



CIGNA MEDICAL COVERAGE POLICY

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Subject Photodynamic Therapy for Ocular Conditions

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Coverage Policy

CIGNA covers photodynamic therapy (PDT) with verteporfin (Visudyne®) for the treatment of predominantly classic subfoveal choroidal neovascularization (CNV) (i.e., the classic lesion comprises ≥ 50% of the entire lesion) due to ANY of the following conditions:

- wet age-related macular degeneration (AMD)
- pathological myopia
- presumed ocular histoplasmosis

CIGNA does not cover PDT with verteporfin (Visudyne®) for EITHER of the following indications because it is considered experimental, investigational or unproven:

- treatment of any other ocular conditions
- combination therapy with intravitreal pharmacotherapy (e.g., antiangiogenic or anti-inflammatory agents)

General Background

Photodynamic therapy (PDT) is a two-step drug and device procedure used for the treatment of defined ocular conditions. The patient is given an intravenous injection of a photosensitizing dye (i.e., verteporfin/Visudyne®)

which is activated in the vessels by a low-energy laser. The dye then binds with low-density lipoproteins generating reactive oxygen species that accumulate in neovascular and neoplastic tissue. This accumulation leads to the destruction of the vascular endothelial tissue resulting in platelet aggregation and vessel thrombosis. Although the vessels typically close shortly after treatment, they can become reperfused within the next three months. Studies have documented the safety and effectiveness of repeat verteporfin treatments every three months when leakage is seen on follow-up fluorescein angiography (Chan, et al., 2005; Atebara and Thall, 2004).

PDT with verteporfin is an established treatment option for classic subfoveal choroidal neovascularization (CNV) due to wet age-related macular degeneration (AMD), pathological myopia, or presumed ocular histoplasmosis. CNV involves the growth of immature blood vessels from the choroid (i.e., choroidal CNV) that leak blood and fluid creating lesions under the central part of the retina below the fovea (i.e., subfoveal). Classic lesions are clearly delineated on fluorescein angiography and leak fluorescein evenly. Predominantly classic lesions occupy $\geq 50\%$ of the lesion baseline (Wormald, et al., 2007; Verteporfin Roundtable Participants, 2005).

U.S. Food and Drug Administration (FDA)

Visudyne therapy is approved by the FDA premarket approval (PMA) process as a two-step combination drug and device treatment. The FDA approved verteporfin for intravitreal injection with PMA approval of the Ceralas™ I laser and Ceralink slit lamp adapter (QLT, Inc., Vancouver, British Columbia, Canada) “for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.” Other approved laser systems include the Coherent Opal Photoactivator™ Laser Console and LaserLink Adapter (Lumenis, Inc., Santa Clara, CA) and the Zeiss VISULAS 690s® laser and VISULINK PDT adapter (Carl Zeiss, Inc., Thornwood, NY) (FDA, 2000; FDA, 2005).

Age-Related Macular Degeneration

There are two types of AMD, “dry” and “wet.” Dry, atrophic, or non-neovascular AMD is characterized by small yellow lipid debris deposits (i.e., drusens) beneath the retina. Wet, exudative, or neovascular AMD is characterized by CNV. The three lesion types associated with wet AMD are classic, occult, and minimally classic or mixed (Wormald, et al., 2007; Verteporfin Roundtable Participants, 2005).

Treatment for AMD depends on the stage of the disease and the type of AMD. Early AMD exhibiting no clinical signs may be observed without medical or surgical intervention. Antioxidant vitamins and mineral supplements are used for the treatment of intermediate and advanced AMD. For advanced conditions an intravitreal injection of pegaptanib (Macugen), ranibizumab (Lucentis) or bevacizumab (Avastin) are available treatment options. PDT is indicated for the treatment of wet AMD with predominantly classic subfoveal CNV (AAO, 2010).

Literature Review: Systematic reviews (Wormald, et al., 2007; Pauleikhoff, 2005; Meads and Hyde, 2004), randomized controlled trials (Azab, et al., 2005; Bressler, et al., 2005; Michels, et al., 2005; Schmidt-Erfurth, et al., 2004; Blumenkranz, et al., 2002; Verteporfin in Photodynamic Therapy Study Group, 2001), and case series (Mataix, et al., 2009; Potter, et al., 2007; Tewari, et al., 2007; Sharma, et al., 2004) support PDT with verteporfin for the treatment of predominantly ($\geq 50\%$) classic subfoveal choroidal neovascularization (CNV) caused by AMD. In general, the randomized controlled trials compared PDT to placebo and reported significantly less visual loss following PDT. PDT also reduced or stopped fluorescein leakage and restricted lesion growth.

