Protocol

Photodynamic Therapy for Choroidal Neovascularization

(90308)

Medical Benefit		**Effective Date**: 10/01/18	**Next Review Date**: 05/19
Preauthorization	No	**Review Dates**: 09/13, 09/14, 09/15, 09/16, 05/17, 05/18	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With classic choroidal neovascularization due to age-related macular degeneration	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Observation only	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to age-related macular degeneration	Interventions of interest are: • Verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy	Comparators of interest are: • Antivascular endothelial growth factor therapy alone	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to age-related macular degeneration	Interventions of interest are: • Verteporfin photodynamic therapy plus corticosteroids and/or antivascular endothelial growth factor therapy	Comparators of interest are: • Corticosteroids and/or antivascular endothelial growth factor therapy	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to pathologic myopia	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Observation only	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to pathologic myopia	Interventions of interest are: • Verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy	Comparators of interest are: • Antivascular endothelial growth factor therapy alone	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to presumed ocular histoplasmosis	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Photocoagulation • Antivascular endothelial growth factor therapies	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life

Populations	Interventions	Comparators	Outcomes
Individuals: • With choroidal neovascularization due to acute central serous chorioretinopathy	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Observation only • Reduced-dose/-fluence verteporfin	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to chronic central serous chorioretinopathy	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Reduced-dose/-fluence verteporfin photodynamic therapy	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to polypoidal choroidal vasculopathy	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Standard of care • Antivascular endothelial growth factor therapies	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to polypoidal choroidal vasculopathy	Interventions of interest are: • Verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy	Comparators of interest are: • Antivascular endothelial growth factor therapy alone	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to choroidal hemangioma	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to angioid streaks	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With choroidal neovascularization due to inflammatory chorioretinal conditions	Interventions of interest are: • Verteporfin photodynamic therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life

DESCRIPTION

Verteporfin photodynamic therapy (VPDT) is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a two-step process, consisting of an injection of the photosensitizer verteporfin, followed 15 minutes later by laser treatment to the targeted sites of retinal neovascularization. The laser treatment selectively damages the vascular endothelium, thereby occluding choroidal neovascularization (CNV) tissue. Patients may be retreated if leakage from choroidal neovascularization persists.

SUMMARY OF EVIDENCE

AGE-RELATED MACULAR DEGENERATION

For individuals who have classic CNV due to age-related macular degeneration (AMD) who receive VPDT, the evidence includes randomized controlled trials (RCTs) and systematic reviews of controlled trials. Relevant out-

comes are symptoms, change in disease status, functional outcomes, and quality of life. Multiple RCTs have supported the superiority of VPDT in reducing vision loss and decreasing retinal thickness compared with placebo or sham procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CNV due to AMD who receive VPDT plus anti-VEGF therapy, the evidence includes two confirmatory RCTs (and their multiple analyses), multiple smaller RCTs, and a meta-analysis of existing trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. This evidence does not demonstrate improvements in visual acuity using combination therapy compared with antivascular endothelial growth factor (anti-VEGF) monotherapy. Combination therapy may reduce the number of intravitreal injections needed, but this result has not been consistently reported across studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CNV due to AMD who receive VPDT plus corticosteroids and/or anti-VEGF therapy, the evidence includes three small RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The evidence does not demonstrate improvements in visual acuity with combination therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

PATHOLOGIC MYOPIA

For individuals who have CNV due to pathologic myopia who receive VPDT, the evidence includes a subgroup analysis from a large RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The subgroup analysis showed VPDT was more effective than placebo in preventing vision loss at one year but not in the second year. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CNV due to pathologic myopia who receive VPDT plus anti-VEGF therapy, the evidence includes a small RCT and a retrospective cohort study. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The single RCT was likely underpowered to detect a clinically meaningful change in visual acuity outcomes. The retrospective cohort study did not demonstrate improvements in visual acuity with combination treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRESUMED OCULAR HISTOPLASMOSIS

For individuals who have CNV due to presumed ocular histoplasmosis who receive VPDT, the evidence includes a small RCT and a prospective cohort study. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Lack of a control arm in the prospective cohort study and 50% lost to follow-up in the RCT preclude a meaningful interpretation of data of observed improvements in visual acuity outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

