

Donidalorsen (DAWNZERA)

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	Prekallikrein-directed antisense oligonucleotide (ASO). It causes ribonuclease H1-mediated degradation of prekallikrein (PKK) mRNA, leading to reduced production of PKK protein. This prevents the excessive production of bradykinin, which is the primary mediator of swelling and pain in hereditary angioedema (HAE).
Indication Under Review	Prophylaxis of HAE attacks in adult and pediatric patients aged 12 years and older.
Dosage Regimen	80 mg subcutaneous (subQ) every 4 weeks (80 mg every 8 weeks may be considered)
Dosage Forms Under Review	80 mg/0.8 mL single-dose autoinjector

EFFICACY CONSIDERATIONS

Trial	Phase 2 trial and open label extension (OLE)²⁻³
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. OLE was multicenter 4 year study.
Population	20 adults (14 donidalorsen, 6 placebo) with HAE and C1 inhibitor deficiency (i.e., HAE type 1 or 2). 17 patients continued on in the OLE.
Intervention	Donidalorsen 80 mg subcutaneously once every 4 weeks (Q4W) for four doses. In the OLE, patients were given donidalorsen 80 mg Q4W (fixed for 12 weeks), followed by flexible dosing (80 mg Q4 or 8W, or 100 mg Q4W) in which dosing interval extensions were based on being attack-free and dose increase to 100 mg was based on inadequate control on 80 mg Q4W.
Results	The primary endpoint of mean investigator-confirmed monthly HAE attack rate (week 1–17) was 0.23 (0.08, 0.39) for donidalorsen versus 2.21 (0.58, 3.85) for placebo (treatment difference -90%; p<0.001). Select secondary endpoints: between weeks 5 and 17, a clinical response of 50% reduction in attack rate was achieved by 13/13 (100%) of donidalorsen patients compared to 2/6 (33%) for placebo; 12/13 (92%) were attack-free compared to 0/6 (0%) for placebo. In the OLE fixed dosing period, the mean monthly HAE attack rate decreased from 2.70 at baseline of the phase 2 trial to 0.05 (average 97% reduction). Flexible dosing at Q4W led to a 97% reduction, while the Q8W subgroup achieved an 83% reduction.
Trial	Phase 3 OASIS-HAE and OLE (OASISplus)⁴⁻⁵
Design	Multinational, double-blind, randomized, placebo-controlled, trial. Available OLE publication is a 1-year interim analysis.
Population	90 patients with HAE type 1 or 2 randomized 2:1, Q4W to Q8W dosing interval. Each dosing interval group was randomized 3:1, donidalorsen 80 mg or placebo. 83 patients continued on in the OLE.
Intervention	Donidalorsen 80 mg subQ Q4W (N=45) or Q8W (N=23). In the OLE, patients remained on the dosing frequency they were assigned in the phase 3 trial, unless Q8W patients were not attack free, then they were switched to Q4W (included 6 patients who were on donidalorsen Q4W, and all placebo Q8W participants).
Results	The primary endpoint of least-squares mean time-normalized attack rate (week 1–25) was 0.44 (0.27, 0.73) in the Q4W group and 1.02 (0.65, 1.59) in the Q8W group, compared to 2.26 (1.66, 3.09) for placebo. This represented a treatment difference of 81% reduction for the Q4W group (p<0.001) and a 55% reduction for the Q8W group (p=0.004). Select secondary endpoints included patients reaching a 70% attack rate reduction (Q4W: 82% (p<0.001); Q8W: 65% (p=0.004)) and patients being attack-free (Q4W: 53% (p=0.003); Q8W: 35% (not significant)). In the OLE, mean HAE attack rate reductions at week 52 from baseline were 94% for the Q4W group and 95% for the Q8W group.
Trial	Phase 3 OASISplus (“Switch cohort”)⁶
Design	Ongoing, global, phase 3, open-label study evaluating 1-year (52-week) outcomes in patients switching from a prior LTP agent.
Population	65 patients with HAE type 1 or 2 previously on stable doses of lanadelumab (n=32), berotralstat (n=11), or C1 inhibitor (C1INH, n=22).
Intervention	Donidalorsen 80 mg administered subQ once Q4W
Results	The overall mean monthly attack rate decreased from 0.85 (SD 1.3) at baseline to 0.28 (SD 0.4) over 52 weeks, representing a 67.6% reduction. Attack rate reductions by prior LTP subgroup were as follows: prior lanadelumab: 63.9% reduction, prior berotralstat 83.1% reduction, prior C1INH: 50.7% reduction. Angioedema Quality of Life (AE-QoL): The mean total score improved by 12.2 points (SD 17.6) from baseline to Week 52, which surpassed the threshold for a minimally clinically important difference of 6 points.

SAFETY CONSIDERATIONS

Donidalorsen does not have any Boxed Warnings or Contraindications besides contraindication in patients with a history of serious hypersensitivity reactions to donidalorsen or any of its excipients

Other Warnings	Serious hypersensitivity reactions, including anaphylaxis, have been reported; treatment should be discontinued if these occur. Donidalorsen can cause reductions in platelet count, though no major bleeding events were observed in trials. Increases in liver enzymes (ALT, AST, and GGT) were also reported.
Top 5 AEs	Based on interim 1-year data from the OASISplus OLE, the most common adverse events were: influenza (18.1%), nasopharyngitis (18.1%), back pain (14.5%), headache (13.3%), injection site reactions (12%), and COVID-19 (12.0%).
Drug Interactions	No dedicated drug interaction studies have been conducted. In vitro studies indicate donidalorsen is not a substrate, inhibitor, or inducer of major CYP enzymes or transporters.
Pregnancy	No available human data regarding use in pregnancy. Animal studies showed no adverse developmental effects at exposures up to 5 times the maximum recommended human dose.
Lactation	No data on the presence of the drug in human milk.

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) ⁷
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) Anti-activated Factor XIIa monoclonal antibody	TBD	SubQ	First-line prophylaxis
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 DONIDALORSEN IN HAE

- 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.
- In phase 2 and 3 studies, donidalorsen had a statistically significant reduction in HAE attack rates compared to placebo. Those reductions were also maintained in the OLEs (to date, the phase 3 OLE has only published up to one year, it is ongoing NCT05392114). 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.⁸ Therapies achieving ≥50% attack rate reduction generally meet or exceed this QoL threshold, including donidalorsen (in the phase 3 OLE, mean AE-QoL reduction from baseline was 27.8 points).
- The Switch Cohort of the OASISplus OLE demonstrated efficacy of donidalorsen in patients who had been on other LTP agents, however, a head-to-head, double-blind, randomized trial would be a stronger study design to assess comparative efficacy and safety of donidalorsen versus other first-line LTP agents.
- Donidalorsen was 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. Donidalorsen has not been studied in HAE with normal C1 inhibitor (HAE-nC1-INH), which is caused by variants in other genes like FXII, PLG, KNG1, ANGPT1, MYOF, HS3ST6, CPN1, or DAB21P, and unidentified genetic causes.
- The 2025 WAO Guidelines⁷ recommend donidalorsen as a first-line option for LTP. Other first-line LTP options include berotrastat, lanadelumab, garadacimab, 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.
- 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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