There are a limited number of studies comparing PDT to other established treatment modalities. The Anti-vascular endothelial growth factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization (CNV) in Age-related Macular Degeneration (ANCHOR) study (Brown, et al., 2009) was a multicenter (83 sites), international, randomized controlled trial that evaluated the efficacy and adverse events of patients (n=423) treated with ranibizumab compared to PDT for predominantly classic subfoveal CNV secondary to AMD. Patients were randomized to PDT plus a monthly sham intraocular injection (n=143) or to sham PDT plus a monthly 0.3 milligram (mg) intravitreal ranibizumab injection (n=140) or to sham PDT plus a monthly 0.5 mg intravitreal ranibizumab injection (n=140). The primary intent-to-treat analyses was conducted at 12-months and followed to 24 months. At the two-year follow-up, the visual acuity benefit following ranibizumab compared to PDT was statistically significant ($p<0.0001$). Compared to baseline, 89.9% of 0.5 mg ranibizumab patients, and 90.0% of 0.3 mg ranibizumab patients lost <15 letters compared to 65.7% of PDT patients. A gain of ≥ 15 letters was achieved by 34% of 0.3 mg and 41% of 0.5 mg ranibizumab patients compared to 6.3% of PDT patients, and visual acuity improved an average of 8.1 letters in the 0.3 mg group and 10.7 letters in the 0.5 mg

patients compared to a mean decline of 9.8 letters in PDT patients. At month 18 or over, 50 PDT patients crossed over to receive ranibizumab injections. At 24 months, there was a significantly higher number of patients in the PDT group who had a visual acuity Snellen equivalent of $\geq 20/200$ ($p < 0.001$). In the PDT group, 16.1% of patients experienced ≥ 30 letters loss compared to 0%–1.4% in the ranibizumab groups. Changes in total lesion area, total area of CNV, mean area of classic CNV, area of occult CNV with no classic component, total area of leakage from CNV were stable or improved following ranibizumab treatment and were significantly worsened following PDT ($p < 0.0001$ in all cases). Overall, there were no significant differences in ocular and nonocular adverse events between the three groups without the data for patients who crossed over. There was however, a significantly higher incidence of cataract formation in the ranibizumab groups ($p = 0.03$). Limitations of the study include the short-term follow-up, the 50 PDT patients who crossed over to ranibizumab injections prior to 24 months follow-up, and the drop-out rate ($n = 80$).

Pathological Myopia

Pathological myopia (PM) or high myopia is a rare form of shortsightedness in which the eyeball is abnormally long, stretching the retina and the sclera of the eye. This greater axial length may cause areas of atrophy and/or cracks in the retina leading to leakage of blood. PM is often accompanied by CNV, chorioretinal atrophy, and retinal detachment. Historically, treatment options for PM have included laser photocoagulation, macular translocation and submacular surgery with poor results, including immediate, permanent loss of visual acuity. PDT has been shown to be effective in stabilizing and retarding the progression of visual deterioration in PM with predominantly classic subfoveal CNV (Chan, et al., 2005; Lam, et al., 2004).

Literature Review: The evidence in randomized controlled trials (Costa, et al., 2006), nonrandomized comparative studies (Hayashi, et al., 2008), case series (Hussain, et al., 2008; Pece, et al., 2007; Krebs, et al., 2005; Lam, et al., 2004), and retrospective reviews (Glacet-Bernard, et al., 2007) support PDT for the treatment of PM. There are a limited number of studies comparing PDT to other treatment modalities.

Presumed Ocular Histoplasmosis Syndrome

Presumed ocular histoplasmosis syndrome (POHS) is a chronic intraocular inflammation caused by the fungus *histoplasma capsulatum*. Normally, patients are unaware of the disease process until they begin to develop visual disturbances from CNV. Depending on the stage and location of the disease, treatment options include corticosteroids, submacular surgery, and photodynamic therapy. PDT is indicated for the treatment of POHS with CNV because of its ability to selectively treat the target area while preserving surrounding tissue (Oliver, et al., 2005).

Literature Review: Although the evidence is primarily in the form of case series (Rosenfeld, et al., 2004; Saperstein, et al., 2002; Sickenberg, et al., 2000) and retrospective reviews (Shah, et al., 2005; Liu JC, et al., 2004), PDT is considered an accepted treatment option for this condition. Following the treatment of POHS with PDT, the studies reported stabilization, and/or improved visual acuity, and/or absence of fluorescein leakage. Studies comparing PDT to other established treatment modalities for POHS are lacking.

Other Indications

PDT has been proposed for the treatment of other ocular conditions including: minimally classic lesions, occult lesions, juxtafoveal lesions, extrafoveal lesions, neovascular glaucoma, corneal neovascularization, CNV secondary to vascular retinochoroidal diseases (e.g., choroiditis, retinochoroiditis, angioid streaks), CNV with macular dystrophy and diseases without CNV (e.g., choroidal hemangioma and melanoma, retinal hemangioma and hamartoma, central serous chorioretinopathy (CSCR), and angiomatous lesions), and polypoidal choroidal vasculopathy. However, studies have primarily been in the form of nonrandomized, small case series and case reports with short-term follow-up and variable, nonsignificant outcomes (Tsuchiya, et al., 2009; Mennel, et al., 2007; Yoon, et al., 2007; Ruiz-Moreno, et al., 2006).

