Policy Number	**OTH903.015**
Policy Effective Date	**12/15/2025**
Policy End Date	**10/14/2026**

Photodynamic Therapy for Choroidal Neovascularization

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses

as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Verteporfin photodynamic therapy as monotherapy **may be considered medically necessary** as a treatment of choroidal neovascularization associated with age-related macular degeneration, pathologic myopia, presumed ocular histoplasmosis, chronic central serous chorioretinopathy, or choroidal hemangioma.

Verteporfin photodynamic therapy **is considered experimental, investigational and/or unproven** as monotherapy for other ophthalmologic disorders.

Verteporfin photodynamic therapy **is considered experimental, investigational and/or unproven** when used in combination with one or more of the antivascular endothelial growth factor therapies: ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Eylea®), brolucizumab-dbll (Beovu®), or faricimab-svoa (Vabysmo®) as a treatment of choroidal neovascularization associated with age-related macular degeneration, pathologic myopia, presumed ocular histoplasmosis, central serous chorioretinopathy, choroidal hemangioma, or for other ophthalmologic disorders.

Policy Guidelines

U.S. Food and Drug Administration (FDA) labeling for verteporfin indicates that the physician should reevaluate the individual every 3 months and, if choroidal neovascularization leakage is detected on fluorescein angiography, therapy should be repeated. However, total number of treatments is not addressed by FDA. Evidence defining when treatment should stop is not available, but experts have suggested stopping “when the situation is judged to be ‘futile’.” FDA labeling states that the “safety and efficacy of Visudyne beyond 2 years have not been demonstrated.”

Acute central serous chorioretinopathy refers to self-limiting disease that resolves spontaneously over a few months without any treatment. Chronic central serous chorioretinopathy has been defined as a serous macular elevation, visible biomicroscopically or detected by optical coherence tomography, that is associated with retinal pigment epithelial atrophic areas and subtle leaks or ill-defined staining by fluorescein angiography; it does not resolve spontaneously within a few months.

Description

Verteporfin photodynamic therapy is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a 2-step process, consisting of an injection of the photosensitizer verteporfin, followed 15 minutes later by laser treatment to the targeted sites of retinal neovascularization. The laser treatment selectively damages the vascular endothelium, thereby occluding choroidal neovascularization tissue. Individuals may be retreated if leakage from choroidal neovascularization persists.

Vision Loss

Severe vision loss can occur with ocular neovascularization, the growth of abnormal blood vessels in the retina or choroid. Neovascularization occurs in a number of ocular diseases, including age-related macular degeneration.

Age-Related Macular Degeneration

Age-related macular degeneration is a degenerative disease of the retina that results in loss of central vision. Two distinctive forms, known as dry and wet degeneration, may be observed. The dry form (also known atrophic or areolar) is more common and is often a precursor of the wet form (also known as exudative neovascular or disciform). The wet form is more devastating and characterized by serous or hemorrhagic detachment of the retinal pigment epithelium and development of choroidal neovascularization, which greatly increases the risk of developing severe irreversible loss of vision. Choroidal neovascularization is categorized as classic or occult. Classic choroidal neovascularization appears as an initial lacy pattern of hyperfluorescence followed by more irregular patterns as the dye leaks into the subretinal space. Occult choroidal neovascularization lacks the characteristic angiographic pattern. Classic choroidal neovascularization carries a worse prognosis for vision than occult choroidal neovascularization, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of age-related macular degeneration.

Pathologic Myopia

Pathologic myopia refers to an abnormal elongation of the eye associated with severe near-sightedness. It generally occurs among people older than 30 years of age and can result in a progressive, severe loss of vision, frequently related to the development of choroidal neovascularization. Verteporfin photodynamic therapy has also been investigated in patients with choroidal neovascularization related to pathologic myopia. Antivascular endothelial growth factor therapy is now considered a first-line intervention in patients with myopic choroidal neovascularization.

Presumed Ocular Histoplasmosis

Presumed ocular histoplasmosis may be the second most common cause of blindness in patients younger than 50 years of age in certain endemic areas (Ohio and Mississippi River Valleys in the United States). This condition is characterized by a positive skin test for histoplasmosis, miliary opacities of the lungs, tiny choroidal scars, peripapillary disruption of the choriocapillaris, and exudation or hemorrhage from choroidal lesions in or near the macula.

The condition is asymptomatic and benign, unless the choroidal neovascularization lesions, which may develop many years after chorioretinal scarring has taken place, affect the macula.

Central Serous Chorioretinopathy

Central serous chorioretinopathy refers to an idiopathic disease in which there is a serous detachment of the macula due to leakage of fluid from the choriocapillaris through the retinal pigment epithelium. This condition is avascular; however, neovascularization can occur as a secondary complication. In most cases, central serous chorioretinopathy resolves spontaneously in 3 to 4 months. However, in a few cases, chronic progression or recurrence can lead to the progressive decline of visual acuity. Central serous chorioretinopathy has been treated with medication and laser photocoagulation, but these treatments have limited efficacy. Multiple definitions have been used in the literature to classify central serous chorioretinopathy as acute or chronic based cutoff time points (e.g., persistent fluid for <3, 4 or 6 months) or less frequently based on the timing of treatment. For example, acute central serous chorioretinopathy defined as the first attempted treatment to improve visual acuity, and chronic central serous chorioretinopathy is defined as being refractory to treatment. Further, multiple verteporfin photodynamic therapy strategies that use either reduced-dose or half-fluency have been evaluated for the treatment of central serous chorioretinopathy because full-dose verteporfin photodynamic therapy used in age-related macular degeneration has shown a potentially higher risk of developing choroidal ischemia and retinal atrophic changes.

Polypoidal Choroidal Vasculopathy

Polypoidal choroidal vasculopathy arises primarily from abnormal choroidal circulation, resulting in characteristic lesions comprising well-defined vascular networks of vessels ending in polyp-like structures. A less common subtype is polypoidal choroidal neovascularization, and it may be considered a subtype of age-related macular degeneration. Eyes that develop a cluster of grape-like polypoidal dilations are at high risk for severe vision loss.

Choroidal Hemangioma

Choroidal hemangioma is an uncommon, benign vascular tumor, manifesting as an orange-red mass in the posterior pole of the eye. Visual loss may be progressive and irreversible because of chronic foveal detachment.

Angioid Streaks

Angioid streaks result from crack-like breaks in the Bruch membrane (the innermost layer of the choroid) and occur in individuals spontaneously or due to blunt trauma or associated with some systemic diseases such as pseudoxanthoma elasticum, Paget disease of bone, or sickle hemoglobinopathy. Vision loss in eyes with angioid streaks occurs most frequently as a result of choroidal neovascularization.

Treatment

Available therapeutic options for choroidal neovascularization include antivascular endothelial growth factor inhibitors, verteporfin photodynamic therapy, antioxidants, thermal laser

photocoagulation, and corticosteroids. The safety and efficacy of each treatment depends on the form and location of the neovascularization.

Verteporfin photodynamic therapy is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a 2-step process, consisting of an injection of the photosensitizer verteporfin, followed 15 minutes later by laser treatment to the targeted sites of retinal neovascularization. The laser treatment selectively damages the vascular endothelium and occludes the neovascularized tissue. Patients may be retreated if leakage from choroidal neovascularization persists.

Monotherapy with vascular endothelial growth factor inhibitors is now standard treatment of choroidal neovascularization due to age-related macular degeneration and pathologic myopia. Combining verteporfin photodynamic therapy with antivascular endothelial growth factor inhibitors, concurrently or sequentially, has a biologic basis and has been investigated in multiple trials particularly in the treatment of choroidal neovascularization due to age-related macular degeneration and pathologic myopia.

The use of verteporfin photodynamic therapy in choroidal neovascularization has decreased substantially with the availability of antivascular endothelial growth factor therapy. Subsequent to U.S. Food and Drug Administration (FDA) approval of verteporfin photodynamic therapy in 2000, the FDA approved pegaptanib in 2004 and ranibizumab in 2006 for treatment of age-related macular degeneration related choroidal neovascularization. The approval of pegaptanib was based on a sham-controlled, randomized trial (1, 2) while ranibizumab was approved based on a head-to-head comparison with verteporfin photodynamic therapy in the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trial. (3) Intravitreal injections of antivascular endothelial growth factor drugs such as ranibizumab and bevacizumab have shown superior efficacy compared with verteporfin photodynamic therapy in multiple head-to-head trials. Currently, verteporfin photodynamic therapy is used for patients in whom vascular endothelial growth factor inhibitors are contraindicated or for those who fail to benefit from vascular endothelial growth factor inhibitors.

Regulatory Status

In 2000, verteporfin (Visudyne®; Novartis [now Bausch & Lomb]), an intravenous photodynamic therapy agent, was approved by the FDA for the treatment of age-related macular degeneration in individuals with predominantly classic subfoveal choroidal neovascularization. Subsequently, in 2001, the indication was expanded to include presumed ocular histoplasmosis and pathologic myopia.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality

of life, and ability to function¾including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

Age-Related Macular Degeneration - Verteporfin Photodynamic Therapy vs Placebo
Choroidal neovascularization is categorized as classic or occult. Classic choroidal neovascularization appears as an initial lacy pattern of hyperfluorescence followed by more irregular patterns as the dye leaks into the subretinal space. Occult choroidal neovascularization lacks the characteristic angiographic pattern. Classic choroidal neovascularization carries a worse prognosis for vision than occult choroidal neovascularization, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of age-related macular degeneration.

Clinical Context and Therapy Purpose
The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with classic choroidal neovascularization due to age-related macular degeneration.

The following PICO was used to select literature to inform this policy.

Population
Individuals with classic choroidal neovascularization due to age-related macular degeneration.

Intervention
Treatment with verteporfin photodynamic therapy.

Comparator
Observation only.

Outcomes
Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Verteporfin Photodynamic Therapy vs Placebo
In 1999, the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) published conclusions that were based on the 1-year follow-up results of 609 patients enrolled in 2 similar, multicenter, double-masked, randomized placebo-controlled trials. (4) Subgroup analysis showed that efficacy was limited to patients in whom the area of classic CNV occupied 50% or more of the area of the lesion. Subsequently, in 2001, 2-year results of the TAP trials showed that beneficial outcomes for visual acuity and contrast sensitivity observed after 1-year of follow-up were sustained through 24 months. (5) At 2 years, 53% of the VPDT arm compared with 38% of the placebo arm lost fewer than 15 letters. Further, an average number of VPDT treatments required was lower in the second year (2.2) compared with the first year (3.4). Subgroup analysis confirmed the earlier findings that efficacy was limited to patients in whom the area of classic CNV occupied 50% or more of the area of the lesion.

