Name of Policy:
Photodynamic Therapy for Choroidal Neovascularization

Policy #: 047  Latest Review Date: March 2018
Category: Medication/Drug  Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health
plans only in cases of medical necessity and only if services or supplies are not investigational,
provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be
considered for coverage:

1. The technology must have final approval from the appropriate government regulatory
   bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology
   on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies,
devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment,
would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an
illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and
   considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider;
   and
4. Not more costly than an alternative service or sequence of services at least as likely to
   produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of
   that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Verteporfin photodynamic therapy (VPDT) 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, followed 15 minutes later by laser treatment to the targeted sites of neovascularization in the retina. The laser treatment selectively damages the vascular endothelium, thereby occluding choroidal neovascularization tissue. Patients 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 (AMD).

**Treatment**
Available therapeutic options for choroidal neovascularization (CNV) include anti-vascular endothelial growth factor (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 initially of an injection of the photosensitizer verteporfin, followed 15 minutes later by laser treatment to the targeted sites of neovascularization in the retina. 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 the current standard of care for treatment of CNV due to age-related macular degeneration 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 age-related macular degeneration and pathologic myopia.

**Policy:**
**Photodynamic therapy (PDT) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used as a treatment for one of the following indications:

- Choroidal neovascularization (CNV) associated with age-related macular degeneration
- Presumed ocular histoplasmosis syndrome
- Pathologic myopia
- Circumscribed choroidal hemangioma
- Chronic central serous chorioretinopathy

U.S. Food and Drug Administration (FDA) labeling for verteporfin indicates that the physician should reevaluate the patient every 3 months and, if choroidal neovascularization leakage is detected on fluorescein angiography, therapy should be repeated. However, the total number of
treatments is not addressed by FDA. Evidence defining when treatment should stop is not available, but expert opinion (convened by Novartis, Visudyne® [verteporfin] manufacturer) suggested stopping “when the situation is judged to be ‘futile’” (Verteporfin Roundtable Participants 2005). FDA labeling states that the “safety and efficacy of Visudyne beyond 2 years have not been demonstrated.”

**Photodynamic therapy does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used as a treatment for other ophthalmologic disorders and is considered investigational.

**Photodynamic therapy does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational when used in combination with one or more of the anti-vascular endothelial growth factor therapies (anti-VEGF), i.e., pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Eylea™) as a treatment of CNV associated with AMD, pathologic myopia, presumed ocular histoplasmosis, circumscribed choroidal hemangioma, chronic central serous chorioretinopathy or for other ophthalmologic disorders.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**
The most recent literature review was updated through January 08, 2018.

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)
Age-related macular degeneration (AMD) is a degenerative disease of retina that results in loss of central vision. Two distinctively different known as dry and wet forms of 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 (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.

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 while ranibizumab was approved based on a head-to-head comparison with VPDT in the ANCHOR trial. 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 those who fail to benefit from VEGF inhibitors.

VPDT versus 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). 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 2000. 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 entire 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. At 2 years, 53% in VPDT arm compared to 38% in the placebo arm lost fewer than 15 letters. Further, average number of VPDT treatment 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. 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 study. 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 and 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. 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 trial, 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 that have included TAP and VIP trials corroborate the treatment benefit of VPDT therapy in preventing visual loss. A 2003 Cochrane review concluded that VPDT is effective at preventing visual loss in classic and occult CNV due to AMD. 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. Reviewers concluded that the safety profile of VPDT therapy 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. 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 is 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 treatment—every 2 or 3 months for first 6 months in 203 patients with CNV caused by AMD showed no differences on overall outcomes regarding visual benefit and lesion anatomic features.

