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Photodynamic Therapy for Choroidal Neovascularization

Policy # 00097
Original Effective Date: 06/05/2002
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company considers photodynamic therapy (PDT) as monotherapy as a treatment of choroidal neovascularization (CNV) associated with age-related macular degeneration, chronic central serous chorioretinopathy, choroidal hemangioma, pathologic myopia, or presumed ocular histoplasmosis to be **eligible for coverage.**

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers photodynamic therapy (PDT) as monotherapy for all other ophthalmologic disorders to be **investigational.***

Based on review of available data, the Company considers photodynamic therapy (PDT) when used in combination with one or more of the anti-vascular endothelial growth factor (anti-VEGF) therapies, i.e., pegaptanib (Macugen®)‡, ranibizumab (Lucentis®)‡, bevacizumab (Avastin®)‡, aflibercept (Eylea™)‡ as a treatment of choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD), chronic central serous chorioretinopathy, choroidal hemangioma, pathologic myopia, presumed ocular histoplasmosis, or for other ophthalmologic disorders to be **investigational.***

Background/Overview

Photodynamic therapy 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. Patients may be re-treated if leakage from CNV persists.

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 AMD. Available therapeutic options for CNV include PDT, antioxidants, thermal laser photocoagulation, corticosteroids, and vascular endothelial growth factor (VEGF) antagonists or angiostatics. The safety and efficacy of each treatment depends on the form and location of the neovascularization. For those whose visual losses impair their ability to perform daily tasks, low-vision rehabilitative services offer resources to compensate for deficits.

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Prior to the availability of PDT, CNV was treated with photocoagulation using either argon, green, or infrared lasers. This conventional photocoagulation was limited to extrafoveal lesions due to the risk of retinal burns. Introduction of a scotoma or enlargement of a preexisting scotoma, with or without visual acuity loss, is an immediate and permanent effect of photocoagulation surgery. Because of the loss of vision associated with laser photocoagulation, photocoagulation is no longer recommended as the initial treatment of subfoveal neovascularization. More recently, infrared lasers used at a low-power setting have been investigated as a technique to photocoagulate subfoveal lesions.

Combining PDT with angiostatic agents, either concurrently or sequentially, has a biological basis and is under active investigation. Angiostatic agents block some stage in the pathway leading to new blood vessel formation (angiogenesis). Drugs currently under study target various parts of the angiogenic pathway: messenger ribonucleic acid (mRNA); VEGFs; endothelial cell proliferation, migration, and proteolysis. The angiostatic agents being studied in trials include pegaptanib, ranibizumab, bevacizumab, anecortave acetate, squalamine, vatalanib, and triamcinolone acetonide. In contrast to palliative treatments for CNV (eg, thermal photocoagulation, PDT), they are potentially disease modifying by inhibiting the development of newly formed vessels.

Intravitreal triamcinolone acetonide was one of the first pharmacologic compounds evaluated for the treatment of CNV secondary to AMD. The most important effects of this treatment consist of the stabilization of the blood-retinal barrier and the down-regulation of inflammation. Triamcinolone acetonide also has antiangiogenic and antifibrotic properties and remains active for months after intravitreal injection.

Age-Related Macular Degeneration

AMD is a painless, insidious process. In its earliest stages, it is characterized by minimal visual impairment and the presence of large drusen and other pigmentary abnormalities on ophthalmoscopic examination. As AMD progresses, 2 distinctively different forms of degeneration may be observed. The first, called the atrophic or areolar or dry form, evolves slowly. Atrophic AMD is the most common form of degeneration and is often a precursor of the second form, the more devastating exudative neovascular form, also referred to as disciform or wet degeneration. The wet form is distinguished from the atrophic form by serous or hemorrhagic detachment of the retinal pigment epithelium and the development of CNV, sometimes called neovascular membranes. Risk of developing severe irreversible loss of vision is greatly increased by the presence of CNV. The pattern of CNV, as revealed by fluorescein or indocyanine angiography, is further categorized as classic or occult. For example, 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, either due to the opacity of coexisting subretinal hemorrhage or, especially in CNV associated with AMD, by a tendency for epithelial cells to proliferate and partially or completely surround the new vessels. Interestingly, lesions consisting only of classic CNV carry a worse visual prognosis than those made up of only occult CNV, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of AMD.

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.

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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.

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

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.

Central Serous Chorioretinopathy
Central serous chorioretinopathy refers to an idiopathic disease in which there is a serous detachment of the macula due to leakage of fluid from the choriocapillaris through the retinal pigment epithelium. This condition is avascular; however, neovascularization can occur as a secondary complication. 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.

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

Angioid Streaks
Angioid streaks are dehiscences in Bruch membrane and occur in patients 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.

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
There is currently one intravenous PDT agent that has received approval by the U.S. FDA, verteporfin (Visudyne®‡, Novartis). The FDA-approved indications include the treatment of predominantly classic

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subfoveal CNV due to 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.

Centers for Medicare and Medicaid Services (CMS)
Since July 2001, ocular PDT has been eligible for Medicare coverage in the treatment of patients with predominantly classical subfoveal CNV (i.e., occupies ³50% of the area of the entire lesion) associated with AMD only when used in conjunction with verteporfin. However, there was no national Medicare coverage policy for other indications. On review in January 2004, Medicare found evidence to conclude that ocular PDT may be reasonable and necessary for patients with AMD with either occult or minimally classic CNV 4 disk areas or less in size with evidence of progression within the 3 months prior to initial treatment. Medicare also reiterated use of ocular PDT with verteporfin for indications such as pathologic myopia or presumed histoplasmosis syndrome may be eligible for coverage through individual contractor discretion.

