Clinical Policy Title: Ocular photodynamic therapy (OPDT) 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, 2016
Next Review Date: September, 2017

Policy contains:
- Macular degeneration.
- Ocular photodynamic therapy (OPDT) with Visudyne® (verteporfin).

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 predominantly classic subfoveal choroidal neovascularization (CNV) lesions (where the area of classic CNV occupies greater than or equal to 50 percent of the area of the entire lesion) attributable to:
  - Wet age-related macular degeneration (AMD).
  - Pathological myopia.
  - Presumed ocular histoplasmosis.
Note: Subsequent follow-up visits (every three months) for re-treatment require either an optical coherence tomography (OCT; CPT codes 92133 or 92134) or a fluorescein angiogram prior to treatment, showing evidence of current leakage from CNV. Retreatment is necessary if fluorescein angiogram or OCT shows any signs of recurrence or persistence of leakage.

Limitations:

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

AmeriHealth Caritas Pennsylvania considers the simultaneous use of OPDT with Visudyne in combination with anti-angiogenic agents for the treatment of CNV due to AMD experimental and investigational, and therefore, not medically necessary. The safety and effectiveness of this combination therapy has not been established.

Alternative covered services:

- Approved Food and Drug Administration (FDA) and plan 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 the most frequent cause of blindness among people over the age of 60 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.

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.
Until recently, 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. Recently, 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 an intravenous lipophilic photosensitive drug with an absorption peak of 690 nm. When verteporfin, a photosensitive compound, is activated by non-thermal laser light, reactive oxygen compounds are formed in abnormal blood vessels in the eye. These reactive compounds then cause thrombosis and stop leakage of these vessels. The goal of verteporfin therapy is to reduce or delay the loss of vision caused by leakage of the abnormal blood vessels. This drug was first approved by the FDA on April 12, 2000, and approved for inclusion in the United States Pharmacopoeia on July 18, 2000, meeting Medicare’s definition of a drug when used in conjunction with OPDT, and furnished intravenously incident to a physician's service.

**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 23, 2016. 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 prevalence of AMD has been estimated in several epidemiological studies and ranges from 2 percent to over 10 percent, depending on the working definition of AMD, the grading system used, and the age and environment of the study population. All the studies, however, point to the association between AMD prevalence and age. AMD occurs most frequently in people above 50 years of age, with a strong increase in prevalence in people over 65 years of age. This rapid increase in AMD prevalence with age will probably pose a growing health problem for developed countries, because of the increasing proportion of the population in older age groups. By 2020, as many as 7.5 million people over 65 years of age may suffer from vision loss due to AMD. Data from the UK have shown that the number of new registrations of blindness due to AMD has increased by 30 percent – 40 percent in the past 50 years.

Because the prevalence of AMD is associated with age, its socioeconomic implications are becoming more important as the proportion of older people increases in developed countries. However, AMD not only affects people in older age groups; people over 50 years of age who are relatively young and active are also at an increased risk of acquiring the disease.

No preventive treatment exists for neovascular AMD, the form of AMD responsible for severe vision loss. Two approaches are under investigation, including micronutrient use (Age Related Eye Disease Study) and light laser photocoagulation (Complications of Age Related Macular Degeneration Prevention Trial). If left untreated, neovascular AMD will usually result in a poor vision outcome.

During the 1990s, laser photocoagulation was used to treat neovascular AMD, but it can only benefit a small proportion of selected cases. Other therapies, such as surgery, radiation therapy and antiangiogenic therapy are under investigation.

OPDT is a proven treatment modality for certain eyes with subfoveal CNV secondary to AMD. Compared with other light-activated drugs, verteporfin is at the most advanced developmental stage. Phase III data from 12 and 24 months demonstrate that verteporfin therapy is safe, with few systemic side effects and no prolonged skin photosensitivity. Phase III data also demonstrates that verteporfin therapy reduces the risk of vision loss in subfoveal cases with predominantly classic CNV. Verteporfin therapy does not
repair irreversibly damaged tissue but might prevent further growth of CNV, as suggested by fluorescein angiography. Verteporfin therapy became available in early 2000 as the first drug therapy for patients with subfoveal neovascular AMD.

Several new treatment opportunities may be afforded by verteporfin therapy because this new treatment modality, without the destructive effects on the neurosensory retina seen with laser photocoagulation, can be of benefit to a greater number of patients with subfoveal lesions, compared with photocoagulation. The results from current clinical investigations will confirm whether verteporfin therapy is useful in the treatment of a wide range of cases of subfoveal CNV due to AMD with occult CNV but no classic CNV. The results will also confirm whether verteporfin therapy is useful in cases with CNV due to non-AMD causes, such as pathological myopia.

In July 2010, the FDA approved a tiny, implantable device that magnifies images onto the retina to improve central vision damaged by AMD.

Currently, there are several forms of PDT available, one of which is OPDT using Visudyne (verteporfin). This therapy is an FDA-approved treatment option for individuals with CNV lesions due to AMD, presumed ocular histoplasmosis or pathologic myopia.