Subsection 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 in Combination with Anti-VEGF Therapies
Because VPDT and ranibizumab target different disease components of AMD, it was hypothesized that combination may lead to a synergistic effect, with decrease in need for monthly VEGF injection and increased durability of response while maintaining visual outcomes. The open-label, phase 2 PROTECT study demonstrated that same-day administration of ranibizumab and VPDT was well tolerated and vision was maintained. Results of the phase
FOCUS trial further supported the idea that combination treatment might be more effective than monotherapy. In this trial, 162 patients with classic CNV secondary to AMD were randomized to VPDT plus ranibizumab (n=106) or 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 ranibizumab monotherapy arm. Subsequently, the 2 larger phase 3 confirmatory trials—DENALI and MONT BLANC—failed to show superiority of ranibizumab plus VPDT versus ranibizumab alone.

DENALI was a multicenter, double-masked, randomized phase 3b trial that tested noninferiority of ranibizumab plus VPDT with 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). Patients received 3 consecutive monthly injections of ranibizumab followed by as-needed retreatments. The 2 main outcome measures were the 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 outcomes was not demonstrated. Trials failed to demonstrate the superiority of combination treatment to reduce treatment-free interval period. The proportion of patients with treatment-free interval of 3 months or more was 92.6% (95% CI, 85.4% to 97.0%) and 83.5% (95% CI, 74.6% to 90.3%) in the ranibizumab plus standard fluence VPDT and reduced fluence arm respectively. Percentage for ranibizumab monotherapy was not reported.

MONT BLANC was similar to DENALI in terms of design and outcome measures except that it did not include a reduced fluence VPDT arm. 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 of BCVA within 7 letters was designated as noninferiority margin. The mean change in BCVA at 12 months was +2.5 and +4.4 letters in ranibizumab plus standard fluence VPDT and ranibizumab plus sham VPDT, respectively, yielding a mean difference 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 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 was 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 a superiority of ranibizumab plus VPDT over VPDT alone in increasing treatment free interval.
A systematic review of anti-VEGF injections for treating wet AMD was published in 2015, including a section comparing anti-VEGF monotherapy with anti-VEGF combination therapy with VPDT. Results showed a significant difference in BCVA of 2.74 letters (95% CI, 0.26 to 5.21; \( p=0.03 \)) in favor of the monotherapy group (note that the conclusions of the systematic review indicate 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 another meta-analysis published in 2016.

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. 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 (SD) was superior in the ranibizumab plus ketorolac group (-0.25 [0.60] logMAR), compared with ranibizumab monotherapy (-0.14 [0.52] logMAR) or ranibizumab combined with VPDT (-0.10 [0.30] logMAR). In a multicenter, unmasked trial, Williams et al (2012) randomized 60 patients to ranibizumab with half-fluence VPDT or ranibizumab alone. 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 versus 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 bevacizumab in combination with VPDT. 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 randomized, open-label assessor-blinded trial from Croatia with short-term (3-month) follow-up evaluated combined treatment with bevacizumab and VPDT (\( N=165 \) eyes). At 3-month follow-up, 22 (42%) of 52 patients improved by more than 0.2 logMAR (logarithm of the minimum angle of resolution) 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 therapy of VPDT in patients who are refractory to anti-VEGF monotherapy suggests favorable effect on visual and anatomic outcomes. 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. 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 treatment, 7 eyes initially showed complete fluid absorption after the initial PDT. At 12 months, BCVA improved by 0.3 logMAR or more or maintained compared with baseline in 27 (96.4%) eyes.

Section Summary: VPDT plus Anti-VEGF Therapies

The evidence for efficacy of addition of VPDT to anti-VEGF therapies compared to anti-VEGF therapies alone includes 2 confirmatory RCTs (and their multiple analysis), multiple smaller RCTs and a meta-analysis. This evidence does not demonstrate an improvement in BCVA with
combination therapy compared with anti-VEGF monotherapy. Combination therapy may lead to a reduction in the number of intravitreal injections needed, but this is not consistently reported across studies.

