

Medical Policy



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(See policy history boxes for previous effective dates)

Title: Photodynamic Therapy for Choroidal Neovascularization

Description/Background

Photodynamic therapy (PDT) is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a 2-step process, consisting initially of an injection of the photosensitizer verteporfin (Visudyne®), followed 15 minutes later by laser treatment to the targeted sites of neovascularization in the retina. The laser treatment selectively damages the vascular endothelium. Patients may be re-treated if leakage from choroidal neovascularization (CNV) 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 (AMD).

Age-Related Macular Degeneration

AMD 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 as 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 (CNV), which greatly increases the risk of developing severe irreversible loss of vision. CNV is categorized as classic or occult. Classic CNV appears as an initial lacy pattern of hyperfluorescence followed by more irregular patterns as the dye leaks into the subretinal space. Occult CNV lacks the characteristic angiographic pattern. Classic CNV carries a worse prognosis for vision than occult CNV, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of AMD.

Pathologic Myopia

Pathologic myopia refers to an abnormal elongation of the eye associated with severe near-sightedness. It generally occurs among people over 30 years of age and can result in a progressive, severe loss of vision, frequently related to the development of CNV.

Verteporfin photodynamic therapy (VPDT) has also been investigated in patients with CNV related to pathologic myopia. Antivascular endothelial growth factor (anti-VEGF) therapy is now considered a first-line intervention in patients with myopic CNV.

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 (the Ohio and Mississippi River valleys in the United States). It is a condition 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 neovascular lesions, which may develop many years after chorioretinal scarring has taken place, affect the macula.

Central Serous Chorioretinopathy

Central serous chorioretinopathy (CSC) 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. Although central serous chorioretinopathy often resolves spontaneously in 3 to 4 months, chronic or recurrent central serous chorioretinopathy can result in 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 CSC as acute or chronic based on 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 CSC defined as the first attempted treatment to improve visual acuity, and chronic CSC is defined as being refractory to treatment. Further, multiple VPDT strategies that use either reduced-dose or half-fluency have been evaluated for the treatment of CSC because full-dose VPDT used in AMD has shown a potentially higher risk of developing choroidal ischemia and retinal atrophic changes.

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.

Polypoidal Choroidal Vasculopathy

Polypoidal choroidal vasculopathy arises primarily due to 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 CNV, and it may be considered a subtype of AMD. Eyes that develop a cluster of grape-like polypoidal dilations are at high risk for severe vision loss.

Angioid Streaks

Angioid streaks result from crack-like breaks in the Bruch membrane (the innermost layer of the choroid) and occur in patients 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 CNV include anti-VEGF inhibitors, VPDT, antioxidants, thermal laser photocoagulation, and corticosteroids. The safety and efficacy of each treatment depends on the form and location of the neovascularization.

VPDT 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 CNV persists.

Monotherapy with VEGF inhibitors is now standard treatment of CNV due to AMD and pathologic myopia. Combining VPDT with anti-VEGF inhibitors, concurrently or sequentially, has a biologic basis and has been investigated in multiple trials particularly in the treatment of CNV due to AMD 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 RCT^{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:

There is currently one intravenous photodynamic therapy (PDT) agent that has received approval by the U.S. Food and Drug Administration (FDA), verteporfin (Visudyne[®], Novartis). The FDA-approved indications include the treatment of predominantly classic subfoveal CNV due to age-related macular degeneration (AMD), pathologic myopia, and presumed ocular histoplasmosis. The label notes that there is insufficient evidence for verteporfin use in predominately occult subfoveal CNV, and it is contraindicated in patients with porphyria.

This policy only addresses combined treatment with PDT and VEGF inhibitors.

Medical Policy Statement

The safety and effectiveness of photodynamic therapy (PDT) with verteporfin for the treatment of choroidal neovascularization have been established. It is a useful therapeutic option for patients meeting patient selection guidelines.

All other uses for photodynamic therapy (PDT) with verteporfin are experimental/ investigational. Its effectiveness for other indications has not been established.

Inclusionary and Exclusionary Guidelines

Use of photodynamic therapy (PDT):

Inclusions:

Monotherapy of predominantly classic subfoveal CNV (Predominantly classic CNV lesions are defined as those in which the classic component comprised 50% or more of the area of the entire lesion) due to:

- Age-related macular degeneration (AMD)
- Chronic central serous chorioretinopathy
- Choroidal hemangioma
- Pathologic myopia
- Presumed ocular histoplasmosis.

Exclusions:

- The label notes that there is insufficient evidence for verteporfin use in predominately occult subfoveal CNV, and it is contraindicated in patients with porphyria.
 - Use of phototherapy with verteporfin as monotherapy for any other conditions other than predominantly classic subfoveal choroidal neovascularization due to any of the above conditions.
 - When used in combination with one or more of the anti-vascular endothelial growth factor therapies (anti-VEGF), including but not limited to pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Eylea™) as a treatment of CNV associated with age-related macular degeneration, chronic central serous chorioretinopathy, choroidal hemangioma, pathologic myopia, presumed ocular histoplasmosis, or for other ophthalmologic disorders.
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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

67221

67225

J3396

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews 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 function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients 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 (AMD)

The use of verteporfin photodynamic therapy (VPDT) in CNV has decreased substantially with the availability of anti-vascular endothelial growth factor (anti-VEGF) therapy. Subsequent to Food and Drug Administration (FDA) approval of VPDT in 2000, FDA approved pegaptanib in 2004 and ranibizumab in 2006 for treatment of AMD-related CNV. The approval of pegaptanib was based on a sham-controlled RCT^{1,2} while ranibizumab was approved based on a head-to-head comparison with VPDT in the ANCHOR trial.³ Intravitreal injections of anti-VEGF drugs such as ranibizumab and bevacizumab have shown superior efficacy compared to VPDT in multiple head-to-head trials. Currently, VPDT is used for patients in whom VEGF inhibitors are contraindicated or for those who fail to benefit from VEGF inhibitors.