Rationale/Source

Randomized, controlled trials (RCTs) are crucial in determining the efficacy of PDT treatment and comprise the bulk of the evidence on which the efficacy of this treatment can be evaluated. Where RCTs are lacking, non-randomized comparative studies provide some evidence for efficacy but are limited by potential selection bias, as patients may be preferentially selected for one treatment over another by disease severity or other clinical factors. Uncontrolled trials and case series offer little useful evidence on the efficacy of PDT.

Age-Related Macular Degeneration
This policy was originally based on a 2000 Technology Assessment Center (TEC) Assessment that offered the following observations and conclusions:

- Two multicenter, double-masked, randomized placebo-controlled trials including 402 patients reported that, at 1 year of follow-up, fewer patients treated with PDT experienced a clinically significant loss of visual acuity compared to those treated with placebo: 38.8% compared to 53.6%, respectively ($p<0.001$).
- Subgroup analysis suggests that the treatment effect is predominantly experienced by patients with AMD characterized by at least 50% classic CNV.
- There were inadequate data to permit scientific conclusions regarding other etiologies of CNV.

Systematic Reviews
A 2003 Cochrane review concluded that PDT is effective in preventing visual loss in classic and occult CNV due to AMD. An updated Cochrane review in 2007 evaluated results from 3 RCTs (total of 1,022 patients), which included the TAP and VIP trials described below. Meta-analysis showed a 24-month risk ratio of losing 6 or more lines of visual acuity of 0.62 compared to the control group. The authors concluded that PDT is probably effective in treating CNV due to AMD, although there is doubt about the size of the effect. In a 2004 meta-analysis of the safety of PDT, Azab and colleagues analyzed data from the 24-month TAP A

and B and VIP trials, totaling 948 patients with AMD. The authors concluded that the safety profile of verteporfin therapy was not statistically different from placebo.

TAP Trial
In 2001, the 2-year results of the pivotal randomized trial Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) were published. Beneficial outcomes regarding visual acuity and contrast sensitivity noted after 12 months were sustained through 24 months. At the end of 2 years, 53% of the treatment group, as compared to 38% of the placebo group, lost fewer than 15 letters. The average number of applications of verteporfin treatment in the second year (2.2) was lower than that required during the first year. Subgroup analysis compared results between those patients with predominantly classic CNV (>50% of lesional area) compared to minimally classic CNV (<50%). For patients with minimally classic disease, no statistically significant differences in visual acuity were noted. Several additional reports from the TAP trial have been published. These reports demonstrated positive outcomes with the use of PDT 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 verteporfin-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, 3 (1%) were noncompliant. Yearly treatment rates declined from 3.5 treatments in the first year to 0.1 in the fifth year; subjects who remained in the study lost an additional 2.3 lines of letters over the 3-year extension.

VIP Trial
The Verteporfin in Photodynamic Therapy (VIP) trial is another randomized study that primarily focused on efficacy of PDT in patients with occult but no classic lesions who were presumed to have progressive disease due to visual or anatomic deterioration within the previous 3 months. Of the 339 patients enrolled in the trial, 76% had occult disease; the remainder had early classic CNV with good visual acuity. Similar to other randomized trials, 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 had lost vision (55% vs. 68%, respectively; p=0.032). These results contrast with those of the TAP trial, although the patient populations are slightly different. The TAP trial 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.

Early Retreatment Study Group Trial
In 2008, Schmidt-Erfurth and Sacu conducted a multicenter clinical trial to compare efficacy and safety of a more intense regimen versus a standard one for retreatment of neovascular AMD during the early period of verteporfin therapy. Patients (n=231) with predominantly classic CNV secondary to AMD were included. During the first 6 months of verteporfin therapy, patients were randomly assigned 1:1 to retreatment every 2 months (group A) or 3 months (group B). After 6 months, both groups underwent retreatment every 3 months for as long as CNV activity was documented. At all follow-up through 24 months, mean best-corrected visual acuities (BCVA) were similar for groups A and B; mean numbers of PDT treatments were similar for both groups (4.07 vs. 4.36, respectively); a lower proportion (51.9% vs. 56.7%) of patients in

group A had lost at least 3 lines of vision at 24 months; and groups A and B had similar increases in mean lesion size from baseline to 24 months. Overall, outcomes regarding visual benefit, lesion anatomic features, and number of retreatments after 6 months, were similar for patients receiving more intense or standard early therapy.

Photodynamic Therapy Compared to Anti-Vascular Endothelial Growth Factor Therapies

Systematic Reviews

A 2008 Cochrane review evaluated anti-VEGF therapies for neovascular AMD. Five RCTs on pegaptanib and ranibizumab were included in the review; all were conducted by pharmaceutical companies. The trials compared pegaptanib or ranibizumab versus sham, ranibizumab versus PDT, and ranibizumab plus PDT versus PDT alone (PDT trials are described in more detail below). Fewer patients treated with pegaptanib lost 15 or more letters of visual acuity at 1-year follow-up compared to sham (pooled relative risk [RR]: 0.71). In a trial of ranibizumab versus sham, RR for loss of 15 or more letters visual acuity at 1 year was 0.14 in favor of ranibizumab. The pooled RR for gain of 15 or more letters of visual acuity at 1 year was 5.81 for ranibizumab versus sham, 6.79 for ranibizumab versus verteporfin PDT, and 4.44 for ranibizumab plus verteporfin PDT versus verteporfin PDT.