Fluorescein angiography is indicated for macular degeneration, along with the following conditions:

- To detect a possibly treatable CNV lesion as the cause of vision loss or distortion that the ophthalmoscopic examination does not explain.
- Suspected exudative (e.g., wet) acute macular degeneration.
- Suspected, treatable CNV lesion.
- Planned treatment of known CNV.
- Detection of persistent or recurrent CNV, following laser treatment.

**Policy updates:**

2016: Added new recruiting clinical trials. Updated LCD to current version.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Hayes (2002) TAP studies suggest PDT with verteporfin | Key points:  
  - Findings from the TAP studies suggest PDT with verteporfin can provide an effective means of achieving short-term (12 weeks) vessel occlusion in individuals with predominantly classic CNV, due to neovascular AMD.  
  - Patients with ≥ 50% classic neovascular lesions who received verteporfin |
treatments had significantly less vision loss at both the 12-month and the 24-month examination than did patients in the placebo group.

- In addition to delaying or limiting vision loss for up to two years, verteporfin therapy was associated with a number of other benefits when compared with placebo, including less progression (growth) of classic CNV beyond the area of the lesion at baseline, less fluorescein leakage from classic CNV and fewer lesions greater than six disc areas, even though most lesions in both groups were less than this size at the time of study entry for the participants.

Hussein D. et al., (1999)

**Effects of photodynamic therapy using verteporfin on experimental choroidal neovascularization and normal retina and choroid up to 7 weeks after treatment.**

**Key points:**

- OPDT leads to absence of angiographic leakage for at least four weeks in experimental CNV in the monkey model.
- In the normal monkey eye, the RPE and choriocapillaris show generalized recovery with preservation of the neurosensory retina, seven weeks after PDT.

Bressler, N. & Bressler S. (2000)

**Photodynamic Therapy with Verteporfin (Visudyne): Impact on Ophthalmology and Visual Sciences**

**Key points:**

- The results of a new treatment, OPDT with verteporfin for selected patients with subfoveal lesions in AMD with predominantly classic CNV, especially in the absence of occult CNV lesions AMD, show that verteporfin therapy can reduce the risk of moderate vision loss for at least one year.
- Although the therapy is not a magic bullet that can stop or reverse vision loss in all patients with AMD, the benefits are another step in the right direction (joining laser photocoagulation) for ophthalmologists and vision scientists pursuing investigations intended to reduce the magnitude of vision loss from AMD and its impact on the quality of life of people with this condition.
- The TAP Investigation should provide encouragement and provide the foundation for future investigations of new treatments for AMD and related conditions by ophthalmologists and vision scientists, as the number of people at risk for AMD at least doubles during the next 30 years.


**Photodynamic therapy with Visudyne in macular degeneration associated with subfoveal classical CNV**

**Key points:**

- Photodynamic therapy with the preparation Visudyne (PDT) is the only treatment which retards statistically and significantly the decline of vision in patients with age-related and myopic macular degeneration, with a subfoveal, predominantly classic CNV.
- The authors present their own experience with the treatment of the first 12 patients. During six-month treatment, a loss of more than three lines of early treatment diabetic retinopathy study (ETDRS) optotypes was recorded in two patients (17%).
- The presented results of FTV are consistent with data published abroad. As the one-year therapeutic results in two patients are encouraging, it will be necessary in the future to prolong the follow-up time and increase the number of patients.
Glossary

**Advanced age-related macular degeneration (AMD)** — The most severe form of AMD, defined as geographic atrophy involving the center of the macula (fovea) or features of CNV.

**Age-related macular degeneration (AMD)** — There is no universally accepted definition of this term. The condition is characterized by the presence of drusen and alterations of the rating of perceived exertion (RPE), as well as by the fundus abnormalities associated with CNV. It generally occurs in persons over age 65. The usual acuity may vary from normal to severe impairment.

**Choroidal neovascularization (CNV)** — The formation of new vessels in the subretinal space. Subretinal hemorrhage or serous macular detachment often follows, leading to vision distortion or loss.

**Drusen** — Represent focal detachment of pigment epithelium in nonexudative AMD.

**Medically Necessary** - A service or benefit is Medically Necessary if it is compensable under the MA Program and if it meets any one of the following standards:

- The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
- The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- The service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age.

**Visudyne (verteporfin for injection)** — A light-activated drug used in photodynamic therapy. Visudyne offers an anatomical treatment, which occludes mature vessels that may be expressing less or no vascular endothelial growth factor (VEGF). It works to effect vaso-occlusion of the arteriolarized neovessels, which may be the cause of exudative manifestations that continue despite anti-VEGF treatments.

**References**

**Professional society guidelines/other:**


Centers for Medicare and Medicaid Services (CMS.gov.)

**Peer-reviewed references:**


The Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): a clinical trial of zinc and antioxidants. AREDS study report no. 2. *J Nutr.* 2000;130:1516S – 1519S.


**Clinical trials:**
Searched clinicaltrials.gov on august 23, 2016 using terms photodynamic therapy with verteporfin | Open Studies. 10 studies found, one relevant.


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

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 ≥ 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.

Local Coverage Determinations (LCDs):

Ocular Photodynamic Therapy (OPT) with Verteporfin (L33705). Effective 10/01/2015


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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<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 (eg, choroidal neovascularization); photodynamic therapy, second eye, at single session (List separately in addition to code for primary eye treatment)</td>
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