Literature Review: In a randomized controlled trial, Parodi et al. (2010) compared the effectiveness of laser treatment (LT) ($n = 17$), PDT ($n = 18$) and intravitreal bevacizumab injection ($n = 19$) on visual acuity in patients with juxtafoveal CNV secondary to pathologic myopia. At the 24-month follow-up, the bevacizumab group maintained its initial improvement in best corrected visual acuity (BCVA) and had a final gain of 1.8 lines compared to baseline. The LT group experienced a nonsignificant visual loss of 1.1 lines, and the mean BCVA in the PDT group was significantly worsened by two lines ($p < 0.05$). Compared to PDT, the bevacizumab group displayed a statistically significant improvement of a mean three line difference ($p < 0.05$). During the first year following treatment, CNV recurrence with subfoveal extension occurred in nine LT eyes (53%) which were subsequently

retreated with PDT. A foveal extension occurred in 13 PDT eyes (72%) and four patients treated with bevacizumab developed a CNV foveal extension. Limitations of the study include the lack of a control group, the small patient population, and the short-term follow-up.

To compare the outcomes of treatment, Kaiser et al. (2009) randomly assigned 244 patients to PDT and 120 patients to placebo for the treatment of AMD with subfoveal occult with no classic CNV. Follow-up visits and subsequent therapy occurred for up to 24 months. During the first 12 months of the study, the PDT group received an average of 2.9 treatments compared to 3.3 treatments in the placebo group. Between month 12 and 24, the PDT group received an additional 1.3 treatments compared to 1.7 treatments in the placebo group. Although less loss of visual acuity was reported in the PDT group, the differences were not statistically significant ($p=0.256$ at 12 months and $p=0.138$ at 24 months). With the exception of infusion-related pain following PDT ($p<0.01$), there were no statistically significant differences in reported adverse events between the two groups.

Chan et al. (2008) recruited 63 patients to participate in a randomized controlled trial evaluating the efficacy of PDT ($n=63$) for the treatment of acute central serous chorioretinopathy (CSC) of three months or less duration. Subjects had impaired vision, subretinal fluid, and angiographic leakage. Patients were randomized to either treatment with PDT using half-dose verteporfin ($n=43$) or to placebo ($n=21$). At the 12-month follow-up visit, a significant difference was seen in the complete resolution of macular subretinal fluid in 37 eyes in the PDT group compared to 11 eyes in the placebo group ($p=0.001$). The mean logarithm of the minimum angle of resolution, mean lines of best corrected vision acuity, and vision stability/improvement were also significantly improved in the PDT group ($p=0.008$, $p=0.002$, $p=0.009$, respectively). The PDT group had significantly better outcomes in the mean central foveal thickness seen on optical coherence tomography ($p=0.001$). No complications or adverse events were experienced. Author-noted limitations included the small sample size, smaller number of eyes in the placebo group vs. the PDT group, use of half-dose verteporfin, exclusion of patients with secondary CSC, and the lack of angiography performed at the 12-month follow-up.

Combination Therapy

It has been proposed that PDT be used in combination with antiangiogenic agents or anti-VEGF agents (e.g., ranibizumab, bevacizumab, pegaptanib). PDT may be administered within a few days (e.g., 6–14) prior to or following intravitreal injection or may be given on the same day as the injection. Retreatments are administered if new leakage occurs and may involve intravitreal injections monthly and PDT every three months. It is hypothesized that using both therapies could possibly result in improved functional visual acuity outcomes, inhibit new vessel growth, reduce the size of CNV, and decrease permeability of new vessels leading to prolonged reduction of leakage and fewer retreatments. PDT has also been proposed for use with anti-inflammatory agents (e.g., corticosteroids). One case series combined PDT, intravitreal ranibizumab and intravitreal dexamethasone for the treatment of CNV due to AMD. The evidence in the published peer-reviewed literature does not support the safety and efficacy of combination therapy. Studies have primarily been in the form of case series and retrospective reviews with various trial designs and treatment parameters, heterogeneous small patient populations ($n=8$ –183), and short-term follow-ups (e.g., 1 day–24 months) (Shah, et al., 2009).