ANCHOR Trial

Ranibizumab was compared with PDT in a multicenter, double-blind study (423 patients) by the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study group in 2006. Patients with subfoveal CNV and a predominantly classic lesion (n=423) were randomized in a 1:1:1 ratio to receive 0.3 mg (n=137) or 0.5 mg (n=139) of intravitreal ranibizumab plus sham verteporfin or sham injections plus active verteporfin (n=142) monthly. Patients were to receive monthly injections for 2 years in the study eye. Only 1 eye per patient was chosen as the study eye, and only the study eye received ranibizumab with sham PDT or sham injection with active PDT. Following 12 monthly treatments, patient groups treated with ranibizumab (0.3 or 0.5 mg) and sham verteporfin had 94% to 96% of subjects lose fewer than 15 letters. The patient group treated with monthly sham injection and active verteporfin therapy (average 2.8 times over the year) had 64% of subjects lose fewer than 15 letters. Visual acuity improved by more than 15 letters in 36% and 40% of the ranibizumab groups (average dose-dependent gain of 8.5 and 11.3 letters), in comparison with 5.6% of subjects in the verteporfin group (average loss of 9.5 letters). Intraocular inflammation occurred in 10.2% and 15% of ranibizumab-treated patients, with presumed endophthalmitis in 1.4% and serious uveitis in 0.7% of patients treated with the highest dose.

In 2009, Brown et al. evaluated the 2-year results of the Phase III multicenter, manufacturer-funded ANCHOR trial. The primary, intent-to-treat (ITT) efficacy analysis was at 12 months, with continued measurements to month 24. Key measures included the following: the percentage losing greater than 15 letters from baseline visual acuity score (month 12 primary efficacy outcome measure); percentage gaining equal to or greater than 15 letters from baseline; and mean change over time in visual acuity score and fluorescein angiography-assessed lesion characteristics. Adverse events were monitored. Of 423 patients, at least 77% in each group completed the 2-year study. Consistent with results at month 12, at month 24, the visual acuity benefit from ranibizumab was statistically significant and felt to be clinically meaningful; 89.9% to 90.0% of ranibizumab-treated patients had lost less than 15 letters from baseline versus 65.7% of

PDT patients; and 34% to 41.0% had gained 15 or more letters versus 6.3% of the PDT group. Changes in lesion anatomic characteristics on fluorescein angiography also favored ranibizumab. There was a trend for an increased incidence of cataract in the ranibizumab groups compared with the PDT group, which was statistically significant at the 0.5-mg dose. There were no statistically significant differences among the 3 treatment groups in the rates of serious nonocular adverse events. In this 2-year study, ranibizumab provided greater clinical benefit than verteporfin PDT in patients with AMD with new-onset, predominantly classic CNV. Rates of serious adverse events were low.

Bressler et al. reported a sub-analysis of the patient-reported outcomes from the ANCHOR trial in 2009. The National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) was administered at baseline and at 1, 2, 3, 6, 9, 12, 18, and 24 months. The primary outcome measure was mean change from baseline in NEI VFQ-25 scores at 12 months. At 12 months, patients treated with ranibizumab had mean improvements in NEI VFQ-25 composite scores of 5.9 (range: 3.6 to 8.3) for the 0.3-mg dose group and 8.1 (range: 5.3 to 10.8) points for the 0.5-mg dose group; patients treated with PDT had a mean improvement of 2.2 points (range: -0.3 to 4.7). At each dose through 24 months, patients treated with ranibizumab were more likely to improve in most subscales, including the prespecified subscales (near activities, distance activities, and vision-specific dependency). The authors concluded that "… patients treated with ranibizumab were more likely to report clinically meaningful improvements in visual function through 24 months compared with those treated with verteporfin PDT."

Photodynamic Therapy in Combination Therapies for Age-Related Macular Degeneration

Angiostatic agents being studied in trials include pegaptanib, ranibizumab, bevacizumab, anecortave acetate, squalamine, vatalanib, and triamcinolone.

Photodynamic Therapy in Combination with Vascular Endothelial Growth Factor Antagonists

Systematic Reviews

A 2005 Technology Evaluation Center (TEC) Special Report found a number of trials in progress combining an angiostatic agent with PDT. For example, in the pegaptanib trial, PDT was administered at physician discretion, but an analysis was not provided that examined possible synergistic effects.

In a 2010 editorial, Kaiser reported an ongoing clinical program (SUMMIT) that is investigating whether treatment with combination PDT and ranibizumab is safe and effective compared to monotherapy. The SUMMIT clinical program will combine results from a North American trial (DENALI, n=321) and a European trial (MONT BLANC, n=255). Both are 12-month, randomized, controlled, double-blinded multicenter trials that evaluate the efficacy and safety of combination treatment with ranibizumab and PDT compared to ranibizumab monotherapy in patients with CNV secondary to AMD. Results from the DENALI and MONT BLANC trials were reported in 2012.

DENALI Trial

DENALI was a multicenter, double-blind, randomized Phase IIIb trial that tested whether ranibizumab in combination with either standard fluence PDT (n=104), or reduced fluence PDT (n=105) was noninferior to ranibizumab given monthly (n=112). The 2 combination-therapy groups received ranibizumab monthly for the first 3 months, followed by retreatment with PDT or ranibizumab as needed (*pro re nata*; PRN) based on

specified retreatment criteria at monthly monitoring. The ranibizumab monotherapy group received sham PDT, and patients in the combination groups who did not require ranibizumab at the monthly follow-up visit received sham intravitreal injections. The 2 main outcome measures were the change in BCVA from baseline and the proportion of patients in the combination therapy groups with a treatment-free interval of 3 months or longer. A ranibizumab-free interval of 3 months or longer was achieved in most of the patients in the standard (92.6%) and reduced (83.5%) fluence combination groups. Patients in the monotherapy arm received an average of 10.5 injections, while patients in the standard and reduced fluence combination groups received an average of 5.1 and 5.7 injections. About 20% of patients in the combination groups did not receive any ranibizumab retreatments after the loading phase up until month 11. However, the mean BCVA change at 12 months was +5.3 and +4.4 letters for standard and reduced fluence PDT, respectively, compared with +8.1 letters for the ranibizumab monotherapy group, and non-inferiority of visual outcomes was not demonstrated. Mean central retinal thickness, measured at a central reading center, was reduced more in the ranibizumab monotherapy group (172.2 microns) compared to the reduced fluence (140.9 microns) group. Florescein leakage was higher in the combination therapy groups (standard fluence: 58.2%, p=0.008; reduced fluence: 54.5%, p=0.075) compared with the ranibizumab monotherapy group (41.8%).