Since 2001, several additional reports from the TAP trials have been published. (6-8) They demonstrated positive outcomes with the use of verteporfin photodynamic therapy for subfoveal choroidal neovascularization, and further supported the findings of the earlier TAP trial reports. Kaiser (2006) reported on results of a 3-year open-label extension of the TAP trials. (9) Of 402 verteporfin photodynamic therapy treated patients who completed the 24-month randomized study, 320 (80%) enrolled in the extension protocol. Of the 320 enrolled, 193 (60%) completed the 60-month examination, 122 (38%) discontinued prematurely, and 3 (1%) were noncompliant. Yearly treatment rates declined from 3.5 treatments in the first year to 0.1 in the fifth year; patients who remained in the study lost an additional 2.3 lines of letters over the 3-year extension.

The Verteporfin in Photodynamic Therapy (VIP) trial (2001) randomized 339 patients to verteporfin photodynamic therapy or placebo. (10) Most (76%) patients had occult disease while the remainder had early classic choroidal neovascularization with good visual acuity. The primary outcome was the proportion of eyes with fewer than 15 letters of visual acuity loss. While there was no significant difference between the treatment and placebo groups at 12 months, by 24 months a significantly lower percentage of those with occult choroidal

neovascularization who were treated with verteporfin photodynamic therapy (55%) had lost vision compared with those who received placebo (68%; p=.032). These results contrast with those of the TAP trials, although the patient populations differed. The TAP trials required all patients to have some percentage of classic choroidal neovascularization, while the VIP trial recruited patients with occult disease without evidence of classic choroidal neovascularization. In addition, the VIP trial required patients with occult disease to have experienced recent deterioration in vision. Results for the subgroup of patients with classic choroidal neovascularization but good visual acuity were not reported separately.

Multiple systematic reviews and meta-analysis have included TAP and VIP trials and corroborated the treatment benefit of verteporfin photodynamic therapy in preventing vision loss. A Cochrane review (2003) concluded that verteporfin photodynamic therapy was effective at preventing vision loss in classic and occult choroidal neovascularization due to age-related macular degeneration. (11) In a meta-analysis of the safety of verteporfin photodynamic therapy, Azab et al. (2004) analyzed data from the 24-month TAP A and B and VIP trials (total N=948 patients with age-related macular degeneration). (12) Reviewers concluded that the safety profile of verteporfin photodynamic therapy did not differ statistically from placebo. An updated Cochrane review (2007) evaluated results from the 3 RCTs (total N=1022 patients), which included the TAP and VIP trials. (13) Meta-analysis showed a 24-month risk ratio of losing 6 or more lines of visual acuity of 0.62 compared with the control group. Reviewers concluded that verteporfin photodynamic therapy was probably effective for treating choroidal neovascularization due to age-related macular degeneration, although the effect size was uncertain.

The result of a multicenter RCT (2008) that compared 2 intensities of initial verteporfin photodynamic therapy-every 2 or 3 months for first 6 months in 203 patients with choroidal neovascularization caused by age-related macular degeneration-showed no differences in overall outcomes for visual acuity or anatomic lesion features. (14)

Section Summary: Age-Related Macular Degeneration - Verteporfin Photodynamic Therapy vs Placebo

The evidence for the efficacy of verteporfin photodynamic therapy includes multiple RCTs that have established its superiority over placebo. However, the efficacy is limited to a subgroup of patients with classic choroidal neovascularization. The use of verteporfin photodynamic therapy has now been largely replaced by antivascular endothelial growth factor therapies.

Age-Related Macular Degeneration - Verteporfin Photodynamic Therapy Plus Anti-Vascular Endothelial Growth Factor Therapy

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to age-related macular degeneration.

The following PICO was used to select literature to inform this policy.

Population
Individuals with choroidal neovascularization due to age-related macular degeneration.

Intervention
Treatment with verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy.

Comparator
Treatment with antivascular endothelial growth factor therapy alone.

Outcomes
Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Because verteporfin photodynamic therapy and antivascular endothelial growth factor agents target different disease components of age-related macular degeneration, it has been hypothesized that combining them might lead to a synergistic effect, with a decreased need for monthly vascular endothelial growth factor injection and increased the durability of response while maintaining visual acuity.

Systematic Reviews
A systematic review (2015) of antivascular endothelial growth factor injections for treating wet age-related macular degeneration compared antivascular endothelial growth factor monotherapy with antivascular endothelial growth factor combination therapy plus verteporfin photodynamic therapy. (15) Results showed a significant difference in best-corrected visual acuity of 2.74 letters (95% CI, 0.26 to 5.21 letters; p=.03) in favor of the monotherapy group (note that the conclusions of this systematic review indicated that the difference favored the combination group, which is incorrect). There were no differences between groups on the central retinal thickness or lesion size. Reviewers did not report a combined analysis of the number of antivascular endothelial growth factor injections performed in each group. Similar results were reported in a meta-analysis published in 2016. (16)

Key Clinical Trials

The open-label, phase 2 study (2006) demonstrated that same-day administration of ranibizumab and verteporfin photodynamic therapy was well tolerated and vision was maintained. (17) Results of the phase 1/2 FOCUS (Intravitreal Injections of rhuFab V2 in Combination With Visudyne in Subjects With Age Related Macular Degeneration) trial further supported the idea that combination treatment might be more effective than monotherapy. (17, 18) In this trial, 162 patients with classic choroidal neovascularization secondary to age-related macular degeneration were randomized to verteporfin photodynamic therapy plus ranibizumab (n=106) or verteporfin photodynamic therapy plus sham (n=56). Verteporfin photodynamic therapy was repeated only if fluorescein angiography revealed persistent or recurrent leakage from choroidal neovascularization at evaluation visits (3-month intervals). Intention-to-treat analysis showed an average improvement in acuity of 5 letters at both 12 and 24 months (85% retention) with ranibizumab compared with a decrease of 8 letters in the verteporfin photodynamic therapy alone group. Visual acuity improved by 15 or more letters in 25% of patients treated with ranibizumab (plus verteporfin photodynamic therapy as needed) compared with 7% of patients treated with verteporfin photodynamic therapy alone. However, the FOCUS trial did not include a ranibizumab monotherapy arm.

Subsequently, the 2 larger phase 3 confirmatory trials - DENALI and MONT BLANC - failed to show the superiority of ranibizumab plus verteporfin photodynamic therapy over ranibizumab alone. DENALI (Efficacy/Safety of Verteporfin Photodynamic Therapy and Ranibizumab Compared With Ranibizumab in Patients With Subfoveal Choroidal Neovascularization) was a multicenter, double-masked, randomized phase 3b trial (2012) that tested the noninferiority of ranibizumab plus verteporfin photodynamic therapy vs verteporfin photodynamic therapy alone. In this trial, patients were randomized to ranibizumab plus standard fluence verteporfin photodynamic therapy (n=104) or reduced-fluence (n=105) or ranibizumab plus sham verteporfin photodynamic therapy (n=112). (19) Patients received 3 consecutive monthly injections of ranibizumab followed by as-needed retreatments. The 2 main outcome measures were change in best-corrected visual acuity from baseline and the proportion of patients in the combination therapy groups with a treatment-free interval of 3 months or more. An improvement in mean best-corrected visual acuity score was observed in all treatment groups, with the largest mean change from baseline in the ranibizumab monotherapy group. The mean change in best-corrected visual acuity at 12 months was +5.3, +4.4, and +8.1 for ranibizumab plus standard fluence verteporfin photodynamic therapy, ranibizumab plus reduced-fluence verteporfin photodynamic therapy, and ranibizumab plus sham verteporfin photodynamic therapy, respectively. Noninferiority for visual acuity was not demonstrated. Trials failed to demonstrate the superiority of combination treatment to reduce treatment-free interval period. The proportion of patients with a treatment-free interval of 3 months or more was 92.6% (95% confidence interval [CI], 85.4% to 97.0%) in the ranibizumab plus standard fluence verteporfin photodynamic therapy and 83.5% (95% CI, 74.6% to 90.3%) in the reduced-fluence arm. Percentages for ranibizumab monotherapy were not reported.

MONT BLANC (Verteporfin Photodynamic Therapy Administered in Conjunction With Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-related

Macular Degeneration) was similar to DENALI regarding design and outcome measures, except that the former did not include a reduced-fluence verteporfin photodynamic therapy arm. (20) In this trial, 255 patients were randomized to ranibizumab plus standard fluence verteporfin photodynamic therapy (n=122) or ranibizumab plus sham verteporfin photodynamic therapy (n=133). Patients received 3 consecutive monthly injections of ranibizumab followed by as-needed retreatments. A difference in mean best-corrected visual acuity within 7 letters was designated as noninferiority margin. The mean change in best-corrected visual acuity at 12 months was +2.5 letters in ranibizumab plus standard fluence verteporfin photodynamic therapy group and +4.4 letters in the ranibizumab plus sham verteporfin photodynamic therapy group, yielding a mean difference (MD) of 1.88. Because this difference was within the noninferiority margin, authors concluded that ranibizumab plus verteporfin photodynamic therapy was noninferior to verteporfin photodynamic therapy alone. At 12 months, the proportion of patients with a treatment-free interval of 3 months or more was similar in the 2 groups (96% combination therapy vs 92% monotherapy). With the sample size of 125 in each arm, the trial as designed had 80% power to identify treatment difference of 20% or more in the proportion of patients with 3 or more months of treatment-free interval in the combination arm vs monotherapy arm. After 12 months, the proportion of patients with 3 or more months of treatment-free interval was 96% and 92% in the combination and monotherapy arm, respectively (difference in proportion, 0.04; 95% CI, -0.02 to 0.09). Thus, the trial failed to show the superiority of ranibizumab plus verteporfin photodynamic therapy over verteporfin photodynamic therapy alone in increasing the treatment-free interval.

