Anthem

Medical Policy

Subject: Implanted Port Delivery Systems to Treat Ocular Disease
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Description/Scope

A port delivery system is a novel type of drug delivery platform using a permanent drug-eluting implant inserted into and through the sclera of the eye to allow delivery of drugs to the intravitreal space. Such systems consist of a transscleral device that includes a reservoir and release control element to distribute drugs within the eye. A self-sealing extrascleral flange, which is visible through the conjunctiva, allows refilling of the reservoir as needed. Port delivery systems have been proposed as an alternative to monthly intravitreal injections in the treatment of retinal and potentially other ocular diseases.

Position Statement

Investigational and Not Medically Necessary:

The use of a port delivery system to treat ocular disease is considered **investigational and not medically necessary** for all indications.

Rationale

Wet or neovascular age-related macular degeneration (AMD)

Untreated AMD will result in progressive vision loss. The current treatments of neovascular AMD include photodynamic or intravitreal injections of an anti-vascular endothelial growth factor (anti-VEGF). Anti-VEGF therapy blocks the VEGF protein, slowing the growth of abnormal blood vessels and slowing the rate of vision loss. The current FDA approved anti-VEGF agents include bevacizumab (Avastin), aflibercept (Eylea) and ranibizumab (Lucentis). Individuals with AMD typically require monthly intravitreal injections. The use of anti-VEGF therapy has been used for other ocular disease including macular edema, diabetic retinopathy and retinal vein occlusion. However, the vision gains reported by the use of anti-VEGF agents in clinical trials have not replicated in clinical practice. In clinical practice, initial vison gains shown were lost or significantly reduced in later years. This reduced efficacy appears to be related to the treatment regimen. Khanani and colleagues (2021) reported that individuals who remain on long-term fixed-interval anti-VEGF therapy maintained vision outcomes through year 7. The implanted, refillable port delivery system has been proposed as a way of reduce treatment burden without compromising vision through the sustained release of an anti-VEGF agent. The port delivery system decreases the number of intravitreal injections an individual needs to undergo, as the reservoir only needs to be refilled approximately every 6 months. Currently the only anti-VEGF agent FDA approved for use with the port delivery system is ranibizumab.

On October 22, 2021 the U.S. Food and Drug Administration (FDA) approved Susvimo™ (Genentech, Inc. South San Francisco, CA), a form of the biologic drug ranibizumab, for intravitreal use via a port delivery system ocular implant for the treatment of neovascular AMD. Susvimo and the ocular implant are meant to be used in those who had previously responded to at least two anti-vascular endothelial growth factor (VEGF) injections.

Holekamp and associates (2021) reported on the results of a phase 3, open-label, randomized, visual acuity assessor-masked noninferiority and equivalence trial. Individuals aged 50 years or older with a diagnosis of neovascular AMD made within 9 months of screening, with a positive response to at least three prior anti-VEGF intravitreal injections, were randomized to receive either the port delivery system with ranibizumab (n=248) or intravitreal injections every 4 weeks(n=167). The primary end point was established as the change in best-corrected visual acuity (BCVA) score from baseline averaged over weeks 36 and 40. A total of 240 (96.8%) individuals in the port delivery system group and 162 (97.0%) individuals in the monthly injection group completed the study through week 40. The change in the BCVA score from baseline averaged over weeks 36 and 40 was +0.2 in the port delivery system group and +0.5 in the monthly injection group. Based on the pre-study standards, the port delivery system was clinically noninferior and equivalent to the monthly injections. The port delivery system group reported more ocular adverse events (AEs) compared to the monthly injection group, with most events occurring during the post-operative period. In addition to non-serious AEs, there were a total of 20 serious AEs occurring in the port delivery system group including conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, necrotizing retinitis, retinal tear, visual acuity reduced, vision impairment, choroidal detachment and implant dislocation. There were 2 serious AEs in the monthly injection group including vitreous hemorrhage and facial bone fracture. The rate of AEs in this trial resulted in the FDA inserting a Black Box Warning to the prescribing information (PI) label. The study analysis included data from only one complete refill interval. Further studies with longer follow-up are needed.