**VPDT Plus Corticosteroids and/or VEGF Inhibitors**

Three RCTs have evaluated combination of VPDT with corticosteroids-1 trial from Italy, RETINA, and 1 trial from Iran. The Italian RCT assigned 84 treatment naïve patients with exudative AMD to VPDT alone (n=41) or combination of intravitreal triamcinolone acetonide plus VPDT (n=43). 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, 100 patients with CNV due to AMD were randomized to VPDT alone or VPDT plus intravitreal triamcinolone. 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 naïve patients with CNV due to AMD to VPDT plus bevacizumab with and without intravitreal triamcinolone. There was no significant difference in the BCVA at week 12 and other time points.

**Section Summary: VPDT Plus Corticosteroids and/or VEGF Inhibitors**

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

**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 CNV. VPDT has also been investigated in patients with CNV related to pathologic myopia. Anti-VEGF therapy is now considered first line intervention in patients with myopic CNV. The initial evidence was based primarily on retrospective studies and clinician experience. RADIANCE is a multi-center, randomized controlled trial that comparing intravitreal ranibizumab to VPDT in the treatment of myopic CNV and reported improved visual acuity at 12 months in the ranibizumab treatment arm. Zhu et al (2016) published a Cochrane systematic review and meta-analysis which reported that treatment with anti-VEGF therapies was more likely to regain vision compared to VPDT.

**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. Patients received an average of 3.4 VPDT treatments over the course of 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 72% (n=58) of patients versus 44% (n=17) who were receiving placebo. Improvement of at least 5 letters was observed in 32% (n=26) of VPDT-treated eyes compared with 15% (n=6) of 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.

**Section Summary: VPDT vs Placebo**

The evidence for 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 visual 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 Anti-VEGF Therapies**

Rinaldi et al (2017) randomized 60 patients to either VPDT (standard and reduced fluence, n=20 each) in combination with ranibizumab or ranibizumab monotherapy (n=20). 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 groups comparisons. Mean BCVA change at 48 weeks was +0.2 and +15 letters with standard and reduced VPDT plus ranibizumab, respectively, compared with +16.8 letters with ranibizumab monotherapy. At 48 weeks, mean central foveal thickness decrease from baseline was 58±15 μm, 91.4±43.8 μm, and 85±41.5 μm for the 3 groups, respectively.

Chenet 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 the patients had myopic CNV. Most of the observed differences between groups did not reach statistical significance, 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 compared with 2.8 lines in the combination therapy group, and 36% of the monotherapy group gained three lines or more compared with 60% in the combination therapy group. The combination group received fewer reinjections (2.6 vs 4.8 injections on average), 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 plus Anti-VEGF Therapy**

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

**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 CNV lesions, which may develop many years after chorioretinal scarring has taken place, affect the macula.

There are few published data on the use of VPDT in patients with CNV related to ocular histoplasmosis. Food and Drug Administration approval in 2001 was based on an prospective single arm 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 an improvement of at least 3 lines (15 letters). Visual acuity decreased by less than 3 lines in 88% of patients during the same time 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. 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 injection 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 PDT group required rescue ranibizumab therapy with a mean of 2.5 (range, 2-3) injections. Mean change in the Early Treatment Diabetic Retinopathy Study (ETDRS) 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 PDT 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 efficacy of VPDT includes 1 small an prospective single arm and 1 RCT. Lack of a control arm in the single arm study and 50% lost to follow-up in the RCT preclude meaningful interpretation of data of the observed improvement in visual acuity outcomes. Comparative trials are needed to evaluate the efficacy of combination therapy of VPDT with anti-VEGF therapies.