Additional Randomized Controlled Trials

In addition to the above trials, several smaller randomized trials have been published. Semeraro et al. (2015) published an RCT evaluating 75 patients with treatment-naive exudative choroidal neovascularization due to age-related macular degeneration. (21) Patients were randomized into 3 groups: ranibizumab monotherapy, ranibizumab plus reduced-fluence verteporfin photodynamic therapy, and ranibizumab plus ketorolac eye drops. At the 12-month follow-up, best-corrected visual acuity was superior in the ranibizumab plus ketorolac group (-0.25 logarithm of the minimum angle of resolution) compared with ranibizumab monotherapy (-0.14 logarithm of the minimum angle of resolution) or ranibizumab combined with verteporfin photodynamic therapy (-0.10 logarithm of the minimum angle of resolution). In a multicenter, unmasked trial, Williams et al. (2012) randomized 60 patients to ranibizumab with half-fluence verteporfin photodynamic therapy or ranibizumab alone. (22) Best-corrected visual acuity improved by 9.9 letters in the ranibizumab group and by 2.6 letters in the combined treatment group. The proportion of patients who gained 15 or more letters was 33% in the monotherapy arm and 31% in the combination arm. A small RCT by Lim et al. (2012) assessed 31 patients with age-related macular degeneration and 10 patients with polypoidal choroidal vasculopathy who were randomized to bevacizumab monotherapy or bevacizumab plus verteporfin photodynamic therapy. (23) At 12 months, the monotherapy and combined treatment groups showed similar improvements in best-corrected visual acuity and central foveal thickness, and the total number of bevacizumab injections was not reduced when verteporfin photodynamic therapy was given. A randomized, open-label assessor-blinded trial (2007) from Croatia with short-term (3-month) follow-up evaluated combination treatment with bevacizumab plus

verteporfin photodynamic therapy (N=165 eyes). (24) At 3-month follow-up, 22 (42%) of 52 patients improved by more than 0.2 logarithm of the minimum angle of resolution following combined treatment compared with 1 (2%) patient treated with bevacizumab alone and none treated with verteporfin photodynamic therapy alone.

Nonrandomized Studies

Data from a retrospective study for adjunctive verteporfin photodynamic therapy in patients refractory to antivascular endothelial growth factor monotherapy has suggested a favorable effect on visual acuity and anatomic outcomes. Lee and Lee (2016) reported on data from a retrospective analysis of 28 eyes of 28 patients who showed persistent subretinal and/or intraretinal fluid after at least 4 antivascular endothelial growth factor injections in the 6 months before adjunctive verteporfin photodynamic therapy and subsequently received additional verteporfin photodynamic therapy and antivascular endothelial growth factor therapies. (25) Patient charts were reviewed until 12 months after the initial verteporfin photodynamic therapy. During a 1-year follow-up, 17 (60.7%) eyes did not demonstrate recurrent fluid accumulation. Among the 11 eyes requiring retreatment, 7 eyes initially showed complete fluid absorption after the initial photodynamic therapy. At 12 months, best-corrected visual acuity had improved by 0.3 logarithm of the minimum angle of resolution or more or was maintained compared with baseline in 27 (96.4%) eyes.

Section Summary: Age-Related Macular Degeneration - Verteporfin Photodynamic Therapy Plus Anti-Vascular Endothelial Growth Factor Therapy

The evidence for the efficacy verteporfin photodynamic therapy plus antivascular endothelial growth factor therapies compared with antivascular endothelial growth factor therapies alone includes 2 confirmatory RCTs (and their multiple analyses), multiple smaller RCTs, and a meta-analysis. This evidence does not demonstrate improvements in best-corrected visual acuity with combination therapy compared with antivascular endothelial growth factor monotherapy. Combination therapy may reduce the number of intravitreal injections needed, but this result has not been consistently reported across studies.

Age-Related Macular Degeneration - Verteporfin Photodynamic Therapy Plus Corticosteroids and/or Vascular Endothelial Growth Factor Inhibitors

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy plus corticosteroids and/or antivascular endothelial growth factor therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to age-related macular degeneration.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to age-related macular degeneration who are treated with verteporfin photodynamic therapy plus corticosteroids and/or antivascular endothelial growth factor therapy.

Intervention
Treatment with verteporfin photodynamic therapy plus corticosteroids and/or antivascular endothelial growth factor therapy.

Comparator
Treatment with corticosteroids and/or antivascular endothelial growth factor therapy.

Outcomes
Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Three RCTs have evaluated the combination of verteporfin photodynamic therapy with corticosteroids¾1 trial from Italy, (26) 1 trial from Canada (Canadian Retinal Trials Group), (27) and 1 trial from Iran. (28) The Italian RCT (2008) assigned 84 treatment-naive patients with exudative age-related macular degeneration to verteporfin photodynamic therapy alone (n=41) or combination intravitreal triamcinolone acetonide plus verteporfin photodynamic therapy (n=43). (26) Mean visual acuity increased at 1 month of follow-up but decreased progressively by the 24-month point in both groups. In the Canadian Retinal Trials Group study (2009), 100 patients with choroidal neovascularization due to age-related macular degeneration were randomized to verteporfin photodynamic therapy alone or verteporfin photodynamic therapy plus intravitreal triamcinolone. (27) Combination treatment did not result in a significant difference in the primary outcome of visual acuity at 1 year compared with verteporfin photodynamic therapy alone. The Iranian trial (2014) randomized 84 treatment-naive patients who had choroidal neovascularization due to age-related macular degeneration to verteporfin photodynamic therapy plus bevacizumab with and without intravitreal triamcinolone. (28) There were no significant differences in the best-corrected visual acuity at week 12 and other time points.

Section Summary: Age-Related Macular Degeneration - Verteporfin Photodynamic Therapy Plus Corticosteroids and/or Vascular Endothelial Growth Factor Inhibitors
The evidence for the efficacy of triple therapy verteporfin photodynamic therapy plus corticosteroid and antivascular endothelial growth factor includes 3 small RCTs. This evidence does not demonstrate improvements in best-corrected visual acuity with this therapy

compared with antivascular endothelial growth factor monotherapy. Comparative trials are needed to evaluate the efficacy of this triple therapy.

Pathologic Myopia - Verteporfin Photodynamic Therapy vs Placebo

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to pathologic myopia.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to pathologic myopia.

Intervention

Treatment with verteporfin photodynamic therapy.

Comparator

Observation only.

Outcomes

Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The initial evidence on pathologic myopia was based primarily on retrospective studies and clinician experience. RADIANCE (Efficacy and Safety of Ranibizumab in Patients With Visual Impairment Due to Choroidal Neovascularization Secondary to Pathologic Myopia), a multicenter RCT (2014) compared intravitreal ranibizumab with verteporfin photodynamic therapy in the treatment of myopic choroidal neovascularization and reported improved visual acuity at 12 months in the ranibizumab treatment arm. (29) Zhu et al. (2016) published a Cochrane review that found treatment with antivascular endothelial growth factor therapies was more likely to restore visual acuity than verteporfin photodynamic therapy. (30)

Verteporfin Photodynamic Therapy vs Placebo

A second arm of the VIP trial focused on 120 patients with pathologic myopia and choroidal neovascularization, either classic, occult, or mixed (although 90% of patients had classic choroidal neovascularization), who were randomized 2:1 to verteporfin photodynamic therapy or placebo. (31) Patients received an average of 3.4 verteporfin photodynamic therapy treatments over 12 months. The primary outcome was the proportion of eyes with fewer than 8 letters of visual acuity loss at 12 months by intention-to-treat analysis. At month 12, 58 (72%) of patients who received verteporfin photodynamic therapy lost fewer than 8 letters on a standard eye chart and 17 (44%) receiving placebo. Improvement of at least 5 letters was observed in 26 (32%) verteporfin photodynamic therapy-treated eyes compared with 6 (15%) placebo-treated eyes. Fluorescein angiography showed the progression of classic choroidal neovascularization in 36% of verteporfin photodynamic therapy-treated eyes compared with 54% of the placebo group. Trialists concluded that verteporfin photodynamic therapy increased the chance of stabilizing or improving vision compared with placebo for at least 1 year. However, the results at 2 years of follow-up were not statistically significant in favor of verteporfin photodynamic therapy. (32)

Section Summary: Pathologic Myopia - Verteporfin Photodynamic Therapy vs Placebo

The evidence for the efficacy of verteporfin photodynamic therapy compared with placebo includes a subgroup analysis from a large RCT. This analysis showed verteporfin photodynamic therapy to be more effective than placebo in preventing vision loss, and these findings have been corroborated in nonrandomized studies. However, the long-term efficacy of verteporfin photodynamic therapy is uncertain. Moreover, use of verteporfin photodynamic therapy for myopic choroidal neovascularization has now been largely replaced by antivascular endothelial growth factor therapies.

Pathologic Myopia - Verteporfin Photodynamic Therapy Plus Anti-Vascular Endothelial Growth Factor Therapy

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to pathologic myopia.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to pathologic myopia who are treated with verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy.

Intervention

Treatment with verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy.

Comparator

Treatment with antivascular endothelial growth factor therapy alone.

Outcomes
Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Rinaldi et al. (2017) randomized 60 patients to verteporfin photodynamic therapy (standard- and reduced-fluence, n=20 each) plus ranibizumab or to ranibizumab monotherapy (n=20). (33) The primary outcomes were mean change in best-corrected visual acuity and mean change in retinal thickening from baseline to week 48. The trial was likely underpowered to detect a clinical meaningful difference in best corrected visual acuity for between-group comparisons. Mean best-corrected visual acuity change at 48 weeks was +0.2 and +15 letters with standard- and reduced-fluence verteporfin photodynamic therapy plus ranibizumab, respectively, compared with +16.8 letters with ranibizumab monotherapy. At 48 weeks, mean central foveal thickness decreased from baseline was 58 µm, 91.4 µm, and 85 µm for the 3 groups, respectively.