In a phase 2, multicenter, randomized, active treatment controlled clinical trial, Campochiaro and colleagues (2020) reported on the safety and efficacy of the port delivery system used with ranibizumab. The inclusion criteria included those aged 50 and older who had been diagnosed within 9 months of study screening and who had been responsive to between 2 and 9 anti-VEGF agent injections. Individuals receiving monthly intravitreal injections (n=41) were compared to individuals receiving ranibizumab at varying concentration levels with the port delivery system including 10 mg/ml (n=58), 40 mg/ml (n=62) and 100 mg/ml (n=59). The primary endpoint was the time to first implant refill. Additionally, improvement in BCVA, central foveal thickness (CFT) and safety endpoints were assessed. The port delivery system used with the 100 mg/ml concentration reported the highest efficacy rate, with only 1.7% of participants not meeting clinical efficacy criteria. The lower concentration groups reported 22.4% and 4.8% of participants did not meet clinical efficacy criteria. The BCVA and CFT were similar across the monthly injection group and the port delivery system concentration 100 mg/ml group. The monthly injection group did not report any serious ocular AEs. The port delivery system groups reported serious ocular AEs in 8.9% (16/179) of participants. This phase 2 study met its primary objective of assessing the relative efficacy of port delivery system therapy at varying formulations. Further studies beyond this proof of concept study are needed to fully evaluate implications of using a permanent refillable intraocular reservoir to deliver biologic therapy for neovascular AMD.

Warnings

The PI label includes the following Black Box Warning regarding endophthalmitis:

> 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.

The FDA also requested the following additional warnings and precautions be included in the label:

> The SUSVIMO implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, implant dislocation, vitreous hemorrhage, conjunctival erosion, conjunctival retraction, and conjunctival blebs. Patients should be instructed to report any signs or symptoms that could be associated with these events without delay. In some cases, these events can present asymptomatically. The implant and the tissue overlying the implant flange should be monitored routinely following the implant insertion, and refill-exchange procedures to permit early medical or surgical intervention as necessary. Special precautions need to be taken when handling SUSVIMO components.
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> 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 decrease in visual acuity usually occurs over the first two postoperative months.

Summary

The use of anti-VEGF agents such as ranibizumab are very effective and are considered standard therapy to treat neovascular AMD. In clinical practice, long-term visual acuity outcomes are worse than outcomes reported in clinical trials. This is likely due to compliance issues resulting in decreased monitoring and treatment frequency (Holekamp, 2021). The port delivery system is being an evaluated as an alternative to monthly injections which may increase treatment compliance. The port devlivery system is more invasive than the current approach and is associated with a significant increased risk of endophthalmitis. Additional research is needed to evaluate the long-term performance and complication rate of the port delivery system. Longitudinal data is needed to confirm potential improved visual outcomes and real world results will not be available for several years. In addition, further investigation is needed to address whether treatment with the port delivery system is generalizable to a more diverse clinical population, including those living with a longstanding neovascular AMD diagnosis. A clinical trial (NCT NCT03683251) is underway to further evaluate the individuals in previous trials for approximately 240 weeks. The estimated study completion date is December 2026.

Other Retinal Disease

Additional clinical trials are being performed investigating port delivery systems for the treatment of other retinal conditions, including diabetic macular edema and diabetic retinopathy. Phase 3 studies are underway (NCT04108156, NCT04503551). The port delivery system is currently FDA approved only for the treatment of neovascular AMD.

Background/Overview

The ocular implant used with Susvimo is inserted during an outpatient procedure, with the reservoir filled prior to placement. The implant is surgically placed in an incision through the sclera and pars plana. The implant contains a self-sealing septum used to refill the port. The drug is continuously released into the vitreous through passive diffusion. The reservoir is refilled approximately every 6 months during an office setting visit.

AMD is the leading cause of vision loss in older adults, affecting approximately 11 million people in the U.S. AMD is categorized as either dry or atrophic AMD, which is more common, and wet or advanced neovascular AMD. Neovascular AMD is characterized by macular or choroidal neovascularization, fluid leakage and central vision loss. Monthly intravitreal anti-VEGF therapy is considered the standard of care therapy for wet AMD. In clinical practice, decreased treatment frequency over time is often reported and has been identified as a possible cause of reduced VEGF therapy effectiveness in clinical practice compared to clinical trials (Khanani, 2021).

