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 reducing 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 (Archway). 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 2023, the 2-year results of the Archway trial were reported by Regillo and colleagues. Following an initial transient and reversible decrease in BCVA in the implantation group, both groups reported similar mean BCVA change from baseline through week 96. An additional 8 serious ocular AEs were reported in the implantation group compared to 2 in the monthly injection group. These serious ocular AEs included 3 cases of implant dislocation and conjunctival erosion, reduced visual acuity, cataract cortical, conjunctival bleb, corneal disorder, retinal pigment epithelial tear, scleral thinning, retinal tear and endophthalmitis. One individual in the implantation group experienced a traumatic cataract which was the result of surgical removal of a dislocated implant. The 4 cases of implant dislocation were treated with implant removal. The vision returned to baseline in 3 individuals. The 4th individual experienced additional complications and the vision remained markedly decreased (Snellen equivalent 20/32 at baseline compared to < 20/200 at last available visit). These cases were attributed to surgical error regarding length of the surgical incision. There were 3 cases of implant septum dislodgement with 2 cases occurring after at least 1 refill-exchange procedure. The third case occurred 112 days after the 3rd refill-exchange procedure. Additional follow-up data is being collected through 5 years post-implantation. The authors note:

> However, whether or not these or other novel long-lasting treatments are able to respond to the unmet medical need for reduced treatment burden in nAMD will depend not only on their effectiveness in gaining and maintaining visual function but also on their overall long-term safety profile.

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.
>
> 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.

Voluntary Recall

In October 2022, the Susvimo ocular implant and initial fill needle were voluntarily recalled due to issues with the durability of the product over the long-term following multiple refills. In clinical trials, the septum of the implant has become dislodged from the implant body resulting a potential for medication leakage. The recall does not include the refill equipment. For individuals with a defective implant, further refill-exchange procedures should not be performed. The manufacturer notes “The long-term risks of retaining vs. removing an implant with a dislodged septum are not well characterized at this time.”

Timmons and associates (2022) reported on an individual who experienced an implanted septum dislodgement case in a clinical trial. Post refill implant photography after the third refill revealed that the septum had fallen into the implant reservoir. The septum began a downward migration following device implantation and progressed with each subsequent refill. The provider confirmed the correct refill procedure was followed and penetration of the septum was achieved on the first attempt at each refill. The presence of the implant with a nonfunctioning seal may be associated with a risk of intraocular inflammation.

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 delivery 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. The implantation of the Susvimo is currently on hold pending further evaluation of the potential for implant failure.

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 (Pagoda), NCT04503551 (Pavilion)). 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:

HCPCS

J2779	Injection, ranibizumab, via intravitreal implant (Susvimo), 0.1 mg

ICD-10 Diagnosis

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

When services may also be 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

	Note: codes billed in addition to the specific code for Susvimo listed above may include, but are not limited to, the following; this document does not apply if the following codes are billed without the specific code for Susvimo or if these codes are used for pharmacologic agents other than Susvimo.
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*]

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. Regillo C, Berger B, Brooks L, et al. Archway Phase 3 Trial of the Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration 2-Year Results. Ophthalmology. 2023; 130(7):735-747.
7. Sharma A, Khanani AM, Parachuri N, et al. Port delivery system with ranibizumab (Susvimo) recall- What does it mean to the retina specialists. Int J Retina Vitreous. 2023; 9(1):6.
8. 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.
9. Timmons K, Heckmann LC, Ren Y, et al. Ranibizumab injection (Susvimo) implant septum dislodgement in a patient with neovascular age-related macular degeneration. JAMA Ophthalmol. 2022; 140(8):832.

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. Genentech. Dear Health Care Provider Letter. Voluntary recall of the Susvimo Ocular Implant. October 2022. Available at: https://www.gene.com/download/pdf/Susvimo_DHCP_Important_Prescribing_Information_2022-10-18.pdf. Accessed on January 11, 2024.
3. 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 11, 2024.
4. 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 11, 2024.
5. 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 22, 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT03683251. Accessed on January 11, 2024.
    - 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 September 13, 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT04108156?term=NCT04108156&draw=1&rank=1. Accessed on January 11, 2024.

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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 11, 2024.
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Index

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
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
	09/27/2023	Updated Coding section, added note to CPT codes for clarification.
Reviewed	02/16/2023	MPTAC review. Updated Rationale and References sections.
	06/29/2022	Updated Coding section with 7/1/2022 HCPCS changes; added J2779 replacing C9093 and deleted J3490, J3590.
New	02/17/2022	MPTAC review. Initial document development.