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. In most cases, CSC often resolves spontaneously in 3 to 4 months. However, in a few cases, chronic progression or recurrence can lead to progressive decline of visual acuity. CSC 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 cut-off time points (e.g. persistent fluid for less than 3, 4 or 6 months) or less frequently based on 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 treatment of central serous chorioretinopathy because full dose VPDT used in AMD showed a potentially higher risk of developing choroidal ischemia and retinal atrophic changes.
A Cochrane systematic review with network meta-analysis on various treatment of CSC that included both acute and chronic CSC was published in 2015. Only RCTs were included. Pairwise (direct) comparison for VPDT treatment 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. Percentage refers 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 treatment of acute CSC probably results in a small improvement in vision (MD, -0.10 logMAR; 95% CI -0.18 to -0.02 logMAR) compared to sham treatment. 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). Visual acuity scores at 12 months did not differ between anti-VEGF versus VPDT or anti-VEGF plus 50% VPDT versus 50% VPDT alone or 50% VPDT versus observation or sham treatment.

Acute Central Serous Chorioretinopathy
Chan et al (2008) conducted a randomized, double-masked, placebo-controlled trial of in 63 patients were randomized in a 2:1 ratio to half-dose VPDT or placebo. Thirty-nine patients and 19 in the VPDT and placebo arm completed the trial respectively. The primary outcome measure-the proportion of eyes with absence of subretinal fluid at the macula at 12 months-was observed in 95% (n=37) of eyes in the VPDT arm and 58% (n=11) of 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 falls 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, non-inferiority trial with 131 patients that compared a 50% versus 30% dose of VPDT for acute (<6 months) central serous chorioretinopathy. The two 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 six 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). The 30% dose did not achieve noninferiority. 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=0.004). Complete disappearance of fluorescein leakage at 12 months was observed in 68.9% of the 30%-dose group versus 92.9% of the half-dose group (p=0.001). 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 VPDT for acute CCC.
Section Summary: Acute Central Serous Chorioretinopathy
The evidence for efficacy of VPDT for acute central serous chorioretinopathy includes 2 RCT. This evidence although demonstrates that full and reduced dose VPDT results in a small improvement in BCVA, did not meet the clinically meaningful threshold. Comparative and adequately powered trials are needed to evaluate the efficacy of VPDT in acute central serous chorioretinopathy.

Chronic Central Serous Chorioretinopathy
Reduction in subretinal fluid and improvement in retinal anatomy, visual acuity and retinal sensitivity has been observed in 70% to 100% cases in multiple retrospective studies. Use of reduced-dose verteporfin 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. 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 (not significantly different). Chan et al (2008) also reported on reduced-dose verteporfin for the treatment of chronic CSC in a prospective series of 48 patients. 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 efficacy of VPDT for chronic CSC includes multiple retrospective studies. Although this relatively large body of retrospective studies indicates that half-dose VPDT is able to yield 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
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 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.

Verteporfin Photodynamic Therapy
The 2010 systematic review by Chan et al included 30 studies on VPDT in patients with polypoidal choroidal vasculopathy. Chan et al found numerous case series reporting favorable anatomical and visual acuity outcomes for patients treated with VPDT. Tang et al (2015) published a systematic review and meta-analysis evaluating treatment for polypoidal choroidal vasculopathy. 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.

Several nonrandomized studies from Asia have been reported. Hikichi et al (2011) reported the largest a prospective consecutive series of 220 eyes of 210 Japanese patients with polypoidal
choroidal vasculopathy who were followed for 1 year after the primary VPDT treatment. 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 25% of eyes, remained stable in 65% of eyes, and decreased more than 0.3 logMAR in 10% of eyes.

Akaza et al (2011) reported three-year follow-up of 43 eyes (43 Patients) treated with VPDT for polypoidal choroidal vasculopathy. Before the initial VPDT, 40 eyes (93%) exhibited polypoidal choroidal vasculopathy in the narrow sense, and three (7%) exhibited polypoidal CNV. The number of treatment sessions during follow-up ranged from one to eight. At 3-year follow-up, mean visual acuity decreased to below baseline. Polypoidal lesions recurred in 33 of the 43 eyes (77%) at three years, although the three eyes with polypoidal CNV showed essentially no changes except for enlargement and recurrence. The authors concluded that long-term visual outcomes following VPDT were not good due to the high frequency of recurrent polypoidal lesions, as well as enlargement and neovascular changes involving abnormal vascular networks. However, because polypoidal lesions recur after VPDT in some cases, further study is needed to confirm the long-term effectiveness of VPDT for polypoidal choroidal vasculopathy.