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 question addressed in this evidence review is: Does the use of verteporfin photodynamic therapy improve the net health outcome in individuals with classic choroidal neovascularization due to age-related macular degeneration?

The following **PICO** was used to select literature to inform this review.

Population

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

Intervention

Treatment with verteporfin photodynamic therapy.

Comparator

Observational 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.

Review of Evidence

VPDT vs. Placebo

A 2000 TEC Assessment concluded that fewer patients treated with VPDT compared to placebo experienced a clinically significant loss of visual acuity (38.8% vs. 53.6%, respectively; $p < 0.001$).⁴ These conclusions were based on the 1-year follow-up results of 609 patients enrolled in 2 similar, multicenter, double-masked, randomized placebo-controlled trials called TAP published in 1999.⁵ 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.⁶ At 2 years, 53% of the VPDT arm compared to 38% of the placebo arm lost fewer than 15 letters. Further, average number of VPDT treatments required was lower in the second year compared to the first year (2.2 vs. 3.4, respectively). 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.⁷⁻⁹ They demonstrated positive outcomes with the use of VPDT for subfoveal CNV, and further supported the findings of the earlier TAP trial reports. In 2006, Kaiser reported results of a 3-year open-label extension of the TAP trials.¹⁰ Of 402 VPDT-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 VPDT or placebo.¹¹ Most (76%) patients had occult disease while the remainder had early classic CNV 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 CNV who were treated with VPDT (55%) had lost vision compared with those who received placebo (68%; $p = 0.032$). 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 CNV, while the VIP trial recruited patients with occult disease without evidence of classic CNV. 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 CNV 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 VPDT in preventing vision loss. A 2003 Cochrane review concluded that VPDT was effective at preventing vision loss in classic and occult CNV due to AMD.¹² In a 2004 meta-analysis of the safety of VPDT, Azab et al analyzed data from the 24-month TAP A and B and VIP trials (total N=948 patients with AMD).¹³ Reviewers concluded that the safety profile of VPDT did not differ statistically from placebo. An updated Cochrane review in 2007 evaluated results from the 3 RCTs (total N=1022 patients), which included the TAP and VIP trials.¹² 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 VPDT was probably effective for treating CNV due to AMD, although the effect size was uncertain.

Result of a 2008 multicenter RCT that compared 2 intensities of initial VPDT—every 2 or 3 months for first 6 months in 203 patients with CNV caused by AMD—showed no differences on overall outcomes for visual acuity or lesion anatomic features.¹³

Section Summary: VPDT vs. Placebo

The evidence for efficacy of VPDT includes multiple RCTs that have established its superiority compared to placebo. However, the efficacy is limited to a subgroup of patients with classic CNV. The use of VPDT has now been largely replaced by anti-VEGF therapies.

VPDT Plus Anti-VEGF Therapy

Review of Evidence

Because VPDT and ranibizumab target different disease components of AMD, it has been hypothesized that combining them might lead to a synergistic effect; with decrease in need for monthly VEGF injection and increased durability of response while maintaining visual acuity. The open-label, phase 2 PROTECT study demonstrated that same-day administration of ranibizumab and VPDT was well tolerated and vision was maintained.¹⁴ Results of the phase 1/2 FOCUS trial further supported the idea that combination treatment might be more effective than monotherapy.^{14,15} In this trial, 162 patients with classic CNV secondary to AMD were randomized to VPDT plus ranibizumab (n=106) or to VPDT plus sham (n=56). VPDT was repeated only if fluorescein angiography revealed persistent or recurrent leakage from CNV at evaluation visits (3-month intervals). Intention-to-treat (ITT) 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 VPDT-alone group. Visual acuity improved by 15 or more letters in 25% of patients treated with ranibizumab (plus VPDT as needed) compared with 7% of patients treated with VPDT 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 VPDT over ranibizumab alone. DENALI was a multicenter, double-masked, randomized phase 3b trial that tested the noninferiority of ranibizumab plus VPDT to VPDT alone. In this trial, patients were randomized to ranibizumab plus standard fluence VPDT (n=104) or reduced fluence (n=105) or ranibizumab plus sham VPDT (n=112).¹⁶ 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 (BCVA) 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 BCVA score was observed in all treatment groups, with the largest mean change from baseline in the

ranibizumab monotherapy group. The mean change in BCVA at 12 months was +5.3, +4.4, and 8.1 for ranibizumab plus standard fluence VPDT, ranibizumab plus reduced fluence VPDT, and ranibizumab plus sham VPDT, 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% CI, 85.4% to 97.0%) in the ranibizumab plus standard fluence VPDT and 83.5% (95% CI, 74.6% to 90.3%) in the reduced fluence arm. Percentages for ranibizumab monotherapy were not reported.

