Clinical Policy Title: Ocular photodynamic therapy with Visudyne® (verteporfin) for macular degeneration treatment

Clinical Policy Number: CCP.1187

Effective Date: January 1, 2016
Initial Review Date: August 19, 2015
Most Recent Review Date: October 1, 2019
Next Review Date: February 2021

Policy contains:
- Macular degeneration.
- Ocular photodynamic therapy with Visudyne (verteporfin).
- Vascular endothelial growth factor.

ABOUT THIS POLICY: AmeriHealth Caritas developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas clinical policies are not guarantees of payment.

Coverage policy

Photodynamic therapy with Visudyne (verteporfin) is clinically proven and, therefore, medically necessary when the following criteria are met:

- Members present with a diagnosis of neovascular wet age-related macular degeneration — when abnormal blood vessels grow under the retina and macula — with prematurely classic subfoveal choroidal neovascularization lesions, where the area of classic choroidal neovascularization occupies at least 50 percent of the entire lesion at the initial visit, as determined by a fluorescein angiogram.

OR

- Members present with a subfoveal occult with no classic choroidal neovascularization associated with age-related macular degeneration, when lesions are small (under four disk areas) at initial treatment within three months prior to initial treatment.
- Members present with minimally classic choroidal neovascularization where the area of classic choroidal neovascularization occupies <50 percent of the entire lesion associated with age-related macular degeneration.
• Members present with juxtafoveal lesions, as an off-label use.
• Members present with lesions that have shown evidence of progression within three months prior to initial treatment, as documented by visual acuity (at least five letters on an eye examination chart), lesion growth at least one disk area, or the appearance of blood associated with the lesions (American Academy of Ophthalmology, 2015; Royal College of Ophthalmologists, 2013).

Limitations:

All other uses of ocular photodynamic therapy with Visudyne (verteporfin) for the treatment of any other indication are not clinically proven, and therefore investigational. Verteporfin is not clinically proven as part of combination therapy with other pharmaceuticals, including corticosteroids for extrafoveal and peripapillary choroidal neovascularization lesions (American Academy of Ophthalmology, 2015).

Verteporfin is contraindicated for
• Members with porphyria
• Members with known allergies or sensitivities
• Members with liver dysfunction
• Pregnant members
• Breastfeeding members

Alternative covered services:

• U.S. Food and Drug Administration-approved pharmaceuticals, such as Lucentis® as approved by the plan.
• Ongoing monitoring of condition by an ophthalmologist.

While no macular degeneration treatment currently approved for use in the United States is likely to completely restore vision lost to this eye disease, some drugs — such as Lucentis® — may be able to slow or prevent additional vision loss or even improve remaining vision to some extent.

Background

Age-related macular degeneration is a common cause of blindness among people over the age of 50 in the western world. Neovascular age-related macular degeneration results when new blood vessels grow across the posterior of the eye, a process known as choroidal neovascularization. These blood vessels often leak blood and serum, causing a blister to form in the retina and eventually damage the macular area of the retina and interfere with central vision. If untreated, the disease results in the distortion of straight lines and, eventually, the loss of central vision. It can be detected in the early, intermediate, and
late stage (National Eye Institute, 2015).

A 2014 analysis of 129,664 individuals estimated the prevalence of late age-related macular degeneration to be 8.69 percent worldwide, with most cases being early stage. Europeans had a much greater prevalence than did Africans (12.3 percent versus 7.4 percent). Due to the aging of the population, the projected number of people worldwide with age-related macular degeneration is expected to rise 47 percent, from 196 million to 288 million, from 2020 to 2040 (Wong, 2014).

Several risk factors for age-related macular degeneration have been identified, in addition to age and race. Smoking doubles age-related macular degeneration risk, and persons with a family history of the disease are at higher risk. Age-related macular degeneration is detected through a dilated eye exam, which can include a visual acuity test, dilated eye exam, Amsler grid viewing, fluorescein angiogram, and optical coherence tomography (National Eye Institute, 2015).

There are two types of age-related macular degeneration: atrophic (dry) age-related macular degeneration and exudative (wet) age-related macular degeneration. Atrophic age-related macular degeneration evolves slowly and is the most common form of age-related macular degeneration. This condition is characterized by small yellow lipid debris deposits beneath the retina. It is often a precursor of exudative age-related macular degeneration. The exudative form is distinguished from the atrophic form by serous or hemorrhagic detachment of the retinal pigment epithelium and the development of choroidal neovascularization. The three lesion types associated with exudative age-related macular degeneration are classic, occult, and minimally classic.

In addition to ocular photodynamic therapy, available treatment options for age-related macular degeneration include thermal laser photocoagulation, corticosteroids, and vascular endothelial growth factor antagonists or angiostatics. The safety and effectiveness of each treatment depends on the form and location of the neovascularization.