Chen et al. (2011) compared bevacizumab monotherapy (n=17) with bevacizumab plus verteporfin photodynamic therapy (n=6) in a retrospective analysis of patients with choroidal neovascularization secondary to causes other than age-related macular degeneration; approximately half of the patients had myopic choroidal neovascularization. (34) Most observed differences between groups were not statistically significant, likely due to the small sample size. For example, mean change in visual acuity at 12-month follow-up was 1.7 lines in the monotherapy group and 2.8 lines in the combination therapy group, and 36% of the monotherapy group gained 3 lines or more compared with 60% in the combination therapy group. The combination group received fewer reinjections (average injections, 2.6 vs 4.8), but this difference was not statistically significant (p=.11). Subgroup analysis for cases of myopic choroidal neovascularization showed no significant difference between groups in mean acuity gains (2.0 lines in the monotherapy group vs 2.3 lines in the combination therapy group), with fewer reinjections (2 vs 7.2, p<.05) needed in the combination group during the 12-month follow-up. No serious ocular complications were observed. Prospective comparison with a larger number of patients is needed.

Section Summary: Pathologic Myopia - Verteporfin Photodynamic Therapy Plus Anti-Vascular Endothelial Growth Factor Therapy

The evidence for the efficacy of verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy includes a small RCT and a retrospective study. This evidence does not demonstrate improvements in best-corrected visual acuity. Comparative trials are needed to evaluate the efficacy of this combination therapy vs relevant comparators.

Presumed Ocular Histoplasmosis

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to presumed ocular histoplasmosis.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to presumed ocular histoplasmosis.

Intervention

Treatment with verteporfin photodynamic therapy.

Comparators

Treatment with photocoagulation or antivascular endothelial growth factor therapies.

Outcomes

Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

There are few published data on the use of verteporfin photodynamic therapy to treat patients with choroidal neovascularization related to ocular histoplasmosis. The U.S. Food and Drug Administration (FDA) approval of verteporfin photodynamic therapy for ocular histoplasmosis in 2001 was based on a prospective single-arm study involving 26 patients with ocular histoplasmosis. Visual acuity improved by an average of more than 1 line (6.7 letters) on a standard eye chart at 12 months, with 28% of patients experiencing improvement of at least 3 lines (15 letters). Visual acuity decreased by fewer than 3 lines in 88% of patients during the same period from a historical control. Ramaiya et al. (2013) reported on results from a small

RCT that assigned 19 patients to ranibizumab or photodynamic therapy with rescue ranibizumab. (35) The primary outcome measure was the change in visual acuity at 1 year. Data from 10 of the 19 randomized patients were excluded from analysis because of lack of follow-up data. The number of injections in the ranibizumab arm was 7.7 (range, 1 to 11). The mean number of photodynamic therapy treatments administered was 2.5 (range, 2 to 3). All patients in the verteporfin photodynamic therapy group required rescue ranibizumab therapy, with a mean of 2.5 (range, 2 to 3) injections. Mean change in the Early Treatment Diabetic Retinopathy Study visual acuity at 1-year follow-up was 19.6 letters in the ranibizumab group and 21 letters in the photodynamic therapy group. Four (80%) of 5 patients showed a greater than 15 letter gain at 1 year in the ranibizumab group, whereas 1 of 2 patients in the verteporfin photodynamic therapy group showed a greater than 15 letter gain. Because of 50% lost to follow-up, a small sample (<6 patients per arm), and incomplete reporting of the trial results, interpretation of data is difficult.

Section Summary: Presumed Ocular Histoplasmosis

The evidence for the efficacy of verteporfin photodynamic therapy includes a small prospective single-arm study and an RCT. Lack of a control arm in the single-arm study and 50% loss to follow-up in the RCT preclude a meaningful interpretation of the data on observed improvements in visual acuity. Comparative trials are needed to evaluate the efficacy of combination verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy.

Acute Central Serous Chorioretinopathy

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to acute central serous chorioretinopathy.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to acute central serous chorioretinopathy.

Intervention

Treatment with verteporfin photodynamic therapy.

Comparators

Treatment with photocoagulation or antivascular endothelial growth factor therapies.

Outcomes

Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

A Cochrane review with network meta-analysis (2015) evaluated various treatments for central serous chorioretinopathy that included both acute and chronic central serous chorioretinopathy. (36) Only RCTs were included. Pairwise (direct) comparison for verteporfin photodynamic therapy included antivascular endothelial growth factor versus verteporfin photodynamic therapy, antivascular endothelial growth factor plus 50% verteporfin photodynamic therapy versus 50% verteporfin photodynamic therapy alone, 50% verteporfin photodynamic therapy versus observation or sham treatment, and 30% verteporfin photodynamic therapy versus 50% verteporfin photodynamic therapy or versus full strength verteporfin photodynamic therapy. (Percentages refer to the dose of verteporfin used.) The primary outcome was visual acuity at 12 months. Low-quality evidence from a 2008 study (58 participants) suggested that half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy probably resulted in a small improvement in vision (MD=-0.10 logarithm of the minimum angle of resolution; 95% CI, -0.18 to -0.02) compared with sham treatment. (37) Moderate-quality evidence from 2 studies suggested that 30% verteporfin photodynamic therapy results in a small improvement in vision compared with verteporfin photodynamic therapy (MD=-0.16 logarithm of the minimum angle of resolution; 95% CI, -0.22 to -0.10) and compared with 50% verteporfin photodynamic therapy (MD=-0.12 logarithm of the minimum angle of resolution; 95% CI, -0.15 to -0.08). (38, 39) Visual acuity scores at 12 months did not differ between antivascular endothelial growth and verteporfin photodynamic therapy (40, 41) or antivascular endothelial growth plus 50% verteporfin photodynamic therapy and 50% verteporfin photodynamic therapy alone, (42) or 50% verteporfin photodynamic therapy and observation or sham treatment. (37)

Chan et al. (2008) conducted a double-masked, placebo-controlled trial of 63 patients who were randomized 2:1 to half-dose verteporfin photodynamic therapy or placebo. (37) Thirty-nine patients in the verteporfin photodynamic therapy and 19 in the placebo arm completed the trial. The primary outcome measure (the proportion of eyes with the absence of subretinal fluid at the macula at 12 months) was observed in 37 (95%) eyes in the verteporfin photodynamic therapy arm and 11 (58%) eyes in the placebo arm. Mean increase of best-corrected visual acuity was 1.8 and 0.6 lines in the verteporfin photodynamic therapy and placebo arm, respectively. The treatment difference was 1.2 lines, which fell below the threshold of 3 lines considered clinically meaningful. A responder analysis was not reported.

Zhao et al. (2015) reported on a double-masked, randomized, noninferiority trial with 131 patients that compared a 50% with a 30% dose of verteporfin photodynamic therapy for acute

(<6 months) central serous chorioretinopathy. (39) The 2 primary outcome measures were the proportion of eyes with complete absorption of subretinal fluid and the proportion of eyes with complete disappearance of fluorescein leakage at 6 and 12 months. At 12 months, the proportion of eyes with complete absorption of retinal fluid was 75.4% in the 30%-dose group and 94.6% in the half-dose group (p=.004). Complete disappearance of fluorescein leakage at 12 months was observed in 68.9% of the 30%-dose group and 92.9% of the half-dose group (p=.001). Visual acuity (a secondary outcome measure) improved from 20/32 to 20/20 in both groups, with a mean between-group difference of 1.7 letters. In the 30%-dose group, 4 (6.6%) eyes lost 5 or more letters compared with 0 eyes in the half-dose group. This study did not provide sufficient evidence of a functional benefit that would outweigh the potential risk of treatment with verteporfin photodynamic therapy for acute central serous chorioretinopathy.

Salehi et al. (2015), in their network meta-analysis which included a total of 25 studies (total N=1098 patients; 1098 eyes), judged these studies to be at low risk of bias in most domains with the exception of attrition bias (6% of the 30% verteporfin photodynamic therapy group vs 13% of the 50% verteporfin photodynamic therapy group) and selective outcomes reporting (primary and secondary outcomes were designated differently on the trial registry entry and the published report). (36) The 30% dose did not achieve noninferiority.

Section Summary: Acute Central Serous Chorioretinopathy

The evidence for the efficacy of verteporfin photodynamic therapy for acute central serous chorioretinopathy includes 2 RCTs. This evidence, although demonstrating that full- and reduced-dose verteporfin photodynamic therapy results in small improvements in best-corrected visual acuity, did not meet the clinically meaningful threshold. Comparative and adequately powered trials are needed to evaluate the efficacy of verteporfin photodynamic therapy in acute central serous chorioretinopathy.

Chronic Central Serous Chorioretinopathy

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to chronic central serous chorioretinopathy.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to chronic central serous chorioretinopathy.

Intervention

Treatment with verteporfin photodynamic therapy.

Comparators

Treatment with reduced-dose/-fluence verteporfin photodynamic therapy.

Outcomes
Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Reductions in subretinal fluid and improvement in retinal anatomy, visual acuity, (43-48) and retinal sensitivity (49-53) have been observed in 70% to 100% of cases in multiple retrospective studies. Use of reduced-dose verteporfin photodynamic therapy for chronic central serous chorioretinopathy also has been reported. Uetani et al. (2012) compared half-dose with one-third dose verteporfin photodynamic therapy in a small (N=16 eyes) prospective open-label trial. (54) At 3 months, all 10 (100%) eyes in the half-dose verteporfin photodynamic therapy group and 2 (33%) eyes in the one-third-dose verteporfin photodynamic therapy group had complete resolution of subretinal fluid. Patients in the half-dose verteporfin photodynamic therapy group gained an average of 5.4 letters while patients in the one-third-dose group gained 1.7 letters (p=not significant [NS]). Chan et al. (2008) also reported on reduced-dose verteporfin for the treatment of chronic central serous chorioretinopathy in a prospective series of 48 patients. (43) Mean duration of central serous chorioretinopathy was 8.2 months (range, 3 to 40 months). At 12 months after verteporfin photodynamic therapy, mean best-corrected visual acuity improved from 0.31 to 0.15 logarithm of the minimum angle of resolution, an improvement of 1.6 lines.

Section Summary: Chronic Central Serous Chorioretinopathy
The evidence for the efficacy of verteporfin photodynamic therapy for chronic central serous chorioretinopathy includes multiple retrospective studies. Although this relatively large body of studies has indicated that half-dose verteporfin photodynamic therapy yields positive functional and anatomic outcomes while, at the same time, reducing the potential adverse events associated with conventional verteporfin photodynamic therapy, no comparative data have shown the relative efficacy of multiple verteporfin photodynamic therapy strategies. Comparative trials are needed to evaluate the efficacy of verteporfin photodynamic therapy strategies in chronic central serous chorioretinopathy.

