Avacincaptad Pegol (IZERVAY) Intravitreal Injection
National Drug Monograph
January 2024
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Avacincaptad pegol is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).
- There are 3 stages of AMD: early, intermediate, and late. In the late stage, there are 2 major forms; dry (non-neovascular) and wet (neovascular, exudative). Geographic atrophy is the advanced late stage of dry AMD.
- While vascular endothelial growth factor is the driver for the growth of neovascularization in nAMD, activation of the complement cascade is one of the main pathways involved in progression of dry AMD.
- With aging, oxidative damage resulting from exposure to intrinsic, extrinsic, and environmental stressors can result in the formation of drusen, yellow deposits of lipids between the retinal pigment epithelium (RPE) and Bruch's membrane (early to intermediate AMD)
- Drusen accumulation may trigger chronic inflammation via multiple pathways including the complement cascade
- Chronic inflammation can eventually lead to photoreceptor, RPE, and choriocapillaris cell death causing the appearance of sharply defined atrophic lesions and can progress to irreversible visual function loss.
- Lesions usually first appear in the nonfoveal (or extrafoveal) region of the macula and progress over time to the central fovea (subfoveal)
- Extrafoveal lesions affect visual performance, such as reading, driving, and low-light vision. Foveal lesions affect central visual acuity.
- Avacincaptad pegol is an RNA aptamer, a PEGylated oligonucleotide that binds to and inhibits complement protein C5. By inhibiting C5, avacincaptad pegol may prevent its cleavage to C5a and C5b thus decreasing membrane attack complex (MAC) formation.

Dosage Form(s) Under Review

- Injection: The recommended dose is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately 28 ± 7 days) **for up to 12 months.**
- The 12-month limitation at this time is due to the limited submitted data to the FDA from patients after Month 12. The company will be submitting the longer-term information when it becomes available.

Clinical Evidence Summary

Efficacy Considerations

Two randomized, double-blind studies, GATHER 1, a phase 2/3 trial and GATHER 2, a phase 3 confirmatory trial, compared the efficacy and safety of avacincaptad with sham in patients with nonfoveal GA secondary to AMD. In GATHER 1, patients were randomized 1:2:2 to avacincaptad 2mg (n=67), avacincaptad 4mg (=83), or sham (110) every month. Only results for the 2mg dose will be presented as this is the marketed dose. The primary outcome was change in the GA area as measured by fundus autofluorescence at 12 months. Patients continued to receive masked treatment for 18 months.

In GATHER 2, monthly administration of avacincaptad 2mg (n=225) was compared to sham (n=223). The primary outcome was mean rate of growth (slope) of GA area from baseline measured by fundus autofluorescence at 6 and 12 months (square root transformation). At month 12, the patients in the avacincaptad group will be re-randomized to receive the study drug either monthly or every other month. The patients initially randomized to sham treatment will continue with monthly sham injections through Month 23. At the time of this writing, only the 12 month results have been published.

- Key inclusion criteria: Age ≥ 50 years; best-corrected visual acuity (BCVA) 20/25 to 20/320; diagnosis of GA secondary to AMD; nonfoveal centered, and in part within 1500µm from the foveal center; total GA lesion area ≥ 2.5 and ≤ 17.5 mm2 (1 to 7 disc areas); If GA is multifocal, at least one focal lesion must be ≥ 1.25 mm2 (0.5 DA;
- Key exclusion criteria: GA secondary to a condition other than AMD in either eye; any prior treatment for AMD excluding oral vitamin supplements; any intravitreal treatment in either eye; any ocular condition that could progress during study that could affect central vision or be a confounding factor; choroidal neovascularization (CNV) in the either eye (GATHER 1) or macular neovascularization (MNV) in the either eye (GATHER 2)

- Baseline characteristic
  - Mean age 77 years; males 30%; White 87%; active smoker 44%
  - Mean total GA lesion size (mm2) 7.39 (GATHER 1), 7.64 (GATHER 2); Mean square root GA lesion size (mm) 2.63 (GATHER 1), 2.68 (GATHER 2)
  - Bilateral GA 96%; unifocal/multifocal 20%/80% (GATHER 2); hyper-autofluorescence number 99% (GATHER 1); hyperautofluorescence type diffuse or banded 97% (GATHER 2)
  - Mean BCVA 71 letters, mean low-luminance letters: 35 (GATHER 1), 40 (GATHER 2)