MONT BLANC Trial
MONT BLANC was a multicenter, double-blind, randomized noninferiority trial that compared combination PDT/ranibizumab versus PRN (as needed) ranibizumab monotherapy (with sham PDT) in 255 patients with CNV related to AMD. Both groups received 3 consecutive monthly injections followed by PRN retreatments (active or sham) based on specified retreatment criteria. As with the DENALI trial, the 2 main outcome measures were the change in BCVA from baseline and the proportion of patients in the combination therapy group with a treatment-free interval of 3 months or longer. 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 and 92% monotherapy), and the change in BCVA with combination therapy (+2.5 letters) was found to be noninferior to ranibizumab monotherapy (+4.4 letters). On average, patients received 4.8 ranibizumab injections in the combination group compared with 5.1 injections in the monotherapy group over 12 months. Decreases in mean central retinal thickness were similar in the combination (115.3 microns) and monotherapy (107.7 microns) groups. This well-conducted study found that PDT did not reduce the number of ranibizumab injections when ranibizumab was administered PRN.

FOCUS Trial
The FOCUS study group reported first- and second-year results of a blinded Phase I/II multicenter, RCT of ranibizumab (0.5 mg) combined with PDT. Patients with subfoveal CNV secondary to AMD were randomized in a 2:1 ratio to ranibizumab (n=106) or sham (n=56) injection (initially 7 days) following verteporfin PDT. Photodynamic therapy was repeated only if fluorescein angiography revealed persistent or recurrent leakage from CNV at evaluation visits (3-month intervals). A higher than expected rate of serious intraocular inflammation occurred in the first patients, and the 2 treatments were subsequently scheduled no closer than 21 days apart. Intent-to-treat analysis showed an average improvement in acuity of 5 letters at both 12 and 24 months (85% retention) with ranibizumab, compared with a decrease of 8 letters in the PDT-alone group. Twenty-nine percent of patients in the ranibizumab group received additional PDT (average of 0.4 treatment), compared with 93% of patients in the PDT-alone group (average of 3

treatments). Visual acuity improved by 15 or more letters in 25% of patients treated with ranibizumab (plus PDT as needed) compared with 7% of the patients treated with PDT alone. Endophthalmitis or intraocular inflammation was observed in 16 (15%) patients treated with ranibizumab. The majority of adverse events (9%) reported for the PDT-alone group were AMD-related (i.e., CNV, macular degeneration, retinal hemorrhage).

Before the Denali and Mont Blanc studies, there were several smaller unmasked randomized trials that examined whether combination therapy was more effective than monotherapy, or if it resulted in fewer anti-VEGF injections. In a multicenter, unmasked trial, Williams et al randomized 60 patients to ranibizumab with half-fluence PDT or ranibizumab alone. The difference between groups in the number of injections was not significantly different. Best-corrected visual acuity improved by a mean of 9.9 letters in the ranibizumab group compared with a gain of 2.6 letters in the combined treatment group. This difference was not significantly different by *t* test. A similar number of patients gained 15 or more letters (33% monotherapy, 31% combination therapy). A small RCT by Lim et al in 2012 included 31 patients with AMD and 10 patients with polypoidal choroidal vasculopathy who were randomized to bevacizumab monotherapy or bevacizumab in combination with PDT. 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 PDT was given. A randomized, open-label assessor-blinded trial (n=165) from Croatia with short-term (3-month) follow-up reported similar results with bevacizumab and PDT. Twenty-two of 52 (42%) patients improved by greater 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 PDT alone.

Photodynamic Therapy in Combination with Corticosteroids

The RETINA Trial

The Retinologists Evaluating Triamcinolone In Neovascular AMD (The RETINA Study), a multicenter double-blind RCT with 100 subjects with CNV related to AMD found that combination therapy with PDT and triamcinolone resulted in no significant difference in the primary outcome of visual acuity at 1 year compared to PDT with sham injection but that subjects receiving triamcinolone required fewer retreatments (1.28 vs. 1.94, respectively) to control lesion leakage/activity. The triamcinolone group also had a larger proportion of subjects with elevated, although managed, intraocular pressure (18 vs. 4, respectively).

Piermarocchi et al

A second prospective randomized study in Italy evaluated combination therapy with corticosteroids and PDT. In this trial, the long-term effect of intravitreal triamcinolone acetonide (IVT) treatment combined with PDT was compared with PDT alone for neovascular AMD. Eighty-four patients were enrolled to receive PDT (n=41) or IVT treatment followed by PDT (n=43) within approximately a 7- to 15-day interval. All patients were naive to treatment. At baseline and each follow-up visit at 3, 6, 12, and 24 months, measurement of BCVA, fluorescein angiography, indocyanine green angiography, and OCT were performed. Mean changes in visual acuity and retreatment rate were considered as primary outcome indicators. Mean visual acuity increased at 1 month of follow-up but decreased progressively by the 24-month point in both groups (p=0.74). The retreatment rate was significantly lower in the combined therapy group. Choroidal hypoperfusion/nonperfusion and areas with decreased/absent fundus autofluorescence

within the PDT spot area were significantly greater with combined therapy. The authors concluded that "… combination IVT treatment with PDT seemed to be more effective for managing neovascular AMD, but long-term analysis failed to demonstrate functional benefits."

