolic events and no subjects discontinued treatment due to bleeding or thrombolic events. There was a greater number of subjects with prolonged aPTT and PT/INR measurements in the garadacimab group compared to placebo; however, these laboratory abnormalities were not associated with clinical bleeding events.[10] Prolongation of coagulation markers is also observed in other approved HAE therapies that target the intrinsic coagulation pathway. The review team has proposed communicating that garadacimab may

[i] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[j] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

cause prolonged coagulation tests in the Prescribing Information, section 6 Adverse Reactions and 7.1 Drug-Interference with Laboratory Test.[2,10]

Another pre-specified adverse event of special interest was hypersensitivity as it is commonly associated with injection products and the therapeutic class of monoclonal antibodies. There were no cases of hypersensitivity in Trial 3001 or 3002. The review team concluded the risk of hypersensitivity is theoretical and did not recommend inclusion in labeling.[2,10]

The review team concluded the overall safety profile is acceptable at the dose of 200 mg administered subcutaneously every month patients with HAE 12 years of age and older.[10]

6. Expected Postmarket Use

Garadacimab is likely to be prescribed by allergists and clinical immunologists who have experience treating patients with HAE. Garadacimab is expected to be used primarily in the outpatient setting as chronic therapy to prevent episodes. Garadacimab is proposed as a subcutaneous injection that may be self-administered by the patient or a caregiver in the outpatient setting. Healthcare providers should provide proper training to patients and/or caregivers on the administration according to the Instructions for Use included in product labeling.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for garadacimab beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The review team recommends approval of garadacimab on the basis of the efficacy and safety information currently available.

Hereditary angioedema is a rare, serious, autosomal dominant disease that results from excessive production of bradykinin. The disease is characterized by recurrent episodes of angioedema that most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. Attacks are self-limited but range in severity from cutaneous swelling to life-threatening laryngeal edema that may cause fatal asphyxiation. HAE attacks are unpredictable and severity ranges from mild to fatal; therefore, it has a high disease burden and negatively impacts patient's quality of life. On-demand therapies are approved to treat HAE attacks; however, prevention of attacks is an important strategy. Although prophylaxis treatment options are approved for HAE, no option eliminates HAE attacks and there are differences in tolerability, administration, and risks across the available products. There remains an unmet need for safe and effective prevention options.

The benefits of garadacimab for prophylaxis to prevent HAE attacks were demonstrated in single, adequate and well-controlled trial (Trial 3001) which showed a statistically significant and clinically meaningful reduction in the monthly HAE attack rates compared to placebo. In addition, garadacimab also demonstrated benefit in clinically meaningful pre-specified secondary endpoints including

reductions in the number of moderate to severe attacks and the number of monthly HAE attacks requiring acute on-demand treatment.

There were no major safety concerns associated with garadacimab based on the available data. The Prescribing Information and Patient Package Insert will communicate the available safety data for prescribers and patients, respectively. The likely prescribers for garadacimab are allergists and clinical immunologists who have experience with HAE and prescribing other similar therapies. The safety profile was similar to other products that act on the kallikrein-bradykinin pathway and there does not appear to be any new or unexpected serious risks.

The recommended regulatory action is a Complete Response due to deficiencies in facility inspection, microbiology, and product quality.[17] None of the deficiencies are related to safety or efficacy. Based on the available safety and efficacy data, this reviewer is not recommending a REMS and concludes that risk mitigation beyond labeling is not required. Final labeling negotiations will not be complete until after the Applicant responds to the Complete Response.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for garadacimab to ensure the benefits outweigh the risks. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

1. CSL Behring LLC. Original BLA resubmission for garadacimab, BLA 761367 (sequence 0009). October 13, 2023.

2. CSL Behring LLC. Prescribing Information for garadacimab, BLA 761367. Agency edits as of August 29, 2024.

3. CSL Behring LLC. Original BLA submission (Orig-1) for garadacimab, BLA 761367 (sequence 0001). June 29, 2023.

4. Won K, Stone K. Refusal to File Letter for garadacimab, BLA 761367 August 28, 2023.

5. Food and Drug Administration. Division of Pulmonology, Allergy, and Critical Care. Mid-Cycle Communication Agenda for garadacimab, BLA 761367. April 5, 2024.

6. Food and Drug Administration. Division of Pulmonology, Allergy, and Critical Care. Late-Cycle Communication Agenda for garadacimab, BLA 761367. July 9, 2024.

7. Zuraw B, Farkas H. Hereditary angioedema: Epidemiology, clinical manifestations, exacerbating factors, and prognosis. In: Saini S, Feldweg A, eds. *UptoDate*. Waltham, MA.

8. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract.* 2021;9(1):132-150.e133.

9. Lumry WR, Settipane RA. Hereditary angioedema: Epidemiology and burden of disease. *Allergy Asthma Proc.* 2020;41(Suppl 1):S08-s13.

10. Food and Drug Administration. Center for Drug Evaluation and Research. Division of Pulmonology, Allergy, and Critical Care. Integrated Review: Garadacimab, BLA 761367. October 7, 2024.

11. Wedner HJ. Hereditary angioedema: Pathophysiology (HAE type I, HAE type II, and HAE nC1-INH). *Allergy Asthma Proc.* 2020;41(Suppl 1):S14-s17.