MONT BLANC was similar to DENALI in terms of design and outcome measures, except that the former did not include a reduced-fluence VPDT arm.¹⁷ In this trial, 255 patients were randomized to ranibizumab plus standard fluence VPDT (n=122) or ranibizumab plus sham VPDT (n=133). Patients received 3 consecutive monthly injections of ranibizumab followed by as-needed retreatments. A difference in mean BCVA within 7 letters was designated as noninferiority margin. The mean change in BCVA at 12 months was +2.5 letters in ranibizumab plus standard fluence VPDT group and +4.4 letters in the ranibizumab plus sham VPDT group, yielding a mean difference (MD) of 1.88. Because this difference was within the noninferiority margin, authors concluded that ranibizumab plus VPDT was noninferior to VPDT 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 versus 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, 4%; 95% CI, -0.02 to 0.09). Thus, the trial failed to show the superiority of ranibizumab plus VPDT over VPDT alone in increasing the treatment-free interval.

A systematic review of anti-VEGF injections for treating wet AMD was published in 2015, including a comparison of anti-VEGF monotherapy to anti-VEGF combination therapy plus VPDT.¹⁸ Results showed a significant difference in BCVA of 2.74 letters (95% CI, 0.26 to 5.21 letters; p=0.03) in favor of the monotherapy group (note that the conclusions of the systematic review indicated that the difference favored the combination group, which is incorrect). There were no differences between groups on central retinal thickness or lesion size. Reviewers did not report combined analysis of the number of anti-VEGF injections performed in each group. Similar results were reported in a meta-analysis published in 2016.¹⁹

In addition to the above trials, several smaller randomized trials have been published. In 2015, Semeraro et al published an RCT of 75 patients with treatment-naive exudative CNV due to AMD.²⁰ Patients were randomized into 3 groups: ranibizumab monotherapy, ranibizumab plus reduced-fluence VPDT, and ranibizumab plus ketorolac eye drops. At the 12-month follow-up, BCVA was superior in the ranibizumab plus ketorolac group (-0.25 logMAR [logarithm of the minimum angle of resolution]) compared with ranibizumab monotherapy (-0.14 logMAR) or ranibizumab combined with VPDT (-0.10 logMAR). In a multicenter, unmasked trial, Williams et al (2012) randomized 60 patients to ranibizumab with half-fluence VPDT or ranibizumab alone.²¹ BCVA 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) included 31 patients with AMD and 10 patients with polypoidal choroidal vasculopathy who were randomized to bevacizumab monotherapy or to bevacizumab plus VPDT.²² At 12 months,

the monotherapy and combined treatment groups showed similar improvements in BCVA and central foveal thickness, and the total number of bevacizumab injections was not reduced when VPDT was given. A 2007 randomized, open-label assessor-blinded trial from Croatia with short-term (3-month) follow-up evaluated combination treatment with bevacizumab plus VPDT (N=165 eyes).²³ At 3-month follow-up, 22 (42%) of 52 patients improved by more than 0.2 logMAR following combined treatment compared with 1 (2%) patient treated with bevacizumab alone and none treated with VPDT alone.

Data from a retrospective study for adjunctive VPDT in patients refractory to anti-VEGF monotherapy has suggested favorable effect on visual acuity and anatomic outcomes. Lee and Lee (2016) reported data from a retrospective analysis of 28 eyes of 28 patients who showed persistent subretinal and/or intraretinal fluid after at least 4 anti-VEGF injections in the 6 months before adjunctive VPDT and subsequently received additional VPDT and anti-VEGF therapies.²⁶ Patient charts were reviewed until 12 months after the initial VPDT. 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 PDT. At 12 months, BCVA had improved by 0.3 logMAR or more or was maintained compared with baseline in 27 (96.4%) eyes.

Section Summary: VPDT Plus Anti-VEGF Therapy

The evidence for the efficacy VPDT plus anti-VEGF therapies compared to anti-VEGF therapies alone includes 2 confirmatory RCTs (and their multiple analyses), multiple smaller RCTs, and a meta-analysis. This evidence does not demonstrate improvements in BCVA with combination therapy compared with anti-VEGF monotherapy. Combination therapy may reduce the number of intravitreal injections needed, but this result has not been consistently reported across studies.

VPDT Plus Corticosteroids and/or VEGF Inhibitors

Three RCTs have evaluated combination of VPDT with corticosteroids—1 trial from Italy,²⁴ RETINA,²⁵ and 1 trial from Iran.²⁶ The Italian RCT (2008) assigned 84 treatment-naive patients with exudative AMD to VPDT alone (n=41) or combination intravitreal triamcinolone acetonide plus VPDT (n=43).²⁴ Mean visual acuity increased at 1 month of follow-up but decreased progressively by the 24-month point in both groups. In the RETINA trial (2009), 100 patients with CNV due to AMD were randomized to VPDT alone or VPDT plus intravitreal triamcinolone.²⁵ Combination treatment did not result in a significant difference in the primary outcome of visual acuity at 1 year compared with VPDT alone. The Iranian trial randomized 84 treatment-naive patients with CNV due to AMD to VPDT plus bevacizumab with and without intravitreal triamcinolone.²⁶ There were no significant differences in the BCVA at week 12 and other time points.

