

Garadacimab-gxii (ANDEMBRY)

National Drug Monograph

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VA Pharmacy Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA PRESCRIBING INFORMATION¹

Description / MOA	Activated Factor XII (FXIIa) inhibitor and a recombinant, fully human, monoclonal antibody (IgG4/-light chain). It binds to the catalytic domain of activated Factor XII (FXIIa and FXIIa) and inhibits its activity which decreases the activation of prekallikrein to kallikrein and the generation of bradykinin, which is the mediator of inflammation and swelling in HAE attacks.
Indication Under Review	Prophylaxis of hereditary angioedema (HAE) attacks in adult and pediatric patients aged 12 years and older.
Dosage Regimen	Initial loading dose of 400 mg (delivered as two 200 mg injections) subcutaneously (subQ); followed by maintenance dosage of 200 mg subQ every month.
Dosage Forms Under Review	200 mg/1.2 mL prefilled autoinjector and prefilled syringe

EFFICACY CONSIDERATIONS

Trial	Integrated Summary of Efficacy and Safety (ISE and ISS) by Craig et al.²
Design	Post hoc analysis of pooled data from phase 2, phase 3 (VANGUARD), and the phase 3 open-label extension (OLE) study. ISS included all studies, ISE included only phase 3 and phase 3 OLE studies.
Population	164 patients receiving garadacimab 200 mg monthly with a median exposure of 2.5 years and 25 patients receiving placebo. Most (32/38) of the patients in the phase 2 and all patients in the phase 3 trial had a diagnosis of HAE with C1 inhibitor deficiency as a result of SERPING1 variants, which, reflects the most common subtype of HAE. Six patients in the phase 2 trial had HAE with normal C1 inhibitor (HAE-nC1-INH) (3/6 with FXII variant and 3/6 with PLG variant). Two of the patients with HAE-nC1-INH, both FXII variant, continued on in the phase 3 OLE.
Results	For the garadacimab group, the mean monthly attack rate during treatment was 0.2 (0.1, 0.2), representing a 94.9% reduction from the baseline run-in attack rate. For the placebo group, the mean monthly attack rate during treatment was 2 (1.4, 2.5), representing a 21.6% reduction from the baseline run-in attack rate. 98.2% patients on garadacimab vs. 33.3% patients on placebo achieved a 50% reduction in attack rate and 84.8% on garadacimab vs. 8.3% of patients on placebo achieved a 90% reduction. The proportion of attack-free patients remained high over time with garadacimab, reaching 88.9% (80/90) during years 2.5-3 of exposure. The median time to first attack after initiation was 2.2 years for garadacimab versus 11 days for placebo. The pooled efficacy findings were consistent with findings from each individual study that garadacimab significantly reduces HAE attacks. Efficacy of garadacimab in the patients with HAE-nC1-INH specifically is described in the potential place in therapy section.

SAFETY CONSIDERATIONS^{1,2}

Garadacimab does not have any Boxed Warnings or Contraindications.

Other Warnings	Garadacimab can prolong activated partial thromboplastin time (aPTT) due to an interaction with the aPTT assay. In the VANGUARD trial, aPTT was prolonged in 3/39 (8%) of patients, but increases were not associated with bleeding events.
Top 5 AEs	Based on pooled long-term data (ISS population ²), the most common adverse events were: COVID-19 (40.1%), nasopharyngitis (22.7%), headache (15.1%), upper respiratory tract infection (13.4%), and injection-site erythema (11.1%).
Drug Interactions	No dedicated drug interaction studies have been conducted. See above for aPTT assay interaction.
Pregnancy	No available data on garadacimab use in pregnant women. As a monoclonal antibody, any potential effect on the fetus would likely be greater during the third trimester of pregnancy. Animal studies in rabbits showed no evidence of fetal harm or maternal toxicity at exposures up to 100 times the maximum recommended human dose.
Lactation	No data on the presence of garadacimab in human milk or its effects on the breastfed infant.

