Clinical Policy Title: Ocular photodynamic therapy (OPDT) 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: September 21, 2017
Next Review Date: September 2018

Related policies:

CP# 10.02.01  Vision therapy for visual system disorders

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’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 AmeriHealth Caritas Pennsylvania 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 Pennsylvania’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. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of ocular photodynamic therapy (OPDT) 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 (AMD) - when abnormal blood vessels grow under the retina and macula - with prematurely classic subfoveal choroidal neovascularization (CNV) lesions, where the area of classic CNV 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 CNV associated with AMD, when lesions are small (under four disk areas) at initial treatment of within three months prior to initial treatment
• Members present with minimally classic CNV where the area of classic CNV occupies <50 percent of the entire lesion associated with AMD
• 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

Limitations:

All other uses of OPDT with Visudyne (verteporfin) for the treatment of any other indication are not medically necessary.

Alternative covered services:

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

AMD is a common cause of blindness among people over the age of 50 in the western world. Neovascular AMD results when new blood vessels grow across the posterior of the eye, a process known as CNV. 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 age 45 to 85 estimated the prevalence of AMD to be 8.69 percent worldwide, with most cases being early stage. Europeans had a much greater prevalence than did Africans (12.3 versus 7.4 percent). Due to the aging of the population, the projected number of people worldwide with AMD is expected to rise 47 percent, from 196 million to 288 million, from 2020 to 2040 (Wong, 2014). Several risk factors for AMD have been identified, in addition to age and race. Smoking doubles AMD risk, and persons with a family history of the disease are at higher risk (NEI, 2015). AMD 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 AMD: atrophic (dry) AMD and exudative (wet) AMD. Atrophic AMD evolves
slowly and is the most common form of AMD. This condition is characterized by small yellow lipid debris deposits beneath the retina. It is often a precursor of exudative AMD. The exudative form is distinguished from the atrophic form by serous or hemorrhagic detachment of the retinal pigment epithelium and the development of CNV. The three lesion types associated with exudative AMD are classic, occult and minimally classic. In addition to OPDT, available treatment options for AMD include thermal laser photocoagulation, corticosteroids, and vascular endothelial growth factor (VEGF) 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 AMD. 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 CNV. This may cause loss of part of the visual field. Beginning in about the year 2000, OPDT with verteporfin (Visudyne, CIBA Vision Corporation, Duluth, GA), was introduced as a treatment for the neovascular form of AMD.

CNV 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 CNV 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. AMD tends to occur in one eye at a time; however, approximately 50 percent of patients who have neovascular AMD 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 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 (VEGF) has recently become the first line treatment for AMD (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).

Searches
AmeriHealth Caritas Pennsylvania 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 (CMS).

We conducted searches on August 14, 2017. 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 (AAO) guideline states that verteporfin is still an approved option for AMD, even though VEG-F 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).

A Hayes review of the three major clinical trials that led to FDA approval of verteporfin found it was well tolerated, as fewer than two percent of subjects withdrew. Subjects given verteporfin in the two trials with >50 percent classic neovascular lesions had a significantly less vision loss (higher proportion of patients with fewer than 15 letters lost within a year) compared to placebo. No statistically significant difference between the two group was evident in patients where classic CNV was present in <50 percent of the area of the entire lesion – contrary to what the third study found (Hayes, 2007).

A United Kingdom review of 8323 eyes in 7748 patients treated with verteporfin for AMD 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. Estimated cost per life-year was similar to the highest estimate in the trials (Reeves, 2012).
A Cochrane review of three trials (n=1022) 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 VEGF 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 AMD 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 rescinded its approval for verteporfin as a treatment for this type of lesion (Cruess, 2009).

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

In recent years, more trials on AMD treatment have addressed VEGF therapy, which generally produces outcomes superior to verteporfin, as VEGF 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 AMD, 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 AMD produced better outcomes (measured in visual gain or loss) compared to controls, but not compared to the VEGF drug ranibizumab (Virgili, 2011).

Photodynamic therapy has been combined with VEGF treatment. A Cochrane review of 12 Randomized Controlled Trials (n=5496) comparing VEGF (using any of three drugs) with photodynamic therapy or sham treatment found that more subjects in each type of VEGF 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 VEGF with and without photodynamic therapy concluded that monotherapy yields improved visual acuity after one year of treatment, in terms of the percent who 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).
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 AMD 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 six guidelines/other and 16 peer-reviewed references were added to this policy in 2017; a total of two guidelines/other and 17 peer-reviewed references were removed.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solomon (2014)</td>
<td><strong>Key points:</strong></td>
</tr>
</tbody>
</table>
| Investigation of anti-VEGF agents as a treatment for AMD | • Cochrane review of 12 trials (n=5496), investigating VEGF; verteporfin prevented clinically significant vision loss, but offered no significant chance for improving vision.  
• 3 of 12 studies compared VEGF (ramibizumab) with verteporfin or sham treatment.  
• Fewer subjects with VEGF 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 UK involving 8323 eyes, 7748 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 AMD, 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 AMD | • A mixed meta-analysis of sham treatments vs. interventions; 10 Randomized Controlled Trials (n=3108); 4 of these included verteporfin (n=1124).  
• 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)

Visual acuity changes for AMD, ranibizumab vs. verteporfin photodynamic therapy

Key points:
- 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:


Virgili G, Novielli N, Menchini F, Murro V, Giacomelli G. Pharmacological treatments for neovascular


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


<table>
<thead>
<tr>
<th>Medicare Statement</th>
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<tr>
<td>For patients with age-related macular degeneration (AMD), verteporfin is only covered with a diagnosis of neovascular AMD with predominately classic subfoveal CNV lesions (where the area of classic CNV occupies &gt; 50 percent of the area of the entire lesion) at the initial visit as determined by an FA. Subsequent follow-up visits will require either an optical coherence tomography or an FA to access treatment response. OPT with verteporfin is covered for the above indication and will remain non-covered for all other indications related to AMD (section 80.2 of National Coverage Determination [NCD]). OPT with Verteporfin for use in non-AMD conditions is eligible for coverage through individual Medicare Administrative Contractor discretion.</td>
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**Local Coverage Determinations (LCDs):**


**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.
<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>67221</td>
<td>Destruction of localized lesion of choroid (e.g., choroidal neovascularization); photodynamic therapy (includes intravenous infusion)</td>
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<tr>
<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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<th>ICD 10 Code</th>
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<tr>
<td>B39.4</td>
<td>Histoplasmosis capsulati, unspecified</td>
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<tr>
<td>B39.5</td>
<td>Histoplasmosis duboisii</td>
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<tr>
<td>B39.9</td>
<td>Histoplasmosis, unspecified</td>
<td></td>
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<tr>
<td>H32</td>
<td>Chorioretinal disorders in diseases classified elsewhere [Histoplasmosis]</td>
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<td>H35.051 – H35.059</td>
<td>Retinal neovascularization</td>
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<td>H35.30</td>
<td>Macular degeneration, unspecified</td>
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<td>H35.3110-H35.3194</td>
<td>Nonexudative age-related macular degeneration</td>
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<td>H35.3210-H35.3293</td>
<td>Exudative age-related macular degeneration</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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<table>
<thead>
<tr>
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