Section Summary: VPDT Plus Corticosteroids and/or VEGF Inhibitors

The evidence for the efficacy of triple-therapy VPDT plus corticosteroid and anti-VEGF includes 3 small RCTs. This evidence does not demonstrate improvements in BCVA with this triple therapy compared to anti-VEGF monotherapy. Comparative trials are needed to evaluate the efficacy of this triple therapy.

PATHOLOGIC MYOPIA

The initial evidence was based primarily on retrospective studies and clinician experience. RADIANCE, a 2014 multicenter RCT compared intravitreal ranibizumab to VPDT in the treatment of myopic CNV and reported improved visual acuity at 12 months in the ranibizumab

treatment arm.²⁷ Zhu et al (2016) published a Cochrane review that found treatment with anti-VEGF therapies was more likely to restore visual acuity than VPDT.²⁸

VPDT vs. Placebo

A second arm of the VIP trial focused on 120 patients with pathologic myopia and CNV, either classic, occult, or mixed (although 90% of patients had classic CNV) who were randomized in a 2:1 ratio to receive VPDT or placebo.²⁹ Patients received an average of 3.4 VPDT treatments over 12 months. The primary outcome was the proportion of eyes with fewer than 8 letters of visual acuity lost at 12 months by ITT analysis. At month 12, VPDT-treated eyes lost fewer than 8 letters on a standard eye chart in 58 (72%) of patients versus 17 (44%) receiving placebo. Improvement of at least 5 letters was observed in 26 (32%) VPDT-treated eyes compared with 6 (15%) placebo-treated eyes. Fluorescein angiography showed progression of classic CNV in 36% of VPDT-treated eyes compared with 54% of the placebo group. The authors concluded that VPDT 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 significantly in favor of VPDT.³⁰

Section Summary: VPDT vs. Placebo

The evidence for the efficacy of VPDT compared with placebo includes a subgroup analysis from a large RCT. This analysis showed VPDT 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 VPDT is uncertain. Moreover, use of VPDT for myopic CNV has now been largely replaced by anti-VEGF therapies.

VPDT Plus With Anti-VEGF Therapy

Rinaldi et al (2017) randomized 60 patients to VPDT (standard- and reduced-fluence, n=20 each) plus ranibizumab or to ranibizumab monotherapy (n=20).³¹ The primary outcomes were mean change in BCVA and mean change in retinal thickening from baseline to week 48. The trial was likely underpowered to detect a clinical meaningful difference in BVCA for between-group comparisons. Mean BCVA change at 48 weeks was +0.2 and +15 letters with standard- and reduced-fluence VPDT 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 VPDT (n=6) in a retrospective analysis of patients with CNV secondary to causes other than AMD; approximately half of patients had myopic CNV.³² 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=0.11). Subgroup analysis for cases of myopic CNV 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<0.05) 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: VPDT in Plus Anti-VEGF Therapy

The evidence for efficacy of VPDT plus anti-VEGF therapy includes 1 small RCT and 1 retrospective study. This evidence does not demonstrate improvements in BCVA. Comparative trials are needed to evaluate the efficacy of this combination therapy versus relevant comparators.

PRESUMED OCULAR HISTOPLASMOSIS

There are few published data on the use of VPDT to treat patients with CNV related to ocular histoplasmosis. Food and Drug Administration approval 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 less than 3 lines in 88% of patients during the same period from a historical control. Ramaiya et al (2013) reported results from a small RCT that assigned 19 patients to ranibizumab or PDT with rescue ranibizumab.³³ The primary outcome measure was the change in visual acuity at 1 year. Data from 10 of the 19 randomized patients was excluded from analysis because of lack of follow-up data. The number of injections in the ranibizumab arm was 7.7 (range, 1-11). The mean number of PDT treatments administered was 2.5 (range, 2-3). All patients in the VPDT group required rescue ranibizumab therapy with a mean of 2.5 (range, 2-3) 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 versus 21 letters in the PDT 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 VPDT group showed a greater than 15 letter gain. Because of 50% lost to follow-up, 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 VPDT includes 1 small prospective single-arm study and 1 RCT. Lack of a control arm in the single-arm study and 50% loss to follow-up in the RCT preclude meaningful interpretation of the data on observed improvements in visual acuity. Comparative trials are needed to evaluate the efficacy of combination VPDT plus anti-VEGF therapy.

CENTRAL SEROUS CHORIORETINOPATHY (CSC)

A Cochrane review with network meta-analysis on various treatments for CSC that included both acute and chronic CSC was published in 2015.³⁴ Only RCTs were included. Pair wise (direct) comparison for VPDT included anti-VEGF versus VPDT, anti-VEGF plus 50% VPDT versus 50% VPDT alone, 50% VPDT versus observation or sham treatment, and 30% VPDT versus 50% VPDT versus VPDT. (Percentages refer to the dose of verteporfin used.) The primary outcome was visual acuity at 12 months. Low-quality evidence from 1 study (58 participants) suggested that half-dose VPDT for acute CSC probably resulted in a small improvement in vision (MD = -0.10 logMAR; 95% CI, -0.18 to -0.02 logMAR) compared to sham treatment.³⁵ Moderate-quality evidence from 2 studies suggested that 30% VPDT results in a small improvement in vision compared to VPDT (MD = -0.16 logMAR; 95% CI, -0.22 to -0.10 logMAR) and compared to 50% VPDT (MD = -0.12 logMAR; 95% CI, -0.15 to -0.08 logMAR).^{36,37} Visual acuity scores at 12 months did not differ between anti-VEGF versus VPDT^{38,39} or anti-VEGF plus 50% VPDT versus 50% VPDT alone,⁴⁰ or 50% VPDT versus observation or sham treatment.³⁵