Initially, photocoagulation with a thermal laser was the only viable treatment for patients with age-related macular degeneration. However, this treatment is only beneficial for a small subset of patients with relatively small, well-demarcated lesions and can cause damage to viable neurosensory retinal tissue overlying the treated choroidal neovascularization. This may cause loss of part of the visual field. Beginning in about the year 2000, ocular photodynamic therapy with verteporfin (Visudyne, CIBA Vision Corporation, Duluth, GA), was introduced as a treatment for the neovascular form of age-related macular degeneration.

Choroidal neovascularization is characterized as classic if there is a well-demarcated area of hyperfluorescence early in the fluorescein angiogram, with increased fluorescence caused by pooling of the dye in the late phases of the study. The lesion is characterized as occult if early frames show poorly demarcated areas of hyperfluorescence during fluorescein angiography, with persistent and increased staining in the late phases of the study.
This form of choroidal neovascularization is more often associated with subretinal blood, fluid, and exudates than the classic form. Lesions can also be mixed when there are both classic and occult neovascular patterns recurrent on the fluorescein angiogram, and recurrent, which occurs in patients with a previous history of leakage or treatment. Age-related macular degeneration tends to occur in one eye at a time; however, approximately 50 percent of patients who have neovascular age-related macular degeneration in one eye will develop this condition in their second eye within five years. The progression of this disease varies from a few months to three years.

Verteporfin, a benzoporphyrin derivative, is the first treatment to reduce moderate to severe vision loss in macular degeneration. It involves the focus and delivery of laser energy to disease tissue, helping close choroidal neovascular and other active proliferating vessels, while not harming normal retinal tissue (Leung, 2013). Verteporfin is administered by intravenous injection for 10 minutes, followed five minutes later by low-intensity non-thermal light for 83 seconds (Leung, 2013). This drug was first approved by the U.S. Food and Drug Administration in April 2000 (Verteporfin in Photodynamic Therapy Study Group, 2001).

Treatment to combat vascular endothelial growth factor has recently become the first-line treatment for age-related macular degeneration (Leung, 2013). This process addresses the secretion of high levels of this protein, and injections are made several times a month to block further growth of the protein (National Eye Institute, 2015).

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.
- The Cochrane library.

We conducted searches on August 7, 2019. Search terms were: “macular degeneration,” “photodynamic therapy,” and “Visudyne® (verteporfin).”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.
Findings

The American Academy of Ophthalmology guideline states that verteporfin is still an approved option for age-related macular degeneration, even though vascular endothelial growth factor is still the preferred therapy. Data do not support combination therapy of the two (American Academy of Ophthalmology, 2015). This consensus matches that of the European Society of Retina Specialists (Schmidt-Erfurth, 2014). The National Institute for Health and Care Excellence 2018 guideline on age-related macular degeneration makes no mention of verteporfin therapy (National Institute for Health and Care Excellence, 2018).

A United Kingdom review of 8,323 eyes in 7,748 patients treated with verteporfin for age-related macular degeneration attempted to understand if administration and results are similar to those in the large clinical trials leading up to approval of this drug, along with effectiveness. Deterioration of visual acuity in practice in patients eligible for trials were similar to those observed in trials. The rate of patients treated beyond one year in practice was less than one-half of that recorded in trials. Adverse reactions were reported for 1.4 percent of first visits, fewer than those in the trials (Reeves, 2012).

A Cochrane review of three trials (n = 1,022) compared verteporfin therapy to controls (five percent dextrose in water). Participants received five treatments over two years. After treatment ended, the risk of losing at least three lines of visual acuity was 23 percent (significantly) less in the intervention group, and 38 percent (significantly) less risk of losing at least six lines. Acute severe visual acuity decrease occurs in about two percent of patients (Wormald, 2007). A Cochrane review of five trials included one that found treatment with the vascular endothelial growth factor drug ranibizumab resulted in fewer subjects with loss of at least 15 letters compared with verteporfin. In addition, the combination of the two therapies was more effective compared to verteporfin alone (Vedula, 2008).

A systematic review of verteporfin in photodynamic therapy for age-related macular degeneration by lesion subtype showed a strong response in patients with 100 percent classic lesions. However, the treatment showed no benefit in 100 percent occult lesions with no classic component, enabling the European Medicines Evaluation Agency to rescind its approval for verteporfin as a treatment for this type of lesion (Cruess, 2009).