Literature Review: In a randomized controlled trial, Piermarocchi et al. (2008) compared the outcomes of PDT alone ($n=41$) to intravitreal triamcinolone acetonide (IVT) followed by PDT ($n=43$) for the treatment of neovascular AMD. Mean follow-up occurred for up to 29.1 months. Although the mean visual acuity increased at the one-month visit, it declined progressively thereafter in both groups. A significantly lower retreatment rate was reported in the combined therapy group ($p<0.001$). Choroidal hypoperfusion and areas with decreased fundus autofluorescence were significantly better in the combined therapy group ($p<0.001$ in each). Limitations of the study include the single-center enrollment, lack of a sham injection in the PDT-only group, small patient population, and short-term follow-up.

Professional Societies/Organizations

American Academy of Ophthalmology (AAO): The 2010 AAO guidelines for the treatment of AMD recommends PDT for the treatment of subfoveal CNV, new or recurrent, with a $>50\%$ classic lesion and an entire lesion of ≤ 5400 microns in greatest linear diameter. PDT may also be considered for the treatment of occult CNV with vision $<20/50$ or CNV with lesion <4 Macular Photocoagulation Study (MPS) disc areas when vision is $>20/50$. AAO also states that there is insufficient evidence on which to make recommendations regarding PDT combined with pharmacologic therapy. Combination therapy is still under investigation.

National Institute for Clinical Excellence (NICE): In a guidance document, NICE (United Kingdom) (2003) recommended PDT for the treatment of wet AMD with a diagnosis of classic with no occult subfoveal CNV and best-corrected visual acuity 6/60 or better. NICE did not recommend PDT for the treatment of AMD when some occult CNV is present.

Verteporfin Roundtable Participants: In 2005, the Verteporfin Roundtable Participants, including input from the American Society of Retina Specialists, the Macula Society, and the Retina Society, updated their guidelines on PDT for the treatment of CNV due to AMD and other causes. Viable candidates for PDT included those whose CNV is associated with AMD, pathologic myopia or other causes in which the outcome of lack of treatment would be more detrimental than PDT itself. Verteporfin therapy is recommended to treat eyes that present with a subfoveal lesion with predominantly classic CNV (area of classic CNV occupying $\geq 50\%$ of the area of the entire lesion at baseline). Lesion location should be subfoveal or may be considered for juxtafoveal lesions if the lesion is so close to the fovea that laser photocoagulation might be more harmful than beneficial. For pathological myopia, lesion composition should not influence patient selection for PDT because it has not shown to influence the outcomes of the therapy. According to the authors, PDT should be initiated within one week of the initial diagnostic fluorescein angiogram. Re-treatment may be indicated every three months if there is evidence of fluorescein leakage on revisits.

Summary

Evidence in the published peer-reviewed scientific literature supports photodynamic therapy (PDT) for the treatment of age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularization (CNV) when the area of the lesion comprises $\geq 50\%$ of the lesion baseline, pathological myopia, and presumed ocular histoplasmosis.

There is insufficient evidence in the published peer-reviewed scientific literature to support PDT for the treatment of other ocular conditions (e.g., minimally classic lesions, occult lesions, juxtafoveal lesions, extrafoveal lesions, angioid streaks and neovascular glaucoma) or for combination therapy in which PDT is administered with intravitreal pharmacotherapy (e.g., antiangiogenic or anti-inflammatory agents).

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
67221	Destruction of localized lesion of choroid (eg, choroidal neovascularization); Photodynamic therapy (includes intravenous infusion)
67225	Destruction of localized lesion of choroid (eg, choroidal neovascularization); Photodynamic therapy, second eye, at single session, (list separately in addition to code for primary eye treatment).

HCPCS Codes	Description
J3396	Injection, verteporfin, 0.1 mg

ICD-9-CM Diagnosis Codes	Description
115.02	Infection by Histoplasma capsulatum, retinitis
115.92	Unspecified Histoplasmosis retinitis
360.21	Progressive high (degenerative) myopia
362.51	Nonexudative senile macular degeneration of retina
362.52	Exudative senile macular degeneration

Experimental/Investigational/Unproven/Not Covered when used as a combination therapy with verteporfin (Visudyne®).

HCPCS Codes	Description
J2503	Injection, pegaptanib sodium, 0.3 mg
J2778	Injection, ranibizumab, 0.1 mg
J9035	Injection, bevacizumab, 10 mg
	All other codes

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
228.03	Hemangioma of retina
362.15	Retinal telangiectasia
362.16	Retinal neovascularization NOS
362.17	Other intraretinal microvascular abnormalities
362.50	Macular degeneration (senile) of retina, unspecified
362.51	Nonexudative senile macular degeneration of retina
363.20	Chorioretinitis, unspecified
363.43	Angioid streaks of choroid
363.61-363.63	Choroidal hemorrhage and rupture
363.72	Hemorrhagic choroidal detachment
365.63	Glaucoma associated with vascular disorders
370.60-370.64	Corneal neovascularization
371.55	Macular corneal dystrophy

***Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	1/15/2008	0036	Photodynamic Therapy for Ocular Conditions

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