Polypoidal Choroidal Vasculopathy - Verteporfin Photodynamic Therapy Alone
Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to polypoidal choroidal vasculopathy.

The following PICO was used to select literature to inform this policy.

Population
Individuals with choroidal neovascularization due to polypoidal choroidal vasculopathy.

Intervention
Treatment with verteporfin photodynamic therapy.

Comparators
Standard of care or antivascular endothelial growth factor therapies.

Outcomes
Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Verteporfin Photodynamic Therapy
A systematic review by Chan et al. (2010) included 30 studies assessing verteporfin photodynamic therapy in patients with polypoidal choroidal vasculopathy. (55) Reviewers found numerous case series reporting favorable anatomic outcomes and visual acuity for patients treated with verteporfin photodynamic therapy. Some of these studies are described below. Tang et al. (2015) also published a systematic review and meta-analysis evaluating treatment for polypoidal choroidal vasculopathy. (56) Two RCTs compared verteporfin photodynamic therapy with ranibizumab and reported a weighted mean difference in visual acuity of 0.06 logarithm of the minimum angle of resolution (95% CI, -0.01 to 0.12) in favor of ranibizumab, but this difference was not statistically significant. Subsequent to the meta-analysis by Tang et al. (2015), Silva et al. (2022) published a randomized controlled trial that compared the efficacy and safety of intravitreal aflibercept plus either verteporfin or sham photodynamic therapy in 50 individuals with polypoidal choroidal vasculopathy. (57) Consistent with the previous RCTs, no statistically significant difference in visual acuity was found between verteporfin photodynamic therapy with antivascular endothelial growth therapies compared

to antivascular endothelial growth therapies alone at week 52 (best corrected visual acuity change: 6.5 vs 5; p=.98).

Several nonrandomized studies from Asia have been reported. Hikichi et al. (2011) reported on the largest prospective consecutive series of 220 eyes of 210 Japanese patients with polypoidal choroidal vasculopathy who were followed for 1 year after the primary verteporfin photodynamic therapy. (58) A single physician, diagnosed, treated and followed all patients (not masked). Retreatment was considered every 3 months based on the examination findings, and there was an average of 1.37 treatments. Fluid, exudates, and hemorrhages had resolved in 205 (93%) eyes at 1-year follow-up. Average visual acuity improved by more than 0.3 logarithm of the minimum angle of resolution in 55 (25%) of eyes, remained stable in 143 (65%) of eyes, and decreased more than 0.3 logarithm of the minimum angle of resolution in 21 (10%) of eyes.

Akaza et al. (2011) reported on 3-year follow-up of 43 eyes (43 patients) treated with verteporfin photodynamic therapy for polypoidal choroidal vasculopathy. (59) Before the initial verteporfin photodynamic therapy, 40 (93%) eyes exhibited polypoidal choroidal vasculopathy in the narrow sense and 3 (7%) exhibited polypoidal choroidal neovascularization. Number of treatment sessions during follow-up ranged from 1 to 8. At 3-year follow-up, mean visual acuity decreased to below baseline. Polypoidal lesions recurred in 33 (77%) of the 43 eyes at 3 years, although the 3 eyes with polypoidal choroidal neovascularization showed little change except for enlargement and recurrence. Long-term visual outcomes following verteporfin photodynamic therapy showed a high frequency of recurrent polypoidal lesions as well as enlargement and neovascular changes of abnormal vascular networks. However, because polypoidal lesions recurred after verteporfin photodynamic therapy in some cases, further study is needed to confirm the long-term effectiveness of verteporfin photodynamic therapy for polypoidal choroidal vasculopathy.

Section Summary: Polypoidal Choroidal Vasculopathy - Verteporfin Photodynamic Therapy Alone

Available evidence on the efficacy of verteporfin photodynamic therapy for polypoidal choroidal vasculopathy consists of several retrospective studies, a meta-analysis that included 2 RCTs, and a subsequently published additional RCT. Retrospective studies have reported favorable anatomic outcomes and visual acuity for patients treated with verteporfin photodynamic therapy. RCTs comparing verteporfin photodynamic therapy with antivascular endothelial growth therapies have reported no statistical differences in visual acuity. Controlled trials are needed to permit conclusions on the efficacy of verteporfin photodynamic therapy monotherapy in polypoidal choroidal vasculopathy.

Polypoidal Choroidal Vasculopathy - Verteporfin Photodynamic Therapy Plus Anti-Vascular Endothelial Growth Factor Therapy

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy plus anti-vascular endothelial growth factor therapy is to provide a treatment option that is an alternative to or an improvement on existing

therapies for individuals with choroidal neovascularization due to polypoidal choroidal vasculopathy.

The following PICO was used to select literature to inform this policy.

Population
Individuals with choroidal neovascularization due to polypoidal choroidal vasculopathy.

Intervention
Treatment with verteporfin photodynamic therapy plus anti-vascular endothelial growth factor therapy.

Comparators
Treatment with antivascular endothelial growth factor therapy alone.

Outcomes
Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Lin et al. (2024) published a meta-analysis of 7 RCTs (N=926 eyes) evaluating the addition of verteporfin photodynamic therapy to antivascular endothelial growth factor for the treatment of polypoidal choroidal vasculopathy. (60) The addition of verteporfin photodynamic therapy improved polyp regression and reduced the number of antivascular endothelial growth factor injections but did not improve visual outcomes. The analysis is limited by the small number of studies and the small sample size of most studies with the exception of Lim et al. (2020) which included 322 eyes. (61) The vast majority of evidence comes from Asian populations.

Table 1. Comparison of Trials/Studies Included in Meta-analyses

Study	Lin et al. (2024) (60)
Silva (2022)	●
Ogura (2021)	●
Lim (2020)	●
Wong (2019)	●

Lai (2018)	●
Koh (2012)	●
Lim (2012)	●

Table 2. Meta-analyses Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Lin et al. (2024) (60)	Through July 2024	7	Pts with PCV enrolled in RCTs comparing anti-VEGF monotherapy to combination anti-VEGF plus VPDT	926 eyes (16 to 168)	RCT	20 to 96 weeks

PCV: polypoidal choroidal vasculopathy; RCTs: randomized controlled trials; VEGF: vascular endothelial growth factor; VPDT: verteporfin photodynamic therapy.

Table 3. Meta-analyses Results

Study	**Complete Polyp Regression**	**Number of Antivascular VEGF Injections**	**BCVA Improvement**	**CRT Reduction**	**Ocular AEs**
Lin et al. (2024) (60)					
Total N	1053[a]	729	1048[a]	730	1232[a]
Pooled effect, RR (95% CI)	1.56 (1.15 to 2.13)	-0.65 (-0.95 to -0.35)	0.96 (-0.45 to 2.36)	0.31 (-0.81 to 1.43)	0.99 (0.85 to 1.16)
I^2 (p)	*74%* (.005)	*60%* (<.0001)	*99%* (.18)	*97%* (.59)	*0%* (.94)

AEs: adverse events; BCVA: best corrected visual acuity; CI: confidence interval; CRT: central retinal thickness; RR: risk ratio; VEGF: vascular endothelial growth factor.
[a]Total N for this analysis exceeds total number of eyes because the Lim (2020) study was included in both subgroups of 1 year or less follow-up and greater than 1 year follow-up.

Nonrandomized Trials

Observational studies have also been published. Weng et al. (2024) retrospectively compared aflibercept alone to aflibercept plus verteporfin photodynamic therapy in patients (N=60 eyes) with polypoidal choroidal vasculopathy. (62) Visual acuity and changes in central retinal thickness were not significantly different between groups at 12 months, but the dry macular rate was greater with combination therapy (96.7% vs 60.0%; p=.001). Kang et al. (2013) reported on 5-year retrospective follow-up for 42 eyes (36 patients) treated with verteporfin photodynamic therapy for polypoidal choroidal vasculopathy. (63) Patients received a mean of 2.21 verteporfin photodynamic therapy treatments during the study, with additional intravitreal injections of antivascular endothelial growth agents if exudative changes were observed. During follow-up, recurrence was observed in 33 (78.6%) eyes, and the mean number of antivascular endothelial growth injections was 6.42 in eyes with recurrence. In the entire group, best-corrected visual acuity improved from 0.78 logarithm of the minimum angle of resolution at baseline (20/120 Snellen equivalent) to 0.67 logarithm of the minimum angle of

resolution (20/93 Snellen equivalent) at 5 years. Using a change of at least 0.3 logarithm of the minimum angle of resolution as a threshold, best-corrected visual acuity improved in 14 (33.3%) eyes, remained stable in 23 (54.8%) eyes, and decreased in 5 (11.9%) eyes. Interpretation of this study is difficult because all patients received combination treatment with intravitreal vascular endothelial growth factor antagonists without comparison groups. Kim and Yu (2011) retrospectively reviewed 39 consecutive patients with polypoidal choroidal vasculopathy who received verteporfin photodynamic therapy (before April 2007) or combination verteporfin photodynamic therapy plus intravitreal bevacizumab (after April 2007). (64) During 12 months of follow-up, patients in the monotherapy group (n=19) received a mean of 1.89 verteporfin photodynamic therapy applications, and patients in the combined therapy group (n=20) received a mean of 1.30 verteporfin photodynamic therapy applications and 2.90 bevacizumab injections. Best-corrected visual acuity improved by 3.0 lines in the combined therapy group compared with 1.6 lines in the verteporfin photodynamic therapy-only group. This level of improvement in best-corrected visual acuity was achieved in 55.0% in the combined therapy group and 36.8% in the monotherapy group.

Section Summary: Polypoidal Choroidal Vasculopathy - Verteporfin Photodynamic Therapy Plus Anti-Vascular Endothelial Growth Factor Therapy

Available evidence on the efficacy of verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy for polypoidal choroidal vasculopathy consists of a meta-analysis of 7 RCTs and retrospective studies. The combination therapy improved polyp regression and reduced the number of antivascular endothelial growth factor injections but did not improve visual acuity compared to monotherapy with antivascular endothelial growth factor therapy. The RCTs included in the meta-analysis generally had small sample sizes and were conducted in Asian populations. Adequately powered controlled trials are needed to permit conclusions on the efficacy of combination verteporfin photodynamic therapy plus antivascular endothelial growth therapy in polypoidal choroidal vasculopathy.