Acute Central Serous Chorioretinopathy

Chan et al (2008) conducted a randomized, double-masked, placebo-controlled trial of 63 patients who were randomized in a 2:1 ratio to half-dose VPDT or placebo.³⁵ Thirty-nine patients in the VPDT and 19 in the placebo arm completed the trial. The primary outcome measure (the proportion of eyes with absence of subretinal fluid at the macula at 12 months) was observed in 37 (95%) eyes in the VPDT arm and 11 (58%) eyes in the placebo arm. Mean increase of BCVA was 1.8 and 0.6 lines in the VPDT 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.

In 2015, Zhao et al reported a double-masked, randomized, noninferiority trial with 131 patients that compared a 50% versus a 30% dose of VPDT for acute (<6 months) CSC.⁴⁰ 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. The 30% dose was not shown to be noninferior to the 50% dose, demonstrating a fluorescein angiography—based improvement rate of 68.9% versus 91.1% at 6 months (p=0.001) and 68.9% versus 92.9% at 12 months (p=0.001).

Salehi et al (2015), in their meta-analysis which included a total of 25 studies (total N=1098 patients; 1098 eyes), judged this study to be at low risk of bias in most domains with the exception of attrition bias (6% of the 30% VPDT group were lost to follow-up vs. 13% of the 50% VPDT group) and selective outcomes reporting (primary and secondary outcomes were designated differently on the trial register entry and the published report).³⁴ The 30% dose did not achieve noninferiority.

Section Summary: Acute Central Serous Chorioretinopathy

The evidence for the efficacy of VPDT for acute CSC includes 2 RCTs. This evidence, although demonstrating that full- and reduced-dose VPDT results in small improvements in BCVA, did not meet the clinically meaningful threshold. Comparative and adequately powered trials are needed to evaluate the efficacy of VPDT in acute CSC.

Chronic Central Serous Chorioretinopathy

Reductions in subretinal fluid and improvement in retinal anatomy, visual acuity⁴¹⁻⁴⁶ and retinal sensitivity⁴⁷⁻⁵¹ have been observed in 70% to 100% of cases in multiple retrospective studies. Use of reduced-dose VPDT for chronic CSC also has been reported. Uetani et al (2012) compared half-dose versus one-third dose VPDT in a small (N=16 eyes) prospective open-label trial.⁵² At 3 months, all 10 (100%) eyes in the half-dose VPDT group and 2 (33%) eyes in the one-third-dose VPDT group had complete resolution of subretinal fluid. Patients in the half-dose VPDT group gained an average of 5.4 letters while patients in the one-third-dose group gained 1.7 letters (p=NS). Chan et al (2008) also reported on reduced-dose verteporfin for the treatment of chronic CSC in a prospective series of 48 patients.⁴⁴ Mean duration of CSC was 8.2 months (range, 3-40 months). At 12 months after VPDT, mean BCVA improved from 0.31 to 0.15 logMAR, an improvement of 1.6 lines.

Section Summary: Chronic Central Serous Chorioretinopathy

The evidence for the efficacy of VPDT for chronic CSC includes multiple retrospective studies. Although this relatively large body of studies has indicated that half-dose VPDT yields positive functional and anatomic outcomes while, at the same time, reducing the potential adverse events associated with conventional VPDT, no comparative data have shown the relative

efficacy of multiple VPDT strategies. Comparative trials are needed to evaluate the efficacy of VPDT strategies in chronic CSC.

POLYPOIDAL CHOROIDAL VASCULOPATHY

Verteporfin Photodynamic Therapy

The 2010 systematic review by Chan et al included 30 studies on VPDT in patients with polypoidal choroidal vasculopathy.⁵³ Chan et al found numerous case series reporting favorable anatomic outcomes and visual acuity for patients treated with VPDT. 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.⁵⁴ Two RCTs Compared VPDT with ranibizumab and reported the weighted mean difference in visual acuity was 0.06 logMAR (95% CI, -0.01 to 0.12 logMAR) 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 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 VPDT.⁵⁸ A single physician diagnosed, treated, and followed all patients (not masked). Retreatment was considered every 3 months based on the findings of examinations, 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 logMAR in 55 (25%) of eyes, remained stable in 143 (65%) of eyes, and decreased more than 0.3 logMAR in 21 (10%) of eyes.

Akaza et al (2011) reported 3-year follow-up of 43 eyes (43 patients) treated with VPDT for polypoidal choroidal vasculopathy.⁵⁹ Before the initial VPDT, 40 (93%) eyes exhibited polypoidal choroidal vasculopathy in the narrow sense and 3 (7%) exhibited polypoidal CNV. 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 CNV showed little change except enlargement and recurrence. Long-term visual outcomes following VPDT 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 VPDT in some cases, further study is needed to confirm the long-term effectiveness of VPDT for polypoidal choroidal vasculopathy.

Section Summary: Verteporfin Photodynamic Therapy for Polypoidal Choroidal Vasculopathy

Available evidence on the efficacy of verteporfin photodynamic therapy for polypoidal choroidal vasculopathy consists of several retrospective studies, and 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.