12. Busse PJ, Christiansen SC. Hereditary Angioedema. *New England Journal of Medicine.* 2020;382(12):1136-1148.

13. Zuraw B, Farkas H. Hereditary angioedema (due to C1 inhibitor deficiency): Pathogenesis and diagnosis. In: Saini S, Feldweg A, eds. *UptoDate*. Waltham, MA.

14. Zuraw B, Bork K. Hereditary angioedema with normal C1 inhibitor. In: Saini S, Feldweg A, eds. *UptoDate*. Waltham, MA.

15. Pancholy N, Craig T. Hereditary angioedema in children: a review and update. *Curr Opin Pediatr.* 2019;31(6):863-868.

16. CSL Behring LLC. Summary of Clinical Safety for garadacimab, BLA 761367 (sequence 0009). October 13, 2023.

17. Zhang L, Dharmasena M, Wang Y. Office of Pharmaceutical Quality. BLA 761367 Quality Executive Summary. August 26, 2024.

18. Danazol. Prescribing Information. DailyMed. National Library of Medicine. Last Revised March 2023. Available from: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=55ad6325-16f6-4f0c-a1dc-734847052d0b. Accessed December 27, 2023.

19. Cinryze (C1 Esterase Inhibitor [Human])Prescribing information. Takeda Pharmaceuticals USA. Lexington, MA. Last Revised March 2022. Available at: https://www.fda.gov/media/75907/download?attachment. Accessed December 27, 2023.

20. Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]), Prescribing information. CSL Behring LLC, Kankakee, IL. Last Revised September 2020. Available at: https://www.fda.gov/media/105611/download?attachment. Accessed December 27, 2023.

21. Takhzyro (lanadelumab-flyo). Prescribing information. Takeda Pharmaceuticals USA. Lexington, MA. Last Revised February 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761090s010lbl.pdf. Accessed December 27, 2023.

22. Orladeyo (berotralstat) Prescribing information. BioCryst Pharmaceuticals, Inc. Durham, NC. Last Revised November 2023. Available at: https://www.biocryst.com/wp-content/uploads/ORLADEYO_USPI.pdf Accessed December 27, 2023.

10.2. FDA-approved treatments for prophylaxis to prevent attacks of hereditary angioedema[18-22]

Product Trade Name (Generic), Year of Approval	Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
Danazol, 1976	For the prevention of attacks of angioedema of all types (cutaneous, abdominal, laryngeal) in males and females[k]	Starting dose 200 mg by mouth two to three times daily Individualize dose based on clinical response, can decrease by 50% or less at intervals of one to three months or longer depending on attacks May be increased up to 200 mg in event of an attack	Boxed Warning Pregnancy, thromboembolic events, hepatic events, intracranial hypertension Contraindications Undiagnosed abnormal genital bleeding, markedly impaired hepatic, renal or cardiac function, pregnancy, breastfeeding, porphyria, androgen dependent tumor, active thrombosis or thromboembolic disease and history of events, and hypersensitivity to product Warnings and Precautions Blood lipid changes, androgenic effects, fluid retention, use with caution in patients with diabetes mellitus, hepatic dysfunction (increased transaminases), exacerbation of acute intermittent porphyria	Labeling Boxed Warning, Contraindications, Warnings and Precautions

[k] Additional FDA-approved indication for endometriosis

Cinryze (C1-esterase inhibitor [human]), 2008	For routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years of age and older) with HAE	Adults and adolescents (12 years and above) 1000 to 2000 international units intravenous (IV) every 3 or 4 days Children (6 to 11 years) 500 to 1000 IU, intravenous (IV)P every 3 or 4 days	Contraindication Life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product Warnings and Precautions Hypersensitivity reactions, thromboembolic events, transmissible infectious agents (blood product)	Labeling Contraindications, Warnings and Precautions, Patient Labeling-Patient Product Infection
Haegarda (C1-esterase inhibitor [human]), 2017	For routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older.	60 IU/kg subcutaneous injection every 3 or 4 days	Contraindication life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or its excipients Warnings and Precautions Hypersensitivity reactions, thromboembolic events, transmissible infectious agents (blood product)	Labeling Contraindications, Warnings and Precautions, Patient Labeling-Patient Product Infection
Takhzyro (lanadelumab-flyo), 2018	For prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 2 years and older.	Adult and pediatric patients 12 years and older 300 mg subcutaneously every 2 weeks, if well controlled for greater than 6 months can consider every administering every 4 weeks Pediatric patients 2 to less than 12 years 150 mg subcutaneously every 2 weeks, if well	Warnings and Precautions Hypersensitivity	Labeling Warnings and Precautions, Patient Information and Instructions for Use

		controlled for greater than 6 months can consider every administering every 4 weeks <u>Pediatric patients 2 to less than 6 years</u> 150 mg subcutaneously every 4 weeks		
Orladeyo (berotralstat), 2020	For prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older[l]	150 mg capsule taken orally once daily with food	<u>Warnings and Precautions</u> Risk of QT prolongation with higher than recommended doses (greater than 150 mg once daily)	<u>Labeling</u> Warnings and Precautions, Patient Information and Instructions for Use

[l] Indication includes a Limitations of Use statement: "The safety and effectiveness of ORLADEYO for the treatment of acute HAE attacks have not been established. ORLADEYO should not be used for treatment of acute HAE attacks. Additional doses or doses of ORLADEYO higher than 150 mg once daily are not recommended due to the potential for QT prolongation"

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/s/

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