Ranibizumab Ocular Implant (SUSVIMO)
National Drug Monograph
February 2022
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

- Ranibizumab is a vascular endothelial growth factor (VEGF) inhibitor. Ranibizumab has been available since 2006 for administration by intravitreal injection under the trade name Lucentis. The new product Susvimo utilizes a port delivery system to deliver ranibizumab. A permanent refillable ocular implant is surgically placed that continuously delivers ranibizumab into the vitreous. The implant reservoir can be refilled with ranibizumab via clinic-based refill exchange procedures. The implant may be surgically removed if necessary.
- There are considerable safety considerations for ranibizumab implant (see Safety Considerations and Other Considerations)

Indication(s) Under Review in This Document

- For the treatment of patients with neovascular age-related macular degeneration (nAMD) who have previously responded to at least two intravitreal injections of a VEGF inhibitor

Dosage Form(s) Under Review

- 100 mg/mL solution in a single-dose vial
- For intravitreal use via SUSVIMO ocular implant
- The recommended dose is 2 mg (0.02 mL of 100 mg/mL solution) continuously delivered via the implant with refills every 24 weeks (approximately 6 months)
- Supplemental treatment with 0.5 mg intravitreal ranibizumab injection may be administered in the affected eye if clinically necessary

Clinical Evidence Summary

Efficacy Considerations

The ARCHWAY study compared ranibizumab via implant given every 24 weeks (n=248) to intravitreal injections of ranibizumab 0.5mg every 4 weeks (n=167) in patients with a diagnosis of nAMD. Patients were to have received at least 3 doses of intravitreal VEGF inhibitors (median received was 4 doses) in the study eye and have demonstrated a response to treatment. Supplemental doses of intravitreal ranibizumab was allowed beginning at week 16 for those randomized to the implant if needed based on nAMD activity criteria.

The study was designed to show non-inferiority and equivalence for the primary endpoint of change in best corrected visual acuity (BCVA) score averaged over weeks 36 and 40.

Key inclusions: age 50 years or greater; nAMD-related neovascular lesions involving the macula diagnosed within 9 months of screening; at least 3 prior VEGF inhibitor intravitreal injections within 6 months of screening with anatomical and visual response

Key exclusions: prior treatments for nAMD other than VEGF inhibitors; subfoveal fibrosis or atrophy; specific ocular conditions (complete list in appendix in Holekamp et al.)

Demographics and baseline Information include mean age 75 years; 41% male; White 97%; BCVA letter score 74.8 (approximate Snellen equivalent 20/32); phakic 40.5%; prior number of VEGF inhibitors 5.0 injections; central point thickness 177µm; time since nAMD diagnosis 5.6 months

Efficacy results are shown in **Table 1**. Mean number of ranibizumab injections was 10.7 in the IVT monthly arm.

Table 1: Efficacy results from ARCHWAY Trial

	RBZ implant (n=251)	RBZ IVT (n=167)	Comments
Change from baseline in BCVA Score averaged over Weeks 36 and 40	0.2	0.5	TD -0.3 (95%CI -1.7, 1.1) Within pre-specified ±4.5 letters noninferiority and equivalence margins
BCVA score >/= 69 letters (Snellen equivalent 20/40) (% pts)	80.5	82.2	
Gain of ≥ 0 ETDRS letters Gain of ≥ 5 ETDRS letters Gain of > 15 ETDRS letters	57.8 20.8 1.6	58.9 23.3 1.2	Data shown as % patients
Loss of < 5 ETDR letters Loss of < 10 ETDR letters Loss of < 15 ETDR letters Loss of ≥ 15 ETDR letters	85.0 95.1 97.6 2.4	88.3 95.1 96.9 3.1	Data shown as % patients
Change in CPT (µm)	5.4	2.6	
Change in CST (µm)	10.3	4.4	
Need for supplemental IVT RBZ before first port refill	4 (1.6)	NA	3 patients received 1 supplemental dose; 1 patient received 2 supplemental doses

Abbreviations: BCVA=best-corrected visual acuity; CPT=central point thickness; CST=central subfield thickness; ETDR=Early Treatment Diabetic Retinopathy; IVT=intravitreal; NA=not applicable; RBZ=ranibizumab; TD=treatment difference

Longer term data show that ranibizumab implant was noninferior to ranibizumab monthly injections for change in BCVA score averaged over weeks 88 and 92 (treatment difference -0.6 [-2.5, 1.3] letters).

Safety Considerations

- **Boxed warnings: The SUSVIMO implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. Many of these events were associated with conjunctival retractions or erosions. Appropriate conjunctiva management and early detection with surgical repair of conjunctival retractions or erosions may reduce the risk of endophthalmitis. In clinical trials, 2.0% of patients receiving a ranibizumab implant experienced at least one episode of endophthalmitis.**

- **Contraindications:**
  - Ocular or periocular infection
  - Active intraocular inflammation
  - Hypersensitivity to ranibizumab or excipients in SUSVIMO

- **Other warnings / precautions**:
  - The SUSVIMO implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, implant dislocation, vitreous hemorrhage, conjunctival retraction, conjunctival erosion, and conjunctival bleb. Patients should be instructed to report signs or symptoms that could be associated with these events without delay. Additional surgical and/or medical management may be required.
  - **Vitreous Hemorrhage:** Temporarily discontinue antithrombotic medication prior to the implant insertion procedure to reduce the risk of vitreous hemorrhage. Vitrectomy may be needed.
  - **Postoperative Decrease in Visual Acuity:** A transient decrease in visual acuity usually occurs over the first two postoperative months. Visual acuity was decreased by 4 letters on average in the first postoperative month and 2 letters on average in the second postoperative month following initial implantation.