- Results
  - Monthly administration of avacincaptad reduced the growth of GA lesions compared to sham **(Table 1)**
  - Treatment effect noted as early as month 6 and maintained at month 12.
  - At 18-month follow up in GATHER 1, the reduction in the growth compared to the sham arm was 32.2%.
  - 24-month data for GATHER 2 has not yet been published; however, topline results from Astellas indicate, monthly administration of avacincaptad significantly slowed GA growth compared to sham by 14%. Every other month dosing of avacincaptad after a year of monthly dosing reduced GA growth by 19% at 2 years versus sham. IZERVAY™ (avacincaptad pegol intravitreal solution) Monthly or Every Other Month Reduced Geographic Atrophy Lesion Growth Through 2 Years - Nov 4, 2023 (astellas.us)
  - There was no impact on change in mean BCVA or low luminance BCVA with avacincaptad compared to sham. BCVA is generally a poor indicator of functional vision in GA because the fovea may not be involved until later stages of the disease. In GATHER 1 and 2, nonfoveal involvement was required for study entry.

Table 1: Change in GA Lesion Baseline to 12 months

	GATHER 1			GATHER 2		
	Avacincaptad (n=67)	**Sham (n=110)**	**Difference [95%CI]; (%)**	**Avacincaptad (n=225)**	**Sham (n=222)**	**Difference [95%CI]; (%)**
Mean Rate of GA Growth (mm^2; slope; observed)	1.22	1.89	0.67 [0.21, 1.13] 35.4%*	1.75	2.12	0.38 [0.12, 0.63] 17.7%*

Abbreviations: GA=geographic atrophy
*significant difference vs sham

Safety Considerations

- **Boxed warnings:** None
- **Contraindications:**

- Ocular or periocular infection
- Active Intraocular Inflammation

- **Other warnings/precautions**:
  - Endophthalmitis and Retinal Detachments
  - **Neovascular AMD. In clinical trials, use of avacincaptad was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving avacincaptad should be monitored for signs of neovascular AMD**
  - Increased Intraocular Pressure. Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with avacincaptad. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

- **Adverse reactions**
  - The most common adverse reactions were conjunctival hemorrhage (13%), increased IOP (9%), blurred vision (8%) and neovascular age-related macular degeneration (7%).

Table 2: Adverse Reactions at 12-months in Study Eye in ≥ 2% of Patients (GATHER 1 and GATHER 2)

	Avacincaptad (n=292)	Sham (n=332)
Conjunctival hemorrhage (%)	13	9
Increased intraocular pressure (%)	9	1
Blurred vision (%)	8	5
Choroidal neovascularization	7	4
Eye pain (%)	4	3
Vitreous floaters (%)	2	<1
Blepharitis (%)	2	<1

Data from product package insert

- **Neovascular AMD**

  Patients with a history of or active CNV (GATHER 1) or macular neovascularization (GATHER 2) in either eye were excluded from the clinical trials. During the extension of GATHER 1 and in GATHER 2, the newer classification macular neovascularization (MNV), was used as it is considered to be more descriptive than CNV because neovascularization does not always originate from the choroid.

  In GATHER 1, the incidence CNV in the study eye at 12 months was 9% and 2.7% for avacincaptad and sham groups respectively. Development of CNV in the fellow eye was reported in 3.5% of patients (all treatment groups combined). The 18-month findings for MNV conversion in GATHER 1 was 11.9% for avacincaptad and 2.7% for sham. Fellow-eye conversion rates were 3% for avacincaptad and 3.6% for sham.

  In GATHER 2, MNV was reported at 12 months in the study eye in 15 (7%) patients in the avacincaptad group (11 exudative MNV, 1 non-exudative MNV, 3 papillary CNV). In the sham group 9 (4%) patients developed MNV in the study eye (7 exudative MNV, 2 papillary CNV). In GATHER 2, patients who developed MNV remained in the study and received treatment for MNV.