VPDT Plus Anti-VEGF Therapy

Tang et al (2015) published a systematic review in 2015 evaluating treatment for polypoidal choroidal vasculopathy.⁵⁶ A single RCT that compared VPDT to VPDT plus ranibizumab reported a nonsignificant weighted mean difference of -0.08 logMAR (95% CI, -0.20 to 0.04 logMAR) in favor of combination therapy.

Lim et al (2012) randomized 31 patients with AMD and 10 patients with polypoidal choroidal vasculopathy to bevacizumab alone or to bevacizumab plus VPDT.²³ Bevacizumab was administered at 6-week intervals for the first 18 weeks, and then at 3-month intervals as needed. At 12 months, the monotherapy and combined treatment groups showed similar improvements in BCVA and central foveal thickness. Patients with polypoidal choroidal vasculopathy did not show significant improvement in BCVA ($p=0.050$) or central foveal thickness ($p=0.088$) when analyzed alone; however, the study was likely underpowered for this subset analysis.

EVEREST (2012) was a small, exploratory, multicenter, double-masked, randomized trial of VPDT, ranibizumab, or VPDT plus ranibizumab in 61 treatment-naive Asian patients with polypoidal choroidal vasculopathy.⁶⁰ Patients in the VPDT-only group (angio-occlusive) received sham ranibizumab, and patients in the ranibizumab monotherapy group (antiangiogenic and antipermeability) received sham VPDT. The primary end point (the proportion of patients with complete regression of polyps at 6 months) showed VPDT alone (71.4%) or in combination with ranibizumab (77.8%) to be superior to ranibizumab monotherapy (28.6%) in achieving complete polyp regression. Mean improvement in BCVA was generally similar for the 3 groups (7.5 letters for VPDT, 10.9 letters for combined treatment, 9.2 letters for ranibizumab alone). The proportion of patients gaining at least 15 letters was 19% in the VPDT group, 21% in the combination group, and 33% in the ranibizumab monotherapy group. Interpretation of the visual acuity results is limited, because the study was not powered to assess differences in BCVA. There were no new safety findings.

Observational studies have also been published. Kang et al (2013) reported 5-year retrospective follow-up for 42 eyes (36 patients) treated with VPDT for polypoidal choroidal vasculopathy.⁶¹ Patients received a mean of 2.21 VPDT treatments during the study, with additional intravitreal injections of anti-VEGF agents if exudative changes were observed. During follow-up, recurrence was observed in 33 (78.6%) eyes, and the mean number of anti-VEGF injections was 6.42 in eyes with recurrence. In the entire group, BCVA improved from 0.78 logMAR at baseline (20/120 Snellen equivalent) to 0.67 logMAR (20/93 Snellen equivalent) at 5 years. Using a change of at least 0.3 logMAR as a threshold, BCVA 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 VEGF antagonists without comparison groups. Kim and Yu (2011) retrospectively reviewed 39 consecutive patients with polypoidal choroidal vasculopathy who received VPDT (before April 2007) or combination VPDT plus intravitreal bevacizumab (after April 2007).⁵⁸ During 12 months of follow-up, patients in the monotherapy group ($n=19$) received a mean of 1.89 VPDT applications, and patients in the combined therapy group ($n=20$) received a mean of 1.30 VPDT applications and 2.90 bevacizumab injections. BCVA improved by 3.0 lines in the combined therapy group compared with 1.6 lines in the VPDT-only group. This level of

improvement in BCVA was achieved in 55.0% in the combined therapy group and 36.8% in the monotherapy group.

Section Summary: VPDT Plus Anti-VEGF Therapy in Polypoidal Choroidal Vasculopathy

Available evidence on the efficacy of VPDT for polypoidal choroidal vasculopathy consists of 2 small RCTs, 1 meta-analysis, and 2 retrospective studies. While results of the RCT reported no difference in visual acuity for patients treated with VPDT plus anti-VEGF therapy versus VPDT alone, the other trial reported improvement in visual acuity but the effect was not statistically significant. Adequately powered controlled trials are needed to permit conclusions on the efficacy of combination VPDT plus anti-VEGF therapy in polypoidal choroidal vasculopathy.

CHOROIDAL HEMANGIOMA

The systematic review by Chan (2010) included 11 case series on VPDT in patients with choroidal hemangioma.⁵⁵ VPDT 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 VPDT regimens.

In 2010, Blasi et al reported on 5-year outcomes for a prospective series of 25 consecutive patients with symptomatic choroidal hemangioma.⁶³ Twenty-two (88%) patients received a single VPDT session and 3 eyes received a second VPDT 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, BCVA 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 resolution of macular exudation in all cases. No treatment-related adverse events were identified.

Section Summary: Choroidal Hemangioma

Available evidence on the efficacy of VPDT for choroidal hemangioma consists of 1 systematic review that included data from 11 case series and 1 prospective study. This body of evidence has suggested a favorable effect of VPDT on various visual acuity and anatomic outcomes in patients with choroidal hemangioma. Controlled trials with a larger number of patients and longer follow-up are needed to permit conclusions regarding the efficacy of VPDT for this indication.

ANGIOID STREAKS

The 2010 systematic review by Chan et al included 8 case series on VPDT in 148 patients with angioid streaks.⁵⁶ Reviewers concluded the VPDT might limit or slow vision loss compared with the expected natural course of CNV due to angioid streaks, but 1 study showed a decrease in visual acuity following VPDT, 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 VPDT in these patients.