- **Adverse reactions**
  - The most common adverse reactions were conjunctival hemorrhage, conjunctival hyperemia, iritis, eye pain, vitreous floaters, and conjunctival bleb/conjunctival filtering bleb leak. **Table 2**

  - Other adverse events reported in the clinical trials include, rhegmatogenous retinal detachments (0.8% vs. 0), implant dislocation (n=1), vitreous hemorrhage (5.2% vs 2%), conjunctival erosion (3.6% vs. 0), conjunctival retraction (2% vs. 0). After initial implantation, visual acuity was decreased by a mean of 4 letters the first postoperative month and a mean of 2 letters the second postoperative month.

Table 2: Adverse Reactions occurring in >/=4% of Patients in Implant Arm

	RBZ implant (n=251)	RBZ IVT (n=167)
Conjunctival hemorrhage (%)	72	6
Conjunctival hyperemia (%)	26	2
Iritis (%)	23	0.6
Eye pain (%)	10	5
Vitreous floaters (%)	9	2
Conjunctival bleb/filtering bleb leak (%)	9	0
Hypotony of eye (%)	6	0
Vitreous detachment (%)	6	5
Vitreous hemorrhage (%)	5	2
Conjunctival edema (%)	5	0
Corneal disorder (%)	4	0
Corneal abrasion (%)	4	0.6
Corneal edema (%)	4	0

  - **Serious Adverse events (SAEs):**
    - **Ocular:** 14 patients (5.6%) in the implant group had 20 SAEs (4 endophthalmitis, 2 conjunctival erosion, 2 rhegmatogenous retinal detachment, 2 reduced visual acuity, 2 visual impairment, 1 vitreous hemorrhage, 1 choroidal detachment, 1 necrotizing retinitis, 1 retinal tear, 2 conjunctival retraction, 1 implant dislocation).

In the monthly IVT group, there were 2 SAEs (1 vitreous hemorrhage, 1 facial bone fracture)
  - **Non-ocular:** 11.3% (implant), 9.6% (IVT injection). None of the events were thought to be related to study drug
  - **Deaths:** 2 (0.8%) in the implant group and 1 (0.6%) in the intravitreal injection group

- **Other**
  - **Discontinuations:** 5 patients in the implant group discontinued treatment due to an adverse event (2 endophthalmitis, 1 retinal pigment epithelium detachment, 1 conjunctival retraction, 1 implant dislocation). No patients in the intravitreal injection group discontinued treatment due to an adverse event
  - **Implant removal:** 4 patients had the implant removed (1 endophthalmitis, 1 recurrent conjunctival retraction, 1 implant dislocation, 1 damaged implant)
  - **Need for additional surgery due to adverse event in the implant group:** 18 patients (7.3%) in the implant arm required 22 additional surgical procedures related to ocular adverse events (e.g., conjunctival repair, vitrectomy, cataracts extraction)

Other Considerations

- Implant and refill procedure must be performed under strict aseptic conditions by an ophthalmologist experienced in vitreoretinal surgery.
- Ranibizumab implant is magnetic resonance conditional. Patients should inform their healthcare provider that they have ranibizumab implanted in their eye and show their healthcare provider the ranibizumab implant card should they require magnetic resonance imaging (MRI). Patents may only receive an MRI under very specific conditions. For details, see Susvimo ocular implant Instructions for Use found on page 50 of product package insert.
- Patient is not to push on the eye, rub the eye, or touch the area of the eye where the implant is located for 30 days following implant surgery and for days following the refill-exchange procedure. Throughout ranibizumab implant treatment, patient should avoid rubbing or touching the area of the eye as much as possible.
- Close monitoring will be needed due to the frequency of adverse events and to assess the need for supplemental IVT ranibizumab
- Ranibizumab implant is under investigation for diabetic macular edema and diabetic retinopathy

Other Therapeutic Options

Alternative formulary anti-VEGF treatments are listed in **Table 3.**

Table 3: Anti-VEGF Formulary Treatment Options

Drug	Comments
Ranibizumab Intravitreal injection	• Dosing for nAMD: 0.5mg once monthly (approximately every 28 days • Although not as effective, pts may be treated monthly x 3 doses followed by less frequent dosing with regular assessment • Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Patients should be assessed regularly
Aflibercept Intravitreal injection	• Dosing for nAMD: 2 mg every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2mg once every 8 weeks (2 months). • Some patients may need every 4-week (monthly) dosing after the first 12 weeks • Although not as effective as the recommended every 8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

Projected Place in Therapy

Ranibizumab implant was found to be noninferior and equivalent to monthly intravitreal injections in patients with nAMD. However, ranibizumab implant has a high frequency of adverse effects including a boxed warning for 3-fold increase in endophthalmitis compared to monthly injections. After assessing risk versus benefit, ranibizumab implant should be reserved for those with nAMD who have demonstrated response to VEGF inhibitors and who would benefit from reducing treatment burden (e.g., long travel times, physical mobility limitations, etc.).

References

Holekamp NM, Campochiaro PA, Chang MA, Miller D, et al. Archway Randomized Phase 3 Trial of the Port Delivery System with **Ranibizumab** for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2021 Sep 29: S0161-6420(21)00734-X. doi: 10.1016/j.ophtha.2021.09.016. Online ahead of print.

SUSVIMO (ranibizumab injection) for intravitreal use via SUSVIMO ocular implant [prescribing information online]. San Francisco, CA: Genetech. October 2021. Available at: label (fda.gov)

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