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

Clinical Policy Number: 10.02.04

Effective Date: January 1, 2016
Initial Review Date: August 19, 2015
Most Recent Review Date: August 30, 2018
Next Review Date: September 2019

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s 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 Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state and federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s 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. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of ocular photodynamic therapy with Visudyne (verteporfin) to be clinically proven and, therefore, medically necessary when the following criteria are met:

- Members 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 of 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 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 (AAO, 2013; RCO, 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/experimental. Verteporfin is not clinically proven as part of combination therapy with other pharmaceuticals.

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 (NEI, 2015).

A 2014 analysis of 129,664 individuals ages 45 to 85 estimated the prevalence of 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 (NEI, 2015). 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 (NEI, 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 5 minutes later by low-intensity nonthermal light for 83 seconds (Leung, 2013). This drug was first approved by the U.S. Food and Drug Administration in April 2000 (VPTSG, 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 (NEI, 2015).

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 (AAO, 2015). This consensus matches that of the European Society of Retina Specialists (Schmidt-Erfurth, 2014).

Searches

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on June 21, 2018. 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**

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 (5 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 2 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).

One concern about any therapy for age-related macular degeneration is long-term recurrence. One study of 68 eyes found a 52.7 percent recurrence after three years, which was within the 40.0 percent – 78.6 percent range of a systematic review of 48 studies (Wong, 2015).

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 >0 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 anti-vascular 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<0.03, p<0.005, p<0.02, and p <0.00001) after treatment (Qian, 2018).

One of the larger randomized trials that found superior results for combination therapy for choroidal vasculopathy analyzed 322 patients given ranibizumab with or without verteporfin. Twelve months after therapy started, mean improvement from baseline was significantly greater for combination therapy (8.3 versus 5.1 letters, p = 0.01), and in the percent achieving complete polyp regression after 12 months (69.3 versus 34.7, p < 0.001). Over 12 months, the combination therapy group received fewer ranibizumab injections (4.0 versus 7.0) (Koh, 2017).

Some evidence suggests that half-doses of verteporfin and half laser light fluence may be equally as effective as a full dose and fluence to treat choroidal vasculopathy. In a study of 40 eyes (40 patients), for both groups, best-corrected visual acuity was significantly improved one, three, and six months after treatment (all p < 0.01). Central retinal thickness was significantly improved at all time points in both groups (p < 0.05). All patients in the half-dose group and 19 patients (95 percent) in the half-fluence group had complete absorption of subretinal fluid three and six months after treatment (Cheng, 2017).

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). Another economic analysis concluded that verteporfin for age-related macular degeneration is more cost effective than conventional macular laser; pegaptanib is likely more cost effective than verteporfin, and ranibizumab is effective but at an unacceptably high cost per quality-adjusted life year (Hodge, 2010).

Policy updates:
A total of three peer-reviewed references were added to and one guideline/other and one peer-reviewed references removed from this policy in June 2018.

Summary of clinical evidence:
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
</table>
| **Solomon (2014)** | **Key points:**  
| Investigation of anti-vascular endothelial growth factor agents as a treatment for age-related macular degeneration |  
|             | - Cochrane review of 12 trials (n=5,496), investigating vascular endothelial growth factor; verteporfin prevented clinically significant vision loss, but offered no significant chance for improving vision.  
|             | - Three of 12 studies compared vascular endothelial growth factor (ramibizumab) with verteporfin or sham treatment.  
|             | - Fewer subjects with vascular endothelial growth factor lost <15 letters after 12 months. |
| **Reeves (2012)** | **Key points:**  
| Improvement of visual acuity after verteporfin treatment compared to persons eligible for prior study |  
|             | - Trial in the United Kingdom involving 8,323 eyes, 7,748 patients.  
|             | - Comparison of visual loss in verteporfin photodynamic therapy-treated eyes with those eligible for an earlier trial, using verteporfin.  
|             | - No difference in visual loss between the two groups.  
|             | - Verteporfin group averaged reduction of 9.9 letters after one year, significantly more than the 9.9 in the earlier group.  
|             | - Verteporfin not prime choice for monotherapy for age-related macular degeneration, but has potential as monotherapy in the management of vascular malformations of the retina and choroid and with trials underway in neovascularization due to myopia and polypoidal choroidopathy. |
| **Virgili (2011)** | **Key points:**  
| Analysis of mixed treatments for age-related macular degeneration |  
|             | - A mixed meta-analysis of sham treatments vs. interventions; 10 randomized controlled trials (n=3,108); four of these included verteporfin (n=1,124).  
|             | - Visual loss defined as loss or gain of at least 15 lines, measured in monthly increments.  
|             | - Ranibizumab is superior to verteporfin in visual loss. |
| **Kaiser (2007)** | **Key points:**  
| Visual acuity changes for age-related macular degeneration, ranibizumab vs. verteporfin photodynamic therapy |  
|             | - Results of phase III trial, comparing number of patients losing at least 15 lines, gaining at least 15 lines, and overall visual acuity after 12 months.  
|             | - Ranibizumab superior to verteporfin in all three categories.  
|             | - Results consistent at 24 months. |

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


Koh A, Lai TY, Takahashi K, et al. Efficacy and safety of ranibizumab with or without verteporfin


**CMS National Coverage Determination (NCDs):**


**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 (LCDs):**

No LCDs 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>CPT Code</th>
<th>Description</th>
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<td>67221</td>
<td>Destruction of localized lesion of choroid (e.g., choroidal neovascularization); photodynamic therapy (includes intravenous infusion)</td>
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<td>+67225</td>
<td>Destruction of localized lesion of choroid (e.g., choroidal neovascularization); photodynamic therapy, second eye, at single session (List separately in addition to code for primary eye treatment)</td>
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<td>Description</td>
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<td>Retinal neovascularization</td>
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<td>H35.30</td>
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<td>H35.711 – H35.719</td>
<td>Central serous retinopathy [serous chorioretinopathy]</td>
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<td>H44.20 – H44.23</td>
<td>Degenerative myopia</td>
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<td>Destruction of localized lesion of choroid (for example, choroidal neovascularization); photocoagulation, feeder vessel technique (one or more sessions)</td>
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<td>J3396</td>
<td>Injection, verteporfin, 0.1 mg</td>
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**Appendix**

No PerformRx policy identified as of the writing of this policy.