Section Summary: Angioid Streaks

Available evidence on the efficacy of VPDT for angioid streaks consists of 1 systematic review on 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 VPDT in angioid streaks, especially if it is effective in limiting the growth of CNV.

INFLAMMATORY CHORIORETINAL CONDITIONS

CNV 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 2010 systematic review by Chan et al included 15 case reports of VPDT in 115 patients with inflammatory eye conditions.⁵³ Encouraging visual acuity and anatomic improvements have been reported with VPDT for punctate inner choroidopathy, choroiditis and toxoplasmic retinochoroiditis, and subfoveal CNV secondary to posterior uveitis. While promising, larger and comparative studies are needed to evaluate the effect of VPDT on health outcomes for this indication.

Section Summary: Inflammatory Chorioretinal Conditions

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

SUMMARY OF EVIDENCE

Age-Related Macular Degeneration

For individuals who have classic choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) who receive VPDT, 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 VPDT in reducing vision loss and decreasing retinal thickness compared to placebo or sham procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CNV due to AMD who receive VPDT plus anti-vascular endothelial growth factor (anti-VEGF) 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 anti-VEGF 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 the effects of the technology on health outcomes.

For individuals who have CNV due to AMD who receive VPDT plus corticosteroids and/or anti-VEGF 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 the effects of the technology on health outcomes.

Pathologic Myopia

For individuals who have CNV due to pathologic myopia who receive VPDT, the evidence includes 1 subgroup analysis from a large RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The subgroup analysis showed VPDT

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 a meaningful improvement in the net health outcome.

For individuals who have CNV due to pathologic myopia who receive VPDT plus anti-VEGF therapy, the evidence includes 1 small RCT and 1 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 clinical 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 the effects of the technology on health outcomes.

For individuals who have CNV due to presumed ocular histoplasmosis who receive VPDT, the evidence includes 1 small RCT and 1 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 meaningful interpretation of data of observed improvements in visual acuity outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Central Serous Chorioretinopathy

For individuals who have CNV due to acute central serous chorioretinopathy who receive VPDT, 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 VPDT result in a small improvement in visual acuity outcomes, the improvements did not meet clinically meaningful thresholds. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CNV due to chronic central serous chorioretinopathy who receive VPDT, 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 VPDT yields positive functional and anatomic outcomes while, at the same time, reducing the potential adverse events associated with conventional VPDT, data from RCTs for multiple VPDT strategies are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Polypoidal Choroidal Vasculopathy

For individuals who have CNV due to polypoidal choroidal vasculopathy who receive VPDT, the evidence includes several prospective cohort studies and 1 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 VPDT. RCTs comparing VPDT with anti-VEGF therapies have reported no statistical differences in visual acuity outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CNV due to polypoidal choroidal vasculopathy who receive VPDT plus anti-VEGF therapy, the evidence includes 2 small RCTs, 1 meta-analysis, and 2 retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Results of the 2 RCTs failed to demonstrate statistical differences in visual acuity outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Choroidal Hemangioma

For individuals who have CNV due to choroidal hemangioma who receive VPDT, the evidence includes 1 systematic review (11 case series) and 1 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 VPDT on various visual acuity and anatomic outcomes in patients with choroidal hemangioma, data from RCTs are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Angioid Streaks

For individuals who have CNV due to angioid streaks who receive VPDT, the evidence includes 1 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 the effects of the technology on health outcomes.

Inflammatory Chorioretinal Conditions

For individuals who have CNV due to inflammatory chorioretinal conditions who receive VPDT, the evidence includes 1 systematic review of case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Methodologic limitations restrict the conclusions drawn from 15 case reports (total N=115 patients) of multiple disease indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03079141	Photodynamic therapy vs. eplerenone: treatment trial for chronic central serous chorioretinopathy (SPECT)	107	Aug 2021
Unpublished			
NCT02452840 ^a	Photodynamic Therapy for PDA in Neovascular Age-Related Macular Degeneration	100	Nov 2021

NCT: national clinical trial

^a Denotes industry-sponsored or cosponsored trial.

SUPPLEMENTAL INFORMATION

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

BCBSA requested input from 2 physician specialty societies and 2 academic medical centers while this policy was under review in 2012. The input agreed that PDT monotherapy is medically necessary for AMD, pathological myopia, and presumed ocular histoplasmosis and also considered PDT monotherapy to be medically necessary for central serous chorioretinopathy and choroidal hemangioma. Input was mixed regarding the use of PDT for other ophthalmologic

disorders. The input agreed that PDT in combination with VEGF antagonists is investigational for all ophthalmologic disorders.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Ophthalmology⁶⁰

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.

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.

National Institute for Health and Care Excellence⁶⁴

In 2018, the National Institute for Health and Care Excellence updated its 2003 guidance on the use of PDT for AMD. The Institute made the following recommendations: it recommended against use of PDT as monotherapy for late (wet) AMD and against use of PDT as first-line adjunctive therapy to anti-VEGF therapies for late (wet) AMD; it recommended for PDT as second-line adjunctive therapy to anti-VEGF therapies for late (wet) AMD in a trial setting.