Choroidal Hemangioma

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to choroidal hemangioma.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to choroidal hemangioma.

Intervention

Treatment with verteporfin photodynamic therapy.

Comparators

Standard of care treatment.

Outcomes
Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The systematic review by Chan et al. (2010) included 11 case series on verteporfin photodynamic therapy in patients with choroidal hemangioma. (55) Verteporfin photodynamic therapy has been reported to induce complete and irreversible occlusion of the microvasculature, although this may require more than 1 treatment. Several case series have demonstrated encouraging visual acuity and anatomic outcomes in 150 patients with circumscribed choroidal hemangioma treated with various verteporfin photodynamic therapy regimens.

Blasi et al. (2010) reported on 5-year outcomes for a prospective series of 25 consecutive patients with symptomatic choroidal hemangioma. (65) Twenty-two (88%) patients received a single verteporfin photodynamic therapy session and 3 eyes received a second verteporfin photodynamic therapy session. Follow-up examinations were performed 2 weeks, 1 month, 3 months, and every 6 months after treatment. All tumors were reduced in size, and there were no recurrences through 5 years of follow-up. At 1 year, best-corrected visual acuity improved by an average of 18.2 letters. Visual acuity improved by 2 or more lines in 20 (80%) eyes and by 3 or more lines in 12 (48%) eyes. No treated eyes lost visual acuity between the 1- and 5-year follow-ups. Foveal center thickness decreased from a mean of 386.20 µm to 179.2 µm at 5 years, and there was the resolution of macular exudation in all cases. No treatment-related adverse events were identified.

Section Summary: Choroidal Hemangioma
Available evidence on the efficacy of verteporfin photodynamic therapy for choroidal hemangioma consists of a systematic review of 11 case series and a prospective study. This body of evidence has suggested a favorable effect of verteporfin photodynamic therapy on various visual acuity and anatomic outcomes in patients with a choroidal hemangioma. Controlled trials with a larger number of patients and longer follow-up are needed to permit conclusions regarding the efficacy of verteporfin photodynamic therapy for this indication.

Angioid Streaks

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to angioid streaks.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to angioid streaks.

Intervention

Treatment with verteporfin photodynamic therapy.

Comparators

Standard of care treatment.

Outcomes

Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The systematic review by Chan et al. (2010) included 8 case series on verteporfin photodynamic therapy assessing 148 patients with angioid streaks. (55) Reviewers concluded that verteporfin photodynamic therapy might limit or slow vision loss compared with the expected natural course of choroidal neovascularization due to angioid streaks, but 1 study showed a decrease in visual acuity following verteporfin photodynamic therapy, and others showed that substantial proportions of patients continued to lose visual acuity. Thus, further studies are warranted to assess long-term safety and efficacy of verteporfin photodynamic therapy in these patients.

Section Summary: Angioid Streaks

Available evidence on the efficacy of verteporfin photodynamic therapy for angioid streaks consists of a systematic review of case series. The data from case series have reported conflicting results for visual acuity. Controlled trials with a larger number of patients and longer follow-up are needed to permit conclusions on the efficacy of verteporfin photodynamic

therapy in angioid streaks, especially if it is effective in limiting the growth of choroidal neovascularization.

Inflammatory Chorioretinal Conditions

Clinical Context and Therapy Purpose

The purpose of verteporfin photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with choroidal neovascularization due to inflammatory chorioretinal conditions.

The following PICO was used to select literature to inform this policy.

Population

Individuals with choroidal neovascularization due to inflammatory chorioretinal conditions.

Intervention

Treatment with verteporfin photodynamic therapy.

Comparators

Standard of care treatment.

Outcomes

Symptoms, change in disease status, a change or improvement of functional status, and quality of life measurement(s). Average follow-up is 12 to 24 months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Choroidal neovascularization can occur as a complication of inflammatory conditions such as uveitis, multifocal choroiditis and panuveitis, and punctate inner choroidopathy. About one-third of patients develop choroidal neovascularization, which can result in severe vision loss if it is subfoveal.

The systematic review by Chan et al. (2010) included 15 case reports evaluating verteporfin photodynamic therapy in 115 patients with inflammatory eye conditions. (55) Encouraging visual acuity, and anatomic improvements have been reported with verteporfin photodynamic therapy for punctuate inner choroidopathy, choroiditis and toxoplasmic retinochoroiditis, and subfoveal choroidal neovascularization secondary to posterior uveitis. While promising, larger

and comparative studies are needed to evaluate the effect of verteporfin photodynamic therapy on health outcomes for this indication.

Section Summary: Inflammatory Chorioretinal Conditions

Available evidence on the efficacy of verteporfin photodynamic therapy for inflammatory chorioretinal conditions consists of multiple case reports. Controlled trials are needed to permit conclusions on the efficacy of verteporfin photodynamic therapy in ocular inflammatory conditions.

Summary of Evidence

Age-Related Macular Degeneration

For individuals who have classic choroidal neovascularization due to age-related macular degeneration who receive verteporfin photodynamic therapy, the evidence includes randomized controlled trials (RCTs) and systematic reviews of controlled trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Multiple RCTs have supported the superiority of verteporfin photodynamic therapy in reducing vision loss and decreasing retinal thickness compared with placebo or sham procedure. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to age-related macular degeneration who receive verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy, the evidence includes 2 confirmatory RCTs (and their multiple analyses), multiple smaller RCTs, and a meta-analysis of existing trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. This evidence does not demonstrate improvements in visual acuity using combination therapy compared with antivascular endothelial growth factor monotherapy. Combination therapy may reduce the number of intravitreal injections needed, but this result has not been consistently reported across studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to age-related macular degeneration who receive verteporfin photodynamic therapy plus corticosteroids and/or antivascular endothelial growth factor therapy, the evidence includes 3 small RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The evidence does not demonstrate improvements in visual acuity with combination therapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Pathologic Myopia

For individuals who have choroidal neovascularization due to pathologic myopia who receive verteporfin photodynamic therapy, the evidence includes a subgroup analysis from a large RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The subgroup analysis showed verteporfin photodynamic therapy was more effective

than placebo in preventing vision loss at 1 year but not in the second year. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to pathologic myopia who receive verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy, the evidence includes a small RCT and a retrospective cohort study. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The single RCT was likely underpowered to detect a clinically meaningful change in visual acuity outcomes. The retrospective cohort study did not demonstrate improvements in visual acuity with combination treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Presumed Ocular Histoplasmosis

For individuals who have choroidal neovascularization due to presumed ocular histoplasmosis who receive verteporfin photodynamic therapy, the evidence includes a small RCT and a prospective cohort study. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Lack of a control arm in the prospective cohort study and 50% lost to follow-up in the RCT preclude a meaningful interpretation of data of observed improvements in visual acuity outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Central Serous Chorioretinopathy

For individuals who have choroidal neovascularization due to acute central serous chorioretinopathy who receive verteporfin photodynamic therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Although the evidence has demonstrated that full and reduced doses of verteporfin photodynamic therapy result in a small improvement in visual acuity outcomes, the improvements did not meet clinically meaningful thresholds. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to chronic central serous chorioretinopathy who receive verteporfin photodynamic therapy, the evidence includes multiple retrospective studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Although this relatively large body of retrospective studies has shown that half-dose verteporfin photodynamic therapy yields positive functional and anatomic outcomes while, at the same time, reducing the potential adverse events associated with conventional verteporfin photodynamic therapy, data from RCTs for multiple verteporfin photodynamic therapy strategies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Polypoidal Choroidal Vasculopathy

For individuals who have choroidal neovascularization due to polypoidal choroidal vasculopathy who receive verteporfin photodynamic therapy, the evidence includes several prospective

cohort studies and a meta-analysis of 2 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Prospective cohort studies have reported favorable anatomic and visual acuity outcomes for patients treated with verteporfin photodynamic therapy. However, RCTs comparing verteporfin photodynamic therapy with antivascular endothelial growth factor therapies have reported no statistically significant differences in visual acuity outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to polypoidal choroidal vasculopathy who receive verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy, the evidence includes a meta-analysis of 7 RCTs, and retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Results of the meta-analysis failed to demonstrate statistically significant differences in visual acuity outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Choroidal Hemangioma

For individuals who have choroidal neovascularization due to choroidal hemangioma who receive verteporfin photodynamic therapy, the evidence includes a systematic review of case series and a prospective cohort study. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Although the prospective cohort suggested a favorable effect of verteporfin photodynamic therapy on various visual acuity and anatomic outcomes in patients with choroidal hemangioma, data from RCTs are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Angioid Streaks

For individuals who have choroidal neovascularization due to angioid streaks who receive verteporfin photodynamic therapy, the evidence includes a systematic review of case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Data from multiple case series have shown conflicting results for visual acuity outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Inflammatory Chorioretinal Conditions

For individuals who have choroidal neovascularization due to inflammatory chorioretinal conditions who receive verteporfin photodynamic therapy, the evidence includes a systematic review of case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Methodologic limitations limit the conclusions drawn from 15 case reports (total N=115 patients) of multiple disease indications. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

2012 Input

Clinical input in 2012 supported the use of verteporfin photodynamic therapy for pathologic myopia, presumed ocular histoplasmosis, acute central serous chorioretinopathy, chronic central serous chorioretinopathy, and choroidal hemangioma. Input was mixed on the use of photodynamic therapy for other ophthalmologic disorders. Input agreed that photodynamic therapy used in combination with vascular endothelial growth factor antagonists is investigational for all ophthalmologic disorders.

Practice Guidelines and Position Statements

American Academy of Ophthalmology

In 2019, the American Academy of Ophthalmology updated its 2015 preferred practice pattern guideline on age-related macular degeneration. The 2019 update states that verteporfin photodynamic therapy has approval by the U.S. Food and Drug Administration for the treatment of age-related macular degeneration-related, predominantly classic, subfoveal choroidal neovascularization. (66)

The 2019 update stated that antivascular endothelial growth factor therapies have become first-line therapy for treating and stabilizing most cases of age-related macular degeneration and suggests that verteporfin photodynamic therapy is rarely needed. An update for this guideline is scheduled for 2025.