Triple Therapy

Triple therapy (PDT, intravitreal dexamethasone and intravitreal bevacizumab) for AMD has been reported. Thirty-two eyes of 30 patients received reduced-fluence PDT followed immediately by intravitreal dexamethasone. At 1 and 7 weeks after PDT and dexamethasone, patients received a bevacizumab injection. At 13 weeks after PDT, patients were evaluated with OCT and fluorescein angiography, with additional triple therapy treatment cycles as needed for visible leakage or increased foveal thickness with vision loss. At 12-month follow-up, the mean number of treatment cycles was 1.4 and the mean number of bevacizumab injections was 2.8. Visual acuity improved from 0.74 logMAR to 0.53 logMAR. Foveal thickness decreased from 328 to 216 microns. Ninety-four percent of patients lost fewer than 3 lines, 31% gained more than 3 lines, and 6% lost more than 3 lines. Comparative trials are needed to evaluate the efficacy of triple therapy.

Ongoing and Unpublished Clinical Trials

A search of online site ClinicalTrials.gov in May 2014 identified a number of ongoing and completed studies of combined PD and pharmacologic therapies for the treatment of CNV. Notably, several industry-sponsored trials (NCT00436553, NCT00433017, NCT00242580) are listed as completed; although results are posted online, no publications from these trials have been identified.

Section Summary

Photodynamic therapy monotherapy is an established treatment for CNV secondary to AMD, with evidence from multiple RCTs supporting benefit compared to placebo. Although PDT is established as superior to no treatment, recent comparative trials show anti-VEGF therapy to be superior to PDT. For combination therapy, the literature to date, which includes 2 high-quality randomized trials, shows no improvement in outcomes or reduction in the number of intravitreal injections with combined PDT and anti-VEGF therapy, nor with a combination of PDT and corticosteroids. Thus, combination therapy is considered investigational.

Pathologic Myopia

Photodynamic therapy has also been investigated in patients with CNV related to pathologic myopia.

Photodynamic Therapy in Comparison with 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 PDT or placebo. Patients received an average of 3.4 PDT 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. Visual acuity, contrast sensitivity, and fluorescein angiographic outcomes were better in the PDT eyes than in the placebo-treated eyes at every follow-up examination through 12 months. At month 12, PDT-treated eyes lost fewer than 8 letters on a standard eye chart in 72% of patients versus 44% who were receiving placebo. Improvement of at least 5 letters was observed in 32% of PDT-treated eyes in comparison with 15% of placebo-treated eyes. Fluorescein angiography showed progression of the classic

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CNV in 36% of PDT-treated eyes compared with 54% of the placebo-treated group. The authors concluded that verteporfin therapy increases the chance of stabilizing or improving vision compared to placebo treatment for at least 1 year. Results were not reported separately for those with predominantly classic CNV versus occult CNV.

Photodynamic Therapy in Comparison with Vascular Endothelial Growth Factor Antagonists

El Matri et al. reported a retrospective comparison of PDT versus bevacizumab for myopic CNV in 2011. Eighty eyes of 80 patients with myopic CNV were treated with standard PDT (2005-2007, n=40) or bevacizumab (2008-2009, n=40). Retreatment was given every 3 months in the PDT group and every 4 weeks in the bevacizumab group as needed; patients received a mean of 1.8 bevacizumab injections and 1.55 PDT treatments during 12 months. At baseline, BCVA was 0.9 logMAR (20/159 Snellen equivalent) in the bevacizumab group and 0.88 logMAR (20/152 Snellen equivalent) in the PDT group. At 3, 6, and 12 month follow-up, mean logMAR BCVA was significantly better in the bevacizumab group (0.5-0.6 logMAR) in comparison with the PDT group (0.85-0.86 logMAR). Best-corrected visual acuity improved by 3 lines or more in 70% of eyes in the bevacizumab group and 22.5% of the PDT group. Mean central retinal thickness was similar at baseline (421 vs. 393) and significantly lower in the bevacizumab group compared to the PDT group at 3 (328 vs. 393 microns), 6 (300 vs. 370 microns), and 12 (305.5 vs. 352 microns) months. Chorioretinal atrophy developed in 6 eyes (15%) treated with bevacizumab and in 24 eyes (60%) treated with PDT. Although limited by the retrospective nature of the comparison, these results are strongly suggestive of the superiority of anti-VEGF treatment over PDT for myopic CNV.

Photodynamic Therapy in Combination with Vascular Endothelial Growth Factor Antagonists

Bevacizumab monotherapy. (n=17) was compared to combination treatment of bevacizumab with PDT (n=6) in a retrospective analysis of patients with CNV secondary to causes other than AMD; about half of the patients had myopic CNV. Most of the observed differences between the groups did not reach statistical significance, likely due to the small sample size. For example, the 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 3 lines or more compared with 60% in the combination therapy group. There was a trend for the combination group to receive fewer reinjections (2.6 vs. 4.8, 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 versus 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 months of follow-up. No serious ocular complications were observed. Prospective comparison with a larger number of patients is needed.

Section Summary

Photodynamic therapy has been shown in one RCT to be more effective than placebo for myopic CNV, and these findings have been corroborated in non-randomized studies. RCTs are needed to evaluate the efficacy and safety of combined PDT and anti-VEGF treatment in patients with myopic CNV.