Government Regulations

National:

National Coverage Determination (NCD) for Ocular Photodynamic Therapy (OPT)

80.2.1, Effective date: 4/3/13

Indications and Limitations of Coverage

B. Nationally Covered Indications

Effective April 1, 2004, OPT with verteporfin continues to be approved for a diagnosis of neovascular AMD with predominately classic subfoveal CNV lesions (where the area of classic CNV occupies $\geq 50\%$ of the area of the entire lesion) at the initial visit as determined by an FA. (CNV lesions are comprised of classic and/or occult components.) Subsequent follow-up visits require either an optical coherence tomography (OCT) (effective April 3, 2013) or an FA (effective April 1, 2004) to assess treatment response. There are no requirements regarding visual acuity, lesion size, and number of re-treatments when treating predominantly classic lesions.

In addition, after thorough review and reconsideration of the August 20, 2002, non-coverage policy, CMS determines that the evidence is adequate to conclude that OPT with verteporfin is reasonable and necessary for treating:

1. Subfoveal occult with no classic CNV associated with AMD; and,
2. Subfoveal minimally classic CNV (where the area of classic CNV occupies $< 50\%$ of the area of the entire lesion) associated with AMD.

The above 2 indications are considered reasonable and necessary only when:

1. The lesions are small (4 disk areas or less in size) at the time of initial treatment or within the 3 months prior to initial treatment; and,
2. The lesions have shown evidence of progression within the 3 months prior to initial treatment. Evidence of progression must be documented by deterioration of visual acuity (at least 5 letters on a standard eye examination chart), lesion growth (an increase in at least 1 disk area), or the appearance of blood associated with the lesion.

C. Nationally Non-Covered Indications

Other uses of OPT with verteporfin to treat AMD not already addressed by CMS will continue to be non-covered. These include, but are not limited to, the following AMD indications:

- Juxtafoveal or extrafoveal CNV lesions (lesions outside the fovea),
- Inability to obtain a fluorescein angiogram,
- Atrophic or "dry" AMD.

D. Other

The OPT with verteporfin for other ocular indications, such as pathologic myopia or presumed ocular histoplasmosis syndrome, continue to be eligible for local coverage determinations through individual Medicare Administrative Contractor discretion.

Indications and Limitations of Coverage

Ocular Photodynamic Therapy (OPT) is used in the treatment of ophthalmologic diseases. OPT is only covered when used in conjunction with verteporfin (see section 80.3, "Photosensitive Drugs").

- Classic Subfoveal Choroidal Neovascular (CNV) Lesions - OPT is covered with a diagnosis of neovascular age-related macular degeneration (AMD) with predominately classic subfoveal choroidal neovascular (CNV) lesions (where the area of classic CNV occupies $\geq 50\%$ of the area of the entire lesion) at the initial visit as determined by a fluorescein angiogram (FA). Subsequent follow-up visits will require either an optical coherence tomography or an FA to assess treatment response. There are no requirements regarding visual acuity, lesion size, and number of re-treatments.
- Occult Subfoveal CNV Lesions - OPT is non-covered for patients with a diagnosis of AMD with occult and no classic CNV lesions.

Other Conditions - Use of OPT with verteporfin for other types of AMD (e.g., patients with minimally classic CNV lesions, atrophic, or dry AMD) is non-covered. OPT with verteporfin for other ocular indications such as pathologic myopia or presumed ocular histoplasmosis syndrome, is eligible for coverage through individual Medicare Administrative Contractor discretion.

Local:

No separate LCD on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Photocoagulation of Macular Drusen
 - Epiretinal Radiation Treatment for Wet ARMD
 - Implantable Miniature Telescope for ARMD
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2023, the date the research was completed.

Joint BCBSA/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/6/02	5/6/02	N/A	Joint policy established
12/5/03	12/5/03	1/16/04	Routine maintenance
1/7/05	1/7/05	12/22/04	Routine maintenance
7/1/06	5/2/06	3/27/06	Routine maintenance
1/1/09	10/13/08	12/30/08	Routine maintenance
3/1/13	12/11/12	12/31/12	Policy title changed from “Visudyne® (Verteporfin) Photodynamic Therapy” to Photodynamic Therapy for Choroidal Neovascularization.” Policy reformatted to mirror BCBSA policy. References added. No change in policy status.
3/1/14	12/10/13	1/6/14	Routine maintenance. References updated.
5/1/15	2/17/15	2/27/15	Routine maintenance. References updated.
5/1/16	2/16/16	2/16/16	Routine maintenance. Rationale updated.
5/1/17	2/21/17	2/21/17	Routine maintenance, rationale and references updated. CMS section updated. No change in policy status.
5/1/18	2/20/18	2/20/18	Extensive reformatting of rationale section, no new references, some references deleted. No changes in policy status.
3/1/19	12/11/18		Routine policy maintenance. No new references, some outdated references removed. No changes in policy status.
3/1/20	12/17/19		Routine policy maintenance. No change in policy status.
3/1/2021	12/15/20		Routine policy maintenance. No change in policy status.
3/1/22	12/14/21		Routine policy maintenance. No change in policy status.
3/1/23	12/20/22		Updated rationale section, added reference 57, removed one

			reference. No change in policy status.
3/1/24	12/19/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)

Next Review: 4th Qtr. 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: 8/10/00	Revised: 5/8/01, 8/20/01
BCBSM: 12/6/00	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: PHOTODYNAMIC THERAPY FOR CHOROIDAL NEOVASCULARIZATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Covered; criteria apply.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.