National Institute for Health and Care Excellence

In 2018, the National Institute for Health and Care Excellence updated its 2003 guidance on the use of photodynamic therapy for age-related macular degeneration. (67) The Institute made the following recommendations: it recommended against use of photodynamic therapy as monotherapy for late (wet) age-related macular degeneration and against use of photodynamic therapy as first-line adjunctive therapy to antivascular endothelial growth factor therapies for late (wet) age-related macular degeneration; it recommended for photodynamic therapy as second-line adjunctive therapy to antivascular endothelial growth factor therapies for late (wet) age-related macular degeneration in a trial setting.

Medicare National Coverage

Since 2001, use of ocular photodynamic therapy has been covered by Medicare for the treatment predominantly classical subfoveal choroidal neovascularization (i.e., occupies ≥50% of the area of the entire lesion) associated with age-related macular degeneration only when used in conjunction with verteporfin. However, there was no national Medicare coverage policy for other indications. In 2004, Medicare found evidence to conclude that photodynamic therapy with verteporfin may be “reasonable and necessary” for patients with age-related macular degeneration with “subfoveal occult or minimally classic choroidal neovascularization … 4 disk areas or less in size…[with] evidence of progression within the three months prior to initial treatment.” (68) Medicare also reiterated that use of ocular photodynamic therapy with verteporfin for indications such as “pathologic myopia or the presumed histoplasmosis syndrome” may be “eligible for coverage through individual contractor discretion.” A 2013 update permitted the use of either fluorescein angiography or optical coherence tomography to assess treatment response.

Ongoing and Unpublished Clinical Trials

No ongoing clinical trials relevant to this policy were identified in a February 2025 search of clinicaltrials.gov.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	67221, 67225
HCPCS Codes	C9257, J0177, J0178, J2503, J2778, J3396, J9035

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Gragoudas ES, Adamis AP, Cunningham ET, Jr. et al. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med. Dec 30 2004; 351(27):2805-2816. PMID 15625332
2. Chakravarthy U, Adamis AP, Cunningham ET, et al. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. Ophthalmology. Sep 2006; 113(9):1508, e1-e25. PMID 16828500
3. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. Oct 5 2006; 355(14):1432-1444. PMID 17021319
4. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Arch Ophthalmol. Oct 1999; 117(10):1329-1345. PMID 10532441
5. Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. Arch Ophthalmol. Feb 2001; 119(2):198-207. PMID 11176980
6. Blumenkranz MS, Bressler NM, Bressler SB, et al. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials--TAP Report no. 5. Arch Ophthalmol. Oct 2002; 120(10):1307-1314. PMID 12365909
7. Bressler NM, Arnold J, Benchaboune M, et al. Verteporfin therapy of subfoveal choroidal neovascularization in patients with age-related macular degeneration: additional

information regarding baseline lesion composition's impact on vision outcomes-TAP report no. 3. Arch Ophthalmol. Nov 2002; 120(11):1443-1454. PMID 12427056
8. Rubin GS, Bressler NM. Effects of verteporfin therapy on contrast on sensitivity: results from the treatment of age-related macular degeneration with photodynamic therapy (TAP) investigation-TAP report no 4. Retina. Oct 2002; 22(5):536-544. PMID 12441717
9. Kaiser PK. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: 5-year results of two randomized clinical trials with an open-label extension: TAP report no. 8. Graefes Arch Clin Exp Ophthalmol. Sep 2006; 244(9):1132-1142. PMID 16538452
10. Verteporfin in Photodynamic Therapy (VIP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization--verteporfin in photodynamic therapy report 2. Am J Ophthalmol. May 2001; 131(5):541-560. PMID 11336929
11. Wormald R, Evans J, Smeeth L, et al. Photodynamic therapy for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2003; (2):CD002030. PMID 12804420
12. Azab M, Benchaboune M, Blinder KJ, et al. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: meta-analysis of 2-year safety results in three randomized clinical trials: treatment of age-related macular degeneration with photodynamic therapy and verteporfin in photodynamic therapy study report no. 4. Retina. Feb 2004; 24(1):1-12. PMID 15076937
13. Wormald R, Evans J, Smeeth L, et al. Photodynamic therapy for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2007; (3):CD002030. PMID 17636693
14. Schmidt-Erfurth U, Sacu S. Randomized multicenter trial of more intense and standard early verteporfin treatment of neovascular age-related macular degeneration. Ophthalmology. Jan 2008; 115(1):134-140. PMID 18166408
15. Ba J, Peng RS, Xu D, et al. Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis. Drug Des Devel Ther. 2015; 9:5397-5405. PMID 26451092
16. Tong Y, Zhao KK, Feng D, et al. Comparison of the efficacy of anti-VEGF monotherapy versus PDT and intravitreal anti-VEGF combination treatment in AMD: a meta-analysis and systematic review. Int J Ophthalmol. Aug 2016; 9(7):1028-1037. PMID 27500113
17. Heier JS, Boyer DS, Ciulla TA, et al. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. Arch Ophthalmol. Nov 2006; 124(11):1532-1542. PMID 17101999
18. Antoszyk AN, Tuomi L, Chung CY, et al. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. Am J Ophthalmol. May 2008; 145(5):862-874. PMID 18321465
19. Kaiser PK, Boyer DS, Cruess AF, et al. Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study. Ophthalmology. May 2012; 119(5):1001-1010. PMID 22444829
20. Larsen M, Schmidt-Erfurth U, Lanzetta P, et al. Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results. Ophthalmology. May 2012; 119(5):992-1000. PMID 22424834

21. Semeraro F, Russo A, Delcassi L, et al. Treatment of exudative age-related macular degeneration with ranibizumab combined with ketorolac eyedrops or photodynamic therapy. Retina. Aug 2015; 35(8):1547-1554. PMID 25784358
22. Williams PD, Callanan D, Solley W, et al. A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration. Clin Ophthalmol. 2012; 6:1519-1525. PMID 23055673
23. Lim JY, Lee SY, Kim JG, et al. Intravitreal bevacizumab alone versus in combination with photodynamic therapy for the treatment of neovascular maculopathy in patients aged 50 years or older: 1-year results of a prospective clinical study. Acta Ophthalmol. Feb 2012; 90(1):61-67. PMID 20337606
24. Lazic R, Gabric N. Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration. Ophthalmology. Jun 2007; 114(6):1179-1185. PMID 17544776
25. Lee JH, Lee WK. One-year results of adjunctive photodynamic therapy for type 1 neovascularization associated with thickened choroid. Retina. May 2016; 36(5):889-895. PMID 27115853
26. Piermarocchi S, Sartore M, Lo Giudice G, et al. Combination of photodynamic therapy and intraocular triamcinolone for exudative age-related macular degeneration and long-term chorioretinal macular atrophy. Arch Ophthalmol. Oct 2008; 126(10):1367-1374. PMID 18852414
27. Maberley D. Photodynamic therapy and intravitreal triamcinolone for neovascular age-related macular degeneration: a randomized clinical trial. Ophthalmology. Nov 2009; 116(11):2149-2157 e1. PMID 19748675
28. Piri N, Ahmadieh H, Taei R, et al. Photodynamic therapy and intravitreal bevacizumab with versus without triamcinolone for neovascular age-related macular degeneration; a randomized clinical trial. J Ophthalmic Vis Res. Oct-Dec 2014; 9(4):469-477. PMID 25709773
29. Wolf S, Balciuniene VJ, Laganoversuska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. Ophthalmology. Mar 2014; 121(3):682-692.e2. PMID 24326106
30. Zhu Y, Zhang T, Xu G, et al. Anti-vascular endothelial growth factor for choroidal neovascularization in people with pathological myopia. Cochrane Database Syst Rev. Dec 15 2016; 12:CD011160. PMID 27977064
31. Verteporfin in Photodynamic Therapy (VIP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial--VIP report no. 1. Ophthalmology. Feb 2001; 108(5):841-852. PMID 11320011
32. Blinder KJ, Blumenkranz MS, Bressler NM, et al. Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial--VIP report no. 3. Ophthalmology. Apr 2003; 110(4):667-673. PMID 12689884
33. Rinaldi M, Semeraro F, Chiosi F, et al. Reduced-fluence verteporfin photodynamic therapy plus ranibizumab for choroidal neovascularization in pathologic myopia. Graefes Arch Clin Exp Ophthalmol. Mar 2017; 255(3):529-539. PMID 27680013

34. Chen L, Miller JW, Vavvas D, et al. Anti-vascular endothelial growth factor monotherapy versus combination treatment with photodynamic therapy for subfoveal choroidal neovascularization secondary to causes other than age-related macular degeneration. Retina. Nov 2011; 31(10):2078-2083. PMID 21691258
35. Ramaiya KJ, Blinder KJ, Ciulla T, et al. Ranibizumab versus photodynamic therapy for presumed ocular histoplasmosis syndrome. Ophthalmic Surg Lasers Imaging Retina. Jan-Feb 2013; 44(1):17-21. PMID 23410808
36. Salehi M, Wenick AS, Law HA, et al. Interventions for central serous chorioretinopathy: a network meta-analysis. Cochrane Database Syst Rev. Dec 22 2015; (12):CD011841. PMID 26691378
37. Chan WM, Lai TY, Lai RY, et al. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial. Ophthalmology. Oct 2008; 115(10):1756-1765. PMID 18538401
38. Zhang YL, You ZP, Wang CY. Different doses of verteporfin photodynamic therapy for central exudative chorioretinopathy. Chin J Exp Ophthalmol. 2012; 30(11):1030-1035.
39. Zhao M, Zhang F, Chen Y, et al. A 50% versus 30% dose of verteporfin (photodynamic therapy) for acute central serous chorioretinopathy: one-year results of a randomized clinical trial. JAMA Ophthalmol. Mar 2015; 133(3):333-340. PMID 25555191
40. Bae SH, Heo JW, Kim C, et al. A randomized pilot study of low-fluence photodynamic therapy versus intravitreal ranibizumab for chronic central serous chorioretinopathy. Am J Ophthalmol. Nov 2011; 152(5):784-792 e2. PMID 21742303
41. Semeraro F, Romano MR, Danzi P, et al. Intravitreal bevacizumab versus low-fluence photodynamic therapy for treatment of chronic central serous chorioretinopathy. Jpn J Ophthalmol. Nov 2012; 56(6):608-612. PMID 22915299
42. Coskun E, Gurler B, Erbagci I. Combined half dose photodynamic therapy with verteporfin and intravitreal bevacizumab for chronic central serous chorioretinopathy [abstract]. Ophthalmologica. 2014; 232(Supp 2):56.
43. Chan WM, Lai TY, Lai RY, et al. Safety enhanced photodynamic therapy for chronic central serous chorioretinopathy: one-year results of a prospective study. Retina. Jan 2008; 28(1):85-93. PMID 18185143
44. Nicolò M, Zoli D, Musolino M, et al. Association between the efficacy of half-dose photodynamic therapy with indocyanine green angiography and optical coherence tomography findings in the treatment of central serous chorioretinopathy. Am J Ophthalmol. Mar 2012; 153(3):474-480.e1. PMID 22019224
45. Lai TY, Chan WM, Li H, et al. Safety enhanced photodynamic therapy with half dose verteporfin for chronic central serous chorioretinopathy: a short-term pilot study. Br J Ophthalmol. Jul 2006; 90(7):869-874. PMID 16597666
46. Valmaggia C, Haueter I, Niederberger H. Photodynamic therapy in the treatment of persistent central serous chorioretinopathy: a two-year follow-up. Klin Monbl Augenheilkd. Apr 2012; 229(4):323-326. PMID 22389262
47. Rouvas A, Stavrakas P, Theodossiadis PG, et al. Long-term results of half-fluence photodynamic therapy for chronic central serous chorioretinopathy. Eur J Ophthalmol. May-Jun 2012; 22(3):417-422. PMID 21928269