Section Summary: VPDT Monotherapy in Polypoidal Choroidal Vasculopathy

Available evidence on the efficacy of VPDT monotherapy for polypoidal choroidal vasculopathy consists of several retrospective studies and 1 meta-analysis that included 2 RCTs. Retrospective studies have reported favorable anatomic and visual acuity outcomes for patients treated with VPDT. RCTs comparing VPDT with anti-VEGF therapies reported no statistical difference in visual acuity outcomes. Controlled trials are needed to permit conclusions regarding the efficacy of VPDT monotherapy in polypoidal choroidal vasculopathy.

VPDT Combination with Anti-VEGF Therapies

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

Lim et al (2012) study randomized 31 patients with AMD and 10 patients with polypoidal choroidal vasculopathy to bevacizumab monotherapy or bevacizumab in combination with VPDT. 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. Patients in the VPDT monotherapy 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 of 42 eyes (36 patients) treated with VPDT for polypoidal choroidal vasculopathy. 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) reported analysis from a retrospective review of 39 consecutive patients with polypoidal choroidal vasculopathy who received VPDT monotherapy (before April 2007) or a combination of VPDT and intravitreal bevacizumab (after April 2007). 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 monotherapy 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 Combination with Anti-VEGF Therapies 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 1 RCT reported no difference in visual acuity outcomes for patients treated with VPDT plus anti-VEGF therapy versus VPDT alone, the other trial reported improvement in visual acuity but effect was not statistically significant. Adequately powered controlled trials are needed to permit conclusions regarding the efficacy of combination therapy of VPDT plus VEGF therapies in polypoidal choroidal vasculopathy.

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

In 2010, Blasi et al reported 5-year outcomes from a prospective series of 25 consecutive patients with symptomatic choroidal hemangioma. 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 with a reduction 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 suggests a favorable effect of VPDT on various visual 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
Angioid streaks results from crack-like breaks in 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 CNV.

The 2010 systematic review by Chan et al included eight case series on VPDT in 148 patients with angioid streaks. Reviewers concluded the VPDT might limit or slow vision loss compared with the expected natural course of CNV due to angioid streaks, but one 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 that reported data collected from case series. The data from case series reports conflicting results for visual outcomes. 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 on VPDT in 115 patients with inflammatory eye conditions. Encouraging visual and anatomical outcomes 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 regarding the efficacy of VPDT in ocular inflammatory conditions.

**Summary of Evidence**

**Age-Related Macular Degeneration**

For individuals who have classic choroidal neovascularization due to age-related macular degeneration (AMD) who receive VPDT monotherapy, 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 support the superiority of VPDT in reducing visual 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 choroidal neovascularization due to AMD who receive VPDT plus anti-vascular endothelial growth factor (VEGF) therapy, the evidence includes 2 confirmatory RCTs (and their multiple analysis), multiple smaller RCTs and a meta-analysis of the existing trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. This evidence does not demonstrate an improvement in visual acuity with combination therapy compared to anti-VEGF monotherapy. Combination therapy may lead to a reduction in the number of intravitreal injections needed, but this is not consistently reported across studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have choroidal neovascularization 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. This evidence does not demonstrate an improvement 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 choroidal neovascularization due to pathologic myopia who receive VPDT monotherapy, 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 to be more effective than placebo in preventing visual 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.

**Presumed Ocular Histoplasmosis**
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.

**Practice Guidelines and Position Statements**
**American Academy of Ophthalmology**
A 2015 Preferred Practice Patterns (practice guidelines) on AMD from the American Academy of Ophthalmology (AAO) describe VPDT as a U.S. Food and Drug Administration–approved option for the treatment of subfoveal lesions and predominantly classic CNV related to AMD.