Presumed Ocular Histoplasmosis

There are minimal published data regarding the use of PDT in patients with CNV related to ocular histoplasmosis. The approval by the U.S. FDA was based on an open-label safety study involving 26

patients with ocular histoplasmosis. Visual acuity improved by an average of more than 1 line on a standard eye chart at 12 months (6.7 letters on a standard eye chart), with 28% of patients experiencing a visual acuity improvement of 3 lines (15 letters) or more. Visual acuity decreased by less than 3 lines of vision in 88% of patients during the same time period.

Central Serous Chorioretinopathy
In 2010, Chan et al. published a systematic review of PDT for non-standard indications, which included 12 case series (119 eyes) on PDT for central serous chorioretinopathy. In addition, 3 nonrandomized comparative studies and 2 small randomized controlled trials with reduced dose (verteporfin) and reduced fluence (laser) PDT have been identified.

Acute Central Serous Chorioretinopathy
Chan et al reported a randomized double-masked placebo controlled trial of reduced dose PDT for acute central serous chorioretinopathy in 2008. Reduced dose verteporfin was examined due to adverse effects, including CNV, with full-dose PDT. A total of 63 patients were randomized in a 2:1 ratio to half-dose verteporfin or placebo prior to laser treatment. The primary outcome measure, the proportion of eyes with absence of subretinal fluid at the macula at 12 months, was observed in 94.9% of eyes in the verteporfin group compared with 57.9% of eyes in the placebo group. The mean central foveal thickness was lower compared to the placebo group at 12 months (161 vs. 278 microns). At 3 months after treatment, the mean logarithm of the minimum angle of resolution (logMAR) of the PDT group was 0.00 (Snellen equivalent 20/20), whereas the placebo group improved to 0.08 (Snellen equivalent 20/24). At 12 months, the mean logMAR remained statistically better in the PDT group compared with placebo (-0.05 vs. 0.05); however, since this is equivalent to visual acuity of 20/18 versus 20/22, this would not be a clinically meaningful difference. The mean increase of BCVA was 1.8 lines compared to 0.6 lines for the placebo group, whereas a difference of 2 lines is considered to be clinically meaningful. No ocular or systemic adverse event was encountered.

Chronic Central Serous Chorioretinopathy
A small, unblinded randomized trial compared low-fluence PDT versus intravitreal bevacizumab in 22 patients with chronic central serous chorioretinopathy. Follow-up visits were scheduled at 1, 3, 6, and 9 months. At 9-month follow-up, BCVA improved from 30 letters to 40 letters in the PDT group and from 20 letters to 43 letters in the bevacizumab group. Central retinal thickness improved to 114 µm with PDT and 127 µm with bevacizumab. There was no significant difference in visual acuity or central retinal thickness between the 2 groups. This study is limited by its small size, unequal baseline measures, and lack of blinding.

Bae et al compared low-fluence PDT versus 3 monthly injections of ranibizumab in a small randomized trial of 16 eyes with chronic or recurrent central serous chorioretinopathy. Rescue with the opposite treatment was allowed after 3 months since a gold standard treatment for chronic central serous chorioretinopathy had not been established. The main outcome measures were excess foveal thickness, resolution of subretinal fluid, choroidal perfusion, and BCVA. For both groups at baseline, the mean logMAR was 0.34 (20/44 Snellen equivalent). The mean excess foveal thickness was significantly higher in the PDT group at baseline (74.1 vs. 26.3 microns), but showed a greater reduction with treatment. Six eyes (75%) in the PDT

group achieved complete resolution of subretinal fluid and reduction of choroidal hyperpermeability compared with 2 (25%) eyes in the ranibizumab group. At 3 months, there was a trend toward improvement in BCVA in the PDT group (from 0.30 to 0.18 logMAR, p=0.075), whereas the ranibizumab group had significantly improved BCVA (from 0.38 to 0.18 logMAR). There was a trend for a greater proportion of eyes needing rescue treatment in the ranibizumab group versus the PDT group (75% vs. 25%, p=0.066). During the follow-up period, no systemic or ocular complications associated with treatment were observed. The main limitations of this study are its small size, lack of investigator blinding, and lack of an untreated control group.

Reibaldi et al compared the efficacy of half-fluence PDT compared to conventional PDT in a prospective multicenter, investigator-masked comparative study of 42 eyes (42 patients) with chronic central serous chorioretinopathy. It is not clear whether the group assignment was based on patient preference or investigator preference, although the groups were comparable at baseline. The primary outcome measures were the changes in BCVA and the proportion of eyes with complete resolution of subretinal fluid. Secondary outcome measures were the changes in mean central foveal thickness and the rate of eyes with post-PDT changes in choroidal perfusion. At 1 month follow-up, BCVA had improved to a similar extent in both the low-fluence group (from 0.46 to 0.28 logMAR) and the conventional fluence group (from 0.43 to 0.27 logMAR). Complete resolution of subretinal fluid was observed in 96% of the low-fluence group and 89% of the conventional PDT group (not significantly different). At 12 months' follow-up, BCVA continued to improve in the low-fluence group (0.16 logMAR) but remained stable in the conventional fluence group (0.24 logMAR). Complete subretinal fluid reabsorption was seen in 91% of low-fluence-treated eyes and 79% of conventional PDT-treated eyes (not significantly different). Moderate choriocapillaris hypoperfusion (an adverse effect) was seen in 0% of low-fluence-treated eyes and 44% of conventional PDT-treated eyes. One eye in the conventional PDT group developed CNV requiring further treatment. A strength of this study is the prospective 12-month follow-up after a single treatment. Limitations of this study are the nonrandomization and the lack of an untreated control group.