In recent years, more trials on age-related macular degeneration treatment have addressed vascular endothelial growth factor therapy, which generally produces outcomes superior to verteporfin, and became the more-used therapy (in Japan, and likely other developed nations), starting in 2009 (Kume, 2016). A review of patients in a phase III clinical trial determined that after 12 months, ranibizumab therapy exceeded outcomes for verteporfin photodynamic therapy for age-related macular degeneration, specifically the proportion losing <15 letters, proportion gaining >15 letters, and average change from baseline visual acuity (Kaiser, 2007).

A systematic review of 10 randomized controlled trials found that verteporfin therapy for age-related
macular degeneration produced better outcomes (measured in visual gain or loss) compared to controls, but not compared to the vascular endothelial growth factor drug ranibizumab (Virgili, 2011).

Photodynamic therapy has been combined with vascular endothelial growth factor treatment. A Cochrane review of 12 randomized controlled trials (n = 5,496) comparing vascular endothelial growth factor (using any of three drugs) with photodynamic therapy or sham treatment found that more subjects in each type of vascular endothelial growth factor treatment resulted in more with an increase of at least 15 letters, and more with a vision of 20/200 or better (Solomon, 2014). Even a study comparing vascular endothelial growth factor with and without photodynamic therapy concluded that monotherapy yields improved visual acuity after one year of treatment, in terms of the percent that gained at least 15 letters of visual acuity (Tong, 2016).

One review of six trials that compared ranibizumab monotherapy to a combination with photodynamic therapy showed no difference between the two groups for 1) central retinal thickness reduction; 2) number of patients with no lines gained; 3) tolerance; and 4) adverse events. Monotherapy actually had more patients with three or more lines gained and better visual acuity correction (Si, 2014).

However, a recent meta-analysis indicated that combination therapy including verteporfin for choroidal vasculopathy may be helpful. The review, made up of three randomized controlled trials and 19 retrospective studies (n = 1,178) compared patients given intravitreal antivascular endothelial growth factor with and without verteporfin. Significantly greater improvements in best-corrected visual acuity was observed in the combined therapy group at three, six, 12, and 24 months (P < .03, P < .005, P < .02, and P < .00001) after treatment (Qian, 2018).

A value-based medicine analysis compared laser photocoagulation, intravitreal pegaptanib therapy, and photodynamic therapy (with verteporfin) for treating classic subfoveal choroidal neovascularization. Using subjects from the large phase III trials, photodynamic therapy/verteporfin had the greatest improvement in quality-adjusted life years (8.1 percent), significantly greater than 5.9 percent for pegaptanib) and 4.4 percent for laser photocoagulation (Brown, 2007).

In a systematic review of 12 randomized controlled trials, five of them (n = 418) found that adding combined intravitreal ranibizumab and photodynamic therapy to intravitreal ranibizumab monotherapy increased visual acuity an average of 2.74 letters (Ba, 2015). A meta-analysis of 16 studies (n = 587) showed that adding photodynamic therapy to anti-vascular endothelial growth factor significantly corrected visual acuity and central retinal thickness (P = .004), and required fewer subsequent injections (P < .001) compared to those patients receiving growth factor as monotherapy (Gao, 2018).

While anti-vascular endothelial growth factor has become the gold standard for treating macular degeneration, a recent Cochrane review recommended that combined treatments of this factor with photodynamic therapy are merited (Solomon, 2019). The common polymorphism 677 C > T of the gene MTHFR-C677T; rs1801133 polymorphism can predict satisfactory short choroidal neovascularization to verteporfin; a study of 371 patients determined a significant (P < .001) reduction in risk of scheduled
future treatments and best-corrected visual acuity (Parmeggiani, 2019).

Policy updates:

A total of one guideline/other and four peer-reviewed references were added to, and one guideline/other and four peer-reviewed references removed from this policy in August 2019.

References

Professional society guidelines/other:


Peer-reviewed references:


**Centers for Medicare & Medicaid Services National Coverage Determination:**

80.2.1 Ocular Photodynamic Therapy.

**Medicare statement:**

For patients with age-related macular degeneration, verteporfin is only covered with a diagnosis of neovascular age-related macular degeneration with predominately classic subfoveal choroidal neovascularization lesions (where the area of classic choroidal neovascularization occupies >50 percent of the area of the entire lesion) at the initial visit as determined by an fluorescein angiography. Subsequent follow-up visits will require either an optical coherence tomography or an fluorescein angiography to access treatment response. Ocular photodynamic therapy with verteporfin is covered for the above indication and will remain noncovered for all other indications related to age-related macular degeneration (section 80.2 of National Coverage Determination). Ocular photodynamic therapy with verteporfin for use in nonacute macular degeneration conditions is eligible for
coverage through individual Medicare Administrative Contractor discretion.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<th>Description</th>
<th>Comments</th>
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<td>J3396</td>
<td>Injection, verteporfin, 0.1 mg</td>
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**Appendix**
No additional information was identified for this section during the writing of this policy.