The 2015 update states that anti-vascular endothelial growth factor (anti-VEGF) therapies have become first line therapy for treatment and stabilizing most cases of AMD. PDT is a less commonly used treatment for neovascular AMD; recommendations state that the following diagnoses are eligible for VPDT:

- Macular CNV, new or recurrent where the classic component is >50% of the lesion, and ≤5400 μm in greatest linear diameter
- Occult CNV may be considered for PDT with vision <20/50 or if the CNV is <4 MPS [macular photocoagulation study] disc areas in size when the vision is >20/50
- Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases
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 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.

Canadian Agency for Drugs and Technologies in Health
In 2008, the Canadian Agency for Drugs and Technologies in Health (CADTH) released a health technology assessment on management of neovascular AMD. CADTH concluded that “Overall, the efficacy of anti-VEGF therapies over V-PDT is well supported by RCTs [randomized controlled trials]. What remains unclear is whether combination therapy (and which combinations) are superior or merely equal to monotherapy.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:
Subfoveal choroidal neovascularization, CNV, presumed ocular histoplasmosis, pathologic myopia, age-related macular degeneration, AMD, photodynamic therapy, VPDT, choroidal hemangioma, verteporfin, Visudyne, central serous chorioretinopathy

Approved by Governing Bodies:
In 2000, verteporfin (Visudyne®; Novartis), an intravenous photodynamic therapy agent, was approved by the U.S. Food and Drug Administration (FDA) for treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization. Subsequently, in 2001, the indication was expanded to include presumed ocular histoplasmosis and pathologic myopia.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity

Current Coding:
CPT codes:

67221 Destruction of localized lesion of choroid (e.g., choroidal neovascularization); photodynamic therapy (includes intravenous infusion)
67225  Destruction of localized lesion of choroid (e.g., choroidal neovascularization); photodynamic therapy, second eye, at single session

HCPCS codes:

J3396  Injection, verteporfin, 0.1 mg

References:


60. Nicolo M, Zoli D, Musolino M, et al. Association between the efficacy of half-dose photodynamic therapy with indocyanine green angiography and optical coherence


84. VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group, Chakravarthy U, Adamis AP, 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 e1501-1525.


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Medical Policy Administration Committee, June 2002
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Medical Policy Group, May 2004 (1)
Medical Policy Administration Committee, May 2004
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Medical Policy Group, June 2006 (1)
Medical Policy Group, August 2008 (1)
Medical Policy Group, September 2009 (1)
Medical Policy Administration Committee, September 2009
Available for comment September 18-November 2, 2009
Medical Policy Group, April 2012 (1): Update to policy statement to include new drug Eylea as an anti-VEGF that is non-covered when used in combo with PDT; Updates to Key Points and References related to MPP update
Medical Policy Panel, August 2012
Medical Policy Group, January 2013 (1): Update to Policy, Key Points and References related to addition of coverage for chronic central serous chorioretinopathy
Medical Policy Administration Committee, January 2013
Available for comment January 10 through February 23, 2013
Medical Policy Panel, June 2013
Medical Policy Group, September 2013 (1): Update to Descriptions, Key Points and References; no change to policy statement
Medical Policy Group, June 2014 (1): Policy updated with literature review through May 2014; no change to policy statement
Medical Policy Panel, June 2015
Medical Policy Group, June 2015 (6): Updated Title, Key Points and References; no change to policy statement.
Medical Policy Panel, March 2016
Medical Policy Group, March 2016 (6): Updates to Description, Key Points, Governing Bodies, Coding (removed codes 67299 and J3490), and References; no change to policy statement.
Medical Policy Panel, March 2017
Medical Policy Group, March 2017 (6): Updates to Description, Key Points, Practice Guidelines, Key Words, Governing Body and References.

Medical Policy Panel, March 2018

Medical Policy Group, March 2018 (6): Updates to Description, Key Points, Practice Guidelines and References.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plans contracts.