Outcomes from low-fluence PDT were also compared to conventional PDT in a retrospective multicenter study of 60 patients with chronic central serous chorioretinopathy (34 eyes treated with low-fluence PDT and 33 eyes treated with conventional PDT). All eyes treated at one center received conventional PDT and all consecutive eyes treated at another center between 2006 and 2009 received low-fluence PDT. Follow-up examinations were done at 1 and 3 months after PDT and as needed thereafter, with a mean follow-up period of 12.6 months (range, 6-33 months) for the low-fluence PDT group and 13.4 months (range, 5-25 months) for the conventional PDT group. Treatment success without recurrence was achieved in 94.1% of eyes treated with low-fluence PDT and 100% of eyes treated with conventional PDT (not significantly different). Best-corrected visual acuity improved with treatment in both groups with no significant difference in final BCVA between the 2 groups (0.17 vs. 0.21 logMAR) at the final follow-up. Choriocapillaris nonperfusion was significantly more severe in the conventional PDT group.

Use of reduced dose verteporfin PDT has also been reported. Uetani et al. compared half-dose versus one-third dose PDT for chronic central serous chorioretinopathy in a small (n=16) prospective open-label trial. Patients were assessed at baseline and at 4 days, 1 month, and 3 months after PDT. At 3 months, all 10 eyes (100%) in the half-dose PDT group and 2 eyes (33%) in the one-third dose PDT group had complete

resolution of subretinal fluid. Patients in the half-dose PDT 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 have also reported reduced dose of verteporfin for the treatment of chronic central serous chorioretinopathy in a prospective series of 48 patients. The mean duration of central serous chorioretinopathy was 8.2 months (range, 3-40 months). At 12 months after PDT, the mean BCVA improved from 0.31 to 0.15 logMAR, an improvement of 1.6 lines.

Section Summary
Quality evidence on use of PDT for central serous chorioretinopathy is limited. The available evidence indicates substantial numbers of adverse events with standard PDT. Reduced-dose PDT may result in improved anatomical outcomes for acute central serous chorioretinopathy, but clinically significant improvements in visual acuity have not been shown for this self-limiting disease. For chronic central serous chorioretinopathy, recent comparative studies of reduced fluence and reduced-dose PDT suggest a possible beneficial effect of this treatment.

Polypoidal Choroidal Vasculopathy
The systematic review by Chan et al. included 30 studies on PDT in patients with polypoidal choroidal vasculopathy. Chan et al. found numerous case series reporting favorable anatomical and visual acuity outcomes for patients treated with PDT. Also reported in the review was an ongoing manufacturer-sponsored RCT of PDT as monotherapy or combined with ranibizumab for treatment of polypoidal choroidal vasculopathy.

This study randomized 31 patients with AMD and 10 patients with polypoidal choroidal vasculopathy to bevacizumab monotherapy or bevacizumab in combination with PDT. 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=0.05037) or central foveal thickness (p=0.0875) when analyzed alone; however, the study is likely to be underpowered for this subset analysis.

EVEREST was a small, exploratory, multicenter double-blind randomized trial of PDT, ranibizumab, or combination treatment in 61 treatment-naive Asian patients with polypoidal choroidal vasculopathy. Patients in the PDT monotherapy group (angio-occlusive) received sham ranibizumab, and patients in the ranibizumab monotherapy group (antiangiogenic and antipermeability) received sham PDT. The primary end point, proportion of patients with complete regression of polyps at 6 months, showed PDT alone (71.4%) or in combination with ranibizumab (77.8%) to be superior to ranibizumab monotherapy (28.6%) in achieving complete polyp regression. The mean improvement in BCVA was generally similar for the 3 groups (7.5 letters for PDT, 10.9 for combined treatment, 9.2 for ranibizumab alone). The proportion of patients gaining at least 15 letters was 19% in the PDT group, 21% in the combination group, and 33.3% in the ranibizumab monotherapy group. Interpretation of the visual acuity results is limited, as the study was not powered to assess differences in BCVA. There were no new safety findings.

Photodynamic Therapy for Choroidal Neovascularization

Policy # 00097
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Several nonrandomized studies from Asia have been reported. The largest was a prospective consecutive series of 220 eyes of 210 Japanese patients with polypoidal choroidal vasculopathy who were followed for 1 year after the primary PDT 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 eyes (93%) 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. Stepwise logistic regression analysis showed that younger age, smaller greatest linear dimension, better baseline visual acuity, less baseline hemorrhage, and the presence of a serous macular detachment at baseline were independent predictors of improvement in visual acuity.

Akaza et al reported 3-year follow-up of 43 eyes treated with PDT for polypoidal choroidal vasculopathy. Before the initial PDT, 40 eyes (93%) exhibited polypoidal choroidal vasculopathy in the narrow sense, and 3 (7%) exhibited polypoidal CNV. The 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 of the 43 eyes (77%) at 3 years, although the 3 eyes with polypoidal CNV showed essentially no changes except for enlargement and recurrence. The authors concluded that long-term visual outcomes following PDT were not good due to the high frequency of recurrent polypoidal lesions, as well as enlargement and neovascular changes involving abnormal vascular networks.

Five-year follow-up was reported by Kang et al in 2013 for 42 eyes treated with PDT for polypoidal choroidal vasculopathy. Patients received a mean of 2.21 PDT treatments over the course of the study, with additional intravitreal injections of anti-VEGF agents if exudative changes were observed. During follow-up, recurrence was observed in 78.6% of 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) at follow-up. Using a change of at least 0.3 logMAR as a threshold, BCVA improved in 33.3% of eyes, remained stable in 54.8%, and decreased in 11.9%. Interpretation of the efficacy of PDT in this study is limited, because all patients received combination treatment with intravitreal VEGF antagonists, and there were no comparison groups.