  According to the 24-month top line results from GATHER 2, The rate of CNV was 12% in patients treated with avacincaptad and 9% in those treated with sham. [Iveric Bio Announces Positive 24-Month Topline Results from Phase 3 Study of IZERVAY™ (avacincaptad pegol intravitreal solution) for Geographic Atrophy - Sep 18, 2023 (astellas.us)]

Table 3: Development of Macular Neovascularization in Study Eye

GATHER 1				GATHER 2			
12 months		18 months		12 months		24 months	
Avacincaptad	Sham	Avacincaptad	Sham	Avacincaptad	Sham	Avacincaptad	Sham
6 (9%)	3 (2.7%)	8 (11.9%)	3 (2.7%)	15 (6.7%)	9 (4%)	12%	9%

- **Other Adverse of Events:**
  There were no cases of endophthalmitis, or ischemic optic neuropathy reported in GATHER 1 and GATHER 2 at 12 months. In the 24-month GATHER 2 topline results, 1 case of culture-positive endophthalmitis and 1 case of non-serious intraocular inflammation. was reported. In GATHER 1, one case of mild transient intraocular inflammation was reported relating to injection procedure.

  As of September, 18, 2023, no cases of occlusive or non-occlusive retinal vasculitis or ischemic neuropathy have been reported.

- **Serious Adverse Events (SAEs):**
  - Ocular SAEs (n): Study eye 3 avacincaptad, 2 sham; no SAEs in fellow eye
  - Systemic SAEs: 13.7% avacincaptad, 19% sham

  Deaths (n): 3 avacincaptad, 2 sham

  Discontinuations due to an Adverse Event:
  - GATHER 1: no discontinuations
  - GATHER 2 Ocular (n): 2 avacincaptad, 0 sham; systemic (n): 4 avacincaptad, 2 sham

  Discontinued trial for any reason:
  - GATHER 1 (18 months): 28.4% avacincaptad, 22.7% sham
  - GATHER 2 (12 months): 11% avacincaptad, 8% sham

Other Considerations

- 2-year data for GATHER 2 have not been published in a peer reviewed journal
- At present, avacincaptad is only approved for up to 12 months of use

Other Therapeutic Options

- Pegcetacoplan intravitreal injection
- Several potential treatments, targeting various pathways, are under investigation. Examples include: anti-inflammatory and complement inhibition, antioxidative, reduction of toxic byproducts, visual cycle modulators, neuroprotection, cell-based therapies, mitochondrial enhancers

Table 4: Comparison of Treatments for GA

Avacincaptad	• Slows progression of GA Difference vs sham in GA rate of growth at month 12* • GATHER 1: 35% • GATHER 2: 17.7% Only patients with extrafoval were included in the trial	• Associated with increased risk of nAMD or CNV (7% vs. 3%) at 12 months; at 24 months (unpublished) the risk was 12% vs. 9% • Patients with active or history of macular neovascularization in either eye were excluded from the trials
Pegcetacoplan	• Slows progression of GA Difference vs sham in GA rate of growth at month 12* • OAKS 21% (monthly); 16% (EOM)	• Associated with increased risk of nAMD or CNV (12%, 7%, 3%) at 24 months • Patients with a history of or active CNV in the study eye were excluded from the clinical trials. Patients with a history of CNV in the

	• DERBY 12% (monthly); 11% (EOM) Patients with subfoveal and extrafoval lesion were included in the trial	contralateral eye were included in the clinical trials. • The risk of developing nAMD or CNV in the study eye was greater in those with a history of CNV in the contralateral eye in those treated with pegcetacoplan. • Post-marketing: reports of at least 10 cases of occlusive retinal vasculitis following injection of pegcetacoplan into the eye.

*Based on non-transformed GA growth slope analysis (mm2)

Abbreviations: BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; GA=geographic atrophy; nAMD=neovascular age-related macular degeneration

Projected Place in Therapy

Avacincaptad is the second FDA approved drug for the treatment of GA. Avacincaptad slowed the progression of GA over 12 months.

Avacincaptad was associated with an increased risk of conversion to wet AMD; 7% and 4% for avacincaptad and sham respectively at 12 months and 12% and 9% at 24 months (24-month data unpublished). Patients with evidence of CNV or MNV in either eye were excluded from the clinical trials.

In the absence of contraindications, use of avacincaptad should be restricted to the treatment of GA secondary to AMD.

References

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