48. Jirarattanasopa P, Ooto S, Tsujikawa A, et al. Assessment of macular choroidal thickness by optical coherence tomography and angiographic changes in central serous chorioretinopathy. Ophthalmology. Aug 2012; 119(8):1666-1678. PMID 22521082
49. Senturk F, Karacorlu M, Ozdemir H, et al. Microperimetric changes after photodynamic therapy for central serous chorioretinopathy. Am J Ophthalmol. Feb 2011; 151(2):303-309.e1. PMID 21168824
50. Fujita K, Shinoda K, Imamura Y, et al. Correlation of integrity of cone outer segment tips line with retinal sensitivity after half-dose photodynamic therapy for chronic central serous chorioretinopathy. Am J Ophthalmol. Sep 2012; 154(3):579-585. PMID 22818904
51. Fujita K, Yuzawa M, Mori R. Retinal sensitivity after photodynamic therapy with half-dose verteporfin for chronic central serous chorioretinopathy: short-term results. Retina. Apr 2011; 31(4):772-778. PMID 20890236
52. Böni C, Kloos P, Valmaggia C, et al. New guidelines in the treatment of persistent central serous chorioretinopathy: PDT with half-dose verteporfin. Klin Monbl Augenheilkd. Apr 2012; 229(4):327-330. PMID 22495997
53. Wu ZH, Lai RY, Yip YW, et al. Improvement in multifocal electroretinography after half-dose verteporfin photodynamic therapy for central serous chorioretinopathy: a randomized placebo-controlled trial. Retina. Jul-Aug 2011; 31(7):1378-1386. PMID 21836413
54. Uetani R, Ito Y, Oiwa K, et al. Half-dose versus one-third-dose photodynamic therapy for chronic central serous chorioretinopathy. Eye (Lond). May 2012; 26(5):640-649. PMID 22573069
55. Chan WM, Lim TH, Pece A, et al. Verteporfin PDT for non-standard indications--a review of current literature. Graefes Arch Clin Exp Ophthalmol. May 2010; 248(5):613-626. PMID 20162298
56. Tang K, Si JK, Guo DD, et al. Ranibizumab alone or in combination with photodynamic therapy versus photodynamic therapy for polypoidal choroidal vasculopathy: a systematic review and Meta-analysis. Int J Ophthalmol. 2015; 8(5):1056-1066. PMID 26558226
57. Silva R, Arias L, Nunes S, et al. Efficacy and safety of intravitreal Aflibercept treat and extend for polypoidal choroidal vasculopathy in the ATLANTIC study: A randomized clinical trial. Ophthalmologica. Jul 13 2021; 245(1):80-90. PMID 34348351
58. Hikichi T, Ohtsuka H, Higuchi M, et al. Factors predictive of visual acuity outcomes 1 year after photodynamic therapy in Japanese patients with polypoidal choroidal vasculopathy. Retina. May 2011; 31(5):857-865. PMID 21124252
59. Akaza E, Yuzawa M, Mori R. Three-year follow-up results of photodynamic therapy for polypoidal choroidal vasculopathy. Jpn J Ophthalmol. Jan 2011; 55(1):39-44. PMID 21331691
60. Lin TH, Lin HY, Tseng PC. Enhancing anti-vascular endothelial growth factor with photodynamic therapy for polypoidal choroidal vasculopathy: A meta-analysis. Surv Ophthalmol. May-Jun 2025; 70(3):380-388. PMID 39709034
61. Lim TH, Lai TYY, Takahashi K, et al. Comparison of Ranibizumab With or Without Verteporfin Photodynamic Therapy for Polypoidal Choroidal Vasculopathy: The EVEREST II Randomized Clinical Trial. JAMA Ophthalmol. Sep 01 2020; 138(9):935-942. PMID 32672800

62. Weng HY, Chen FT, Wang LU, et al. Comparison of One-Year Outcome of Intravitreal Aflibercept with or without Photodynamic Therapy for Polypoidal Choroidal Vasculopathy. Medicina (Kaunas). Aug 14 2024; 60(8):1311. PMID 39202592
63. Kang HM, Kim YM, Koh HJ. Five-year follow-up results of photodynamic therapy for polypoidal choroidal vasculopathy. Am J Ophthalmol. Mar 2013; 155(3):438-447 e1. PMID 23218705
64. Kim SJ, Yu HG. Efficacy of combined photodynamic therapy and intravitreal bevacizumab injection versus photodynamic therapy alone in polypoidal choroidal vasculopathy. Retina. Oct 2011; 31(9):1827-1834. PMID 21734621
65. Blasi MA, Tiberti AC, Scupola A, et al. Photodynamic therapy with verteporfin for symptomatic circumscribed choroidal hemangioma: five-year outcomes. Ophthalmology. Oct 2010; 117(8):1630-1637. PMID 20417564
66. American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern Guidelines. Age-related macular degeneration. Updated June 2019. Available at: <https://www.aao.org> (accessed February 5, 2025).
67. National Institute for Health and Care Excellence (NICE). Age-related macular degeneration [NG82]. 2018. Available at: <https://www.nice.org.uk> (accessed February 5, 2025).
68. Centers for Medicare and Medicaid Services. Decision Memo for Ocular Photodynamic Therapy with Verteporfin for Macular Degeneration (CAG-00066R3) (2013). Available at: <https://www.cms.gov> (accessed February 5, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2025	Document updated. The following changes were made to Coverage: 1) Removed section on continuation therapy; 2) Removed preferred product criteria; 3) Added list of antivascular endothelial growth factor therapies to experimental, investigational and/or unproven statement on combination therapy. Added reference 11 and 60-62.
02/01/2025	Document updated. The following change was made to Coverage: Added language regarding drug shortages/recalls to “Initial Therapy” criteria. No new references added.

06/01/2024	Document updated. The following change was made to Continuation Therapy in Coverage: removed “through a previously authorized pharmacy or medical benefit” in the statement “Continuation of verteporfin photodynamic therapy may be considered medically necessary for all members (including new members…” Now reads: Continuation of verteporfin photodynamic therapy may be considered medically necessary for all Members (including new members): who are currently receiving the requested medication, AND who are experiencing benefit from therapy as evidenced by disease stability or disease improvement, AND when dosing is in accordance with an authoritative source.” No new references added.
10/01/2023	Document updated. The following change was made to Coverage: Added preferred criteria for bevacizumab (Avastin™). No new references added.
01/01/2023	Document updated with literature review. Coverage unchanged. The following references were added/updated: 56, 63 and 65; others removed.
01/01/2022	Reviewed. No changes.
01/01/2021	Document updated with literature review. The following changes were made to Coverage: 1) Added “verteporfin” to describe photodynamic therapy on both experimental, investigational and/or unproven statements; 2) Removed “chronic” from description of central serous chorioretinopathy on combination therapy experimental, investigational and/or unproven statement; and 3) Modified NOTEs to remove NOTE 2 and 3. No new references added; others removed.
07/01/2019	Reviewed. No changes.
10/15/2018	Document updated with literature review. Coverage unchanged. The following was added: NOTE 1: Acute CSC (central serous chorioretinopathy) refers to self-limiting disease that resolves spontaneously over a few months without any treatment. Chronic CSC has been defined as a serous macular elevation, visible biomicroscopically or detected by optical coherence tomography, that is associated with retinal pigment epithelial atrophic areas and subtle leaks or ill-defined staining by fluorescein angiography; it does not resolve spontaneously within a few months. References 2, 5, 21, 26, 29-31, 33-34, 36-37, 39, 43, and 45-54 added; numerous references removed.
07/15/2017	Reviewed. No changes.
08/15/2016	Document updated with literature review. Coverage unchanged.
11/01/2015	Reviewed. No changes.
10/01/2014	Document updated with literature review. Verteporfin (Visudyne™) was added as an example to the medically necessary coverage statement. Verteporfin (Visudyne™) was previously found in OTH903.020. Otherwise, coverage unchanged. CPT/HCPCS code(s) updated.
02/01/2013	Document updated with literature review. The following was added to Coverage section: Photodynamic therapy (PDT) as monotherapy may be considered medically necessary as a treatment of choroidal neovascularization (CNV) associated with chronic central serous

	chorioretinopathy, choroidal hemangioma, and pathologic myopia. Entire document has been revised. Title has changed from Photodynamic Therapy for Subfoveal Choroidal Neovascularization. CPT/HCPCS code(s) updated.
11/01/2010	CPT/HCPCS code(s) updated.
01/15/2010	Revised/updated entire document with addition of Photodynamic therapy as experimental, investigational and unproven when used in combination with one or more of the anti-vascular endothelial growth factor therapies.
11/01/2007	Revised/updated entire document
12/01/2003	New medical document