THERAPEUTIC ALTERNATIVES FOR LONG-TERM PROPHYLAXIS (LTP) AND THEIR PLACE IN THERAPY

Drug and Mechanism of Action	VANF	Route	Guideline Recommendation on Long-Term Prophylaxis (LTP) ³
C1-INH, plasma-derived (CINRYZE, HAEGARDA) C1-INH replacement	Non-formulary w/ CFU	SubQ (HAEGARDA) IV (CINRYZE)	SubQ: First-line prophylaxis IV: SubQ: Second-line prophylaxis Preferred in pregnancy if prophylaxis needed.
Lanadelumab (TAKHZYRO) Anti-plasma kallikrein monoclonal antibody	Non-formulary w/ CFU	SubQ	First-line prophylaxis
Berotrastat (ORLADEYO) Oral plasma kallikrein inhibitor	Non-formulary w/ CFU	PO	First-line prophylaxis
Garadacimab (ANDEMBRY)	TBD	SubQ	First-line prophylaxis

Anti-activated Factor XIIa monoclonal antibody			
Donidalorsen (DAWNZERA) Antisense oligonucleotide targeting prekallikrein mRNA	TBD	SubQ	First-line prophylaxis
Danazol Attenuated androgen	Formulary	PO	Second-line
Tranexamic acid Antifibrinolytic	Formulary, PA-F with CFU	PO	Second-line. Considered least effective prophylactic modality

POTENTIAL PLACE IN THERAPY OF GARADACIMAB IN HAE

1. HAE attacks are characterized by unpredictable episodes of subcutaneous or submucosal edema affecting the skin, gastrointestinal tract, and upper airway. Laryngeal attacks can be life-threatening. Current guidelines recommend evaluating all patients for LTP at each visit and reassessing annually using an individualized treat-to-target approach.
2. Garadacimab is a first in class anti-activated Factor XIIa monoclonal antibody. The pooled efficacy findings from the phase 2, phase 3, and OLE data² were consistent with findings from each individual study that garadacimab significantly reduces HAE attacks. There is a 73.3 percentage point treatment difference in reduction of monthly attack rate from baseline. Though often a secondary endpoint in clinical trials, clinical significance in HAE improvement is often defined by Angioedema Quality of Life (AE-QoL) Scale. The minimal clinically important difference (MCID) for the AE-QoL total score is a reduction of 6 points.⁴ Therapies achieving ≥50% attack rate reduction generally meet or exceed this QoL threshold, including garadacimab (in the phase 3 VANGAURD trial, mean treatment difference in AE-QoL reduction from baseline was 26.7 points at month 6).
3. No head-to-head trials currently exist comparing garadacimab to other first-line LTP agents. A network meta-analysis of RCTs by Walsh et al.⁵ demonstrated that garadacimab had a statistically significant reduction in the time-normalized rate of attacks compared to subQ C1-INH, berotralstat, and lanadelumab Q4 weeks. There was no significant difference between garadacimab and lanadelumab Q2 weeks. There was no significant difference between any of the included agents on proportion of attack-free patients. This NMA was funded by CSL Behring (manufacturer of garadacimab). Concerns of limitations to this NMA have been raised⁶ and include: study designs of the included RCTs don't reflect standard prescribing for therapies like lanadelumab, use of a fixed-effect model (random-effects published in supplementary data showed lack of statistical significance in any endpoints for garadacimab and both doses of lanadelumab).
4. Garadacimab was largely studied in clinical trials in the most common subtype of HAE with C1 inhibitor deficiency (traditionally identified as HAE types 1 and 2) which is a result of SERPING1 variants. HAE with normal C1 inhibitor (HAE-nC1-INH) is caused by variants in other genes like FXII, PLG, KNG1, ANGPT1, MYOF, HS3ST6, CPN1, or DAB21P, and unidentified genetic causes. Garadacimab was studied in a small number (n=6) of patients with HAE-nC1-INH due to FXII and PLG variants. Though these patients were included in the integrated summary described above, a separate article by Cohn et al⁷ describes the outcomes of this small subgroup. All 3 patients with HAE-PLG did not continue to the phase 3 OLE due to inconsistent efficacy. Two of the three patients with HAE-FXII continued on to the phase 3 OLE with a 98.5% and 94.6% reduction vs run-in attack rate with both patients being attack-free (100% reduction vs run-in) for more than 18 months in the phase 3 OLE study. The third patient with HAE-FXII did experience some efficacy initially in the phase 2 trial, but did not continue in the phase 3 OLE due to lack of efficacy.
5. The 2025 WAO Guidelines³ recommend garadacimab as a first-line option for LTP. Other first-line LTP options include berotralstat, lanadelumab, donidalorsen, and subQ C1-INH. The guidelines do not preference any one of the first-line agents over another. The guidelines also do not have recommendations specific to patients with HAE-nC1-INH. They do state some patients have been successfully treated with other therapies like lanadelumab, IV C1-INH, garadacimab, or berotralstat. The guidelines also state tranexamic acid performs better in patients with HAE-nC1-INH (compared to C1-INH deficiency), particularly involving PLG or FXII variants.
6. Individual patient factors including HAE subtype, ability to self-inject, concomitant medications, and attack characteristics should guide therapy selection.

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References

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