Kim and Yu conducted a retrospective review of 39 consecutive patients with polypoidal choroidal vasculopathy who received PDT monotherapy (before April 2007) or a combination of PDT and intravitreal bevacizumab (after April 2007). During 12 months of follow-up, the patients in the monotherapy group (n=19) received a mean of 1.89 PDTs, and patients in the combined therapy group (n=20) received a mean of 1.30 PDTs and 2.90 bevacizumab injections. Best-corrected visual acuity improved by 3.0 lines in the combined therapy group compared with 1.6 lines in the PDT monotherapy group. Improvement in BCVA of 3 lines or more was achieved in 55.0% of patients in the combined therapy group versus 36.8% of patients in the monotherapy group.

Section Summary
The available evidence from case series is insufficient to permit conclusions regarding the efficacy of PDT for polypoidal choroidal vasculopathy. Controlled trials with longer follow-up are needed to evaluate the efficacy of PDT (monotherapy or combined) compared to anti-VEGF therapy.

Photodynamic Therapy for Choroidal Neovascularization

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

In 2010, Blasi et al. reported 5-year outcomes from a prospective series of 25 consecutive patients with symptomatic choroidal hemangioma. Twenty-two of the patients (88%) received a single PDT session, and 3 eyes received a second PDT session. Follow-up examinations were performed 2 weeks, 1 month, 3 months, and every 6 months after treatment. All tumors responded with a reduction in size, and there were no recurrences through the 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 eyes (80%) and by 3 or more lines in 12 eyes (48%). No treated eyes lost visual acuity between the 1- and 5-year follow-up. Foveal center thickness decreased from a mean of 386.20 to 179.2 microns at 5 years, and there was resolution of macular exudation in all cases. No treatment-related adverse events or complications were identified.

Angioid Streaks
The 2010 systematic review by Chan et al. included 8 case series on PDT in 148 patients with angioid streaks. The authors concluded the PDT 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 PDT, and others showed that substantial proportions of patients continued to lose visual acuity. Thus, further studies to assess its long-term safety and efficacy are warranted.

Inflammatory Conditions
The 2010 systematic review by Chan et al. included 15 case reports on PDT in 115 patients with inflammatory eye conditions. Encouraging visual and anatomical outcomes have been reported with PDT for punctuate 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 PDT on health outcomes for this indication. Therefore, PDT for inflammatory eye conditions is considered investigational.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 physician specialty societies and 2 academic medical centers 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.

Summary

The available published literature, together with clinical input, supports the use of PDT as monotherapy for the treatment of CNV associated with AMD, chronic central serous chorioretinopathy, choroidal hemangioma, pathologic myopia, or presumed ocular histoplasmosis. Therefore, PDT may be considered medically necessary for these indications. Current evidence does not support the use of PDT in combination with anti-VEGF therapies or corticosteroids for the treatment of CNV associated with AMD or other ophthalmologic disorders.

Based on numerous case reports and case series, PDT is being used in an attempt to decrease CNV of many different etiologies. For example, PDT has been reported to slow down, but not prevent or reverse, the progression of disease of CNV associated with polypoidal choroidal vasculopathy, angioid streaks, and inflammatory chorioretinal disease. There is insufficient evidence to support the use of PDT as monotherapy or in combination therapy for these other ophthalmologic disorders. As a result, PDT is considered investigational for ophthalmologic disorders other than AMD, chronic central serous chorioretinopathy, choroidal hemangioma, pathologic myopia, or presumed ocular histoplasmosis.

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Photodynamic Therapy for Choroidal Neovascularization

Policy # 00097
Original Effective Date: 06/05/2002
Current Effective Date: 08/20/2014

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	67221, 67225
HCPCS	J3396, G0186
ICD-9 Diagnosis	115.92, 228.09, 360.21, 360.41, 362.50 thru 362.52
ICD-9 Procedure	No codes

Policy History

Original Effective Date: 06/05/2002
Current Effective Date: 08/20/2014

04/18/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
06/01/2004	Medical Director review
06/15/2004	Medical Policy Committee review
06/28/2004	Managed Care Advisory Council approval
05/03/2005	Medical Director review
05/17/2005	Medical Policy Committee review. Format revision. Patient selection criteria added.
05/23/2005	Managed Care Advisory Council approval
05/03/2006	Medical Director review
05/17/2006	Medical Policy Committee approval. Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/04/2007	Medical Director review
04/18/2007	Medical Policy Committee approval. No change to coverage eligibility.
08/06/2008	Medical Director review
08/20/2008	Medical Policy Committee approval. Added Updates from BCBSA to Rationale. Changed the verbiage in the Coverage section from “When Services May Be Eligible for Coverage” to “When Services Are Eligible for Coverage”. Criteria dropped in Coverage section due to redundancy. No change to coverage eligibility.
08/06/2009	Medical Policy Committee approval.
08/26/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility.
08/05/2010	Medical Policy Committee review
08/18/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2011	Medical Policy Committee review
08/17/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. New drug listed under investigational section.
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. PDT monotherapy considered eligible for coverage for central serous chorioretinopathy and choroidal hemangioma added as investigational.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2014	Coding updated- code G0186 Destruction of localized lesion of choroid (for example, choroidal neovascularization); photocoagulation, feeder vessel technique (one or more sessions) - added to policy

Next Scheduled Review Date: 8/2015

Photodynamic Therapy for Choroidal Neovascularization

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*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.