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

67027	Implantation of intravitreal drug delivery system (eg, ganciclovir implant), includes concomitant removal of vitreous [when specified as implantation of Susvimo]
67028	Intravitreal injection of a pharmacologic agent (separate procedure) [when specified as refill injection of Susvimo]

HCPCS

C9093	Injection, ranibizumab, via sustained release intravitreal implant (Susvimo), 0.1 mg
J3490	Unclassified drugs [when specified as Susvimo refill]
J3590	Unclassified biologics [when specified as Susvimo refill]

ICD-10 Diagnosis

	All diagnoses, including but not limited to
H35.3210-H35.3293	Exudative age-related macular degeneration

References

Peer Reviewed Publications:

1. Campochiaro PA, Maass KF, Singh N, Barteselli G. Reply. Ophthalmology. 2019; 126(11):e88-e89.
2. Campochiaro PA, Marcus DM, Awh CC, et al. The port delivery system with ranibizumab for neovascular age-related macular degeneration: Results from the randomized Phase 2 Ladder clinical trial. Ophthalmology. 2019; 126(8):1141-1154.
3. Holekamp NM, Campochiaro PA, Chang M, et al; Archway Investigators. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. Ophthalmology. 2021: S0161-6420(21)00734-X.
4. Khanani AM, Aziz AA, Weng CY, et al. Port delivery system: a novel drug delivery platform to treat retinal diseases. Expert Opin Drug Deliv. 2021; 18(11):1571-1576.
5. Khanani AM, Callanan D, Dreyer R, et al; of the Ladder Investigators. End-of-study results for the Ladder Phase 2 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. Ophthalmol Retina. 2021; 5(8):775-787.
6. Sharma A, Kumar N, Kuppermann BD, Francesco B. Re: Campochiaro et al.: The port delivery system with ranibizumab for neovascular age-related macular degeneration: results from the randomized phase 2 Ladder clinical trial (Ophthalmology. 2019;126:1141-1154). Ophthalmology. 2019; 126(11):e87-e88.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Academy of Ophthalmology (AAO). Age-Related Macular Degeneration Preferred Practice Pattern®. Approved on September 7, 2019. For additional information, see the AAO website at https://www.aao.org/.
2. Susvimo [Product Information], South San Francisco, CA. Genentech, Inc.; Updated on October 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761197s000lbl.pdf. Accessed on January 4, 2022.

3. U.S. Food and Drug Administration (FDA). Biologics License Application Approval. SUSVIMO (ranibizumab injection). BLA 761197. October 22. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761197Orig1s000_ltr.pdf. Accessed on January 4, 2022.
4. U.S. National Library of Medicine. Clinical Trials.
    - NCT03683251. A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of the Port Delivery System With Ranibizumab in Patients With Neovascular Age-Related Macular Degeneration (Portal). Last updated December 15, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03683251. Accessed on January 4, 2022.
    - NCT04108156. A Phase III, Multicenter, Randomized, Visual Assessor-Masked, Active-comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System With Ranibizumab in Patients With Diabetic Macular Edema (Pagoda). Last updated on October 28, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04108156?term=NCT04108156&draw=1&rank=1. Accessed on January 4, 2022.
    - NCT04503551. A Phase III, Multicenter, Randomized Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System With Ranibizumab in Patients With Diabetic Retinopathy. Last updated on October 28, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04503551?term=NCT04503551&draw=2&rank=1. Accessed on January 4, 2022.

Websites for Additional Information

1. National Institute of Health (NIH). National Eye Institute. Age-Related Macular Degeneration. Last updated: June 22, 2021. Available at: https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/age-related-macular-degeneration. Accessed on January 3, 2022.
2. The American Society of Retina Specialists (ASRS). Age-Related Macular Degeneration. Available at: https://www.asrs.org/patients/retinal-diseases/2/agerelated-macular-degeneration. Accessed on January 3, 2022.

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Susvimo

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	02/17/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.