CENTRAL SEROUS CHORIORETINOPATHY

For individuals who have CNV due to acute central serous chorioretinopathy who receive VPDT, the evidence includes two RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Although the evidence has demonstrated that full and reduced doses of VPDT result in a small improvement in visual acuity outcomes, the improvements did not meet clinically meaningful thresholds. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CNV due to chronic central serous chorioretinopathy who receive VPDT, the evidence includes multiple retrospective studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Although this relatively large body of retrospective studies has shown that half-dose VPDT yields positive functional and anatomic outcomes while, at the same time, reducing the potential

adverse events associated with conventional VPDT, data from RCTs for multiple VPDT strategies are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLYPOIDAL CHOROIDAL VASCULOPATHY

For individuals who have CNV due to polypoidal choroidal vasculopathy who receive VPDT, the evidence includes several prospective cohort studies and a meta-analysis of two RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Prospective cohort studies have reported favorable anatomic and visual acuity outcomes for patients treated with VPDT. However, RCTs comparing VPDT with anti-VEGF therapies have reported no statistically significant differences in visual acuity outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CNV due to polypoidal choroidal vasculopathy who receive VPDT plus anti-VEGF therapy, the evidence includes two small RCTs, a meta-analysis, and two retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Results of the two RCTs failed to demonstrate statistically significant differences in visual acuity outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

CHOROIDAL HEMANGIOMA

For individuals who have CNV due to choroidal hemangioma who receive VPDT, the evidence includes a systematic review of case series and a prospective cohort study. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Although the prospective cohort suggested a favorable effect of VPDT on various visual acuity and anatomic outcomes in patients with choroidal hemangioma, data from RCTs are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

ANGOID STREAKS

For individuals who have CNV due to angioid streaks who receive VPDT, the evidence includes a systematic review of case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Data from multiple case series have shown conflicting results for visual acuity outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

INFLAMMATORY CHORIORETINAL CONDITIONS

For individuals who have CNV due to inflammatory chorioretinal conditions who receive VPDT, the evidence includes a systematic review of case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Methodologic limitations limit the conclusions drawn from 15 case reports (total N=115 patients) of multiple disease indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Verteporfin photodynamic therapy as monotherapy may be considered **medically necessary** as a treatment of choroidal neovascularization (CNV) associated with age-related macular degeneration, pathologic myopia, presumed ocular histoplasmosis, chronic central serous chorioretinopathy, or choroidal hemangioma.

Verteporfin photodynamic therapy is considered **investigational** as monotherapy for other ophthalmologic disorders.

Verteporfin photodynamic therapy is considered **investigational** when used in combination with one or more of the antivascular endothelial growth factor therapies: pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), or aflibercept (Eylea™) as a treatment of CNV associated with age-related macular

degeneration, pathologic myopia, presumed ocular histoplasmosis, central serous chorioretinopathy, choroidal hemangioma, or for other ophthalmologic disorders.

POLICY GUIDELINES

U.S. Food and Drug Administration (FDA) labeling for verteporfin indicates that the physician should reevaluate the patient every three months and, if CNV leakage is detected on fluorescein angiography, therapy should be repeated. However, the total number of treatments is not addressed by the FDA. Evidence defining when treatment should stop is not available, but experts have suggested stopping "when the situation is judged to be 'futile'". FDA labeling states "safety and efficacy of Visudyne beyond 2 years have not been demonstrated."

Acute central serous chorioretinopathy refers to self-limiting disease that resolves spontaneously over a few months without any treatment. Chronic central serous chorioretinopathy has been defined as a serous macular elevation, visible biomicroscopically or detected by optical coherence tomography, that is associated with retinal pigment epithelial atrophic areas and subtle leaks or ill-defined staining treatment by fluorescein angiography, and which does not resolve spontaneously within a few months.

MEDICARE ADVANTAGE

Ocular photodynamic therapy (OPT) is only **medically necessary** when used in conjunction with verteporfin.

OPT with verteporfin is **medically necessary** for the of subfoveal choroidal neovascularization (CNV) in patients with the wet form of age-related macular degeneration.

OPT with Verteporpin is considered **medically necessary** with a diagnosis of neovascular age-related macular degeneration (AMD) with predominately classic subfoveal choroidal neovascular (CNV) lesions (where the area of classic CNV occupies 50 percent or more of the area of the entire lesion) at the initial visit as determined by a fluorescein angiogram (FA).

There are no requirements regarding visual acuity, lesion size, and number of retreatments when treating predominantly classic lesions.

In addition, OPT with verteporfin is **medically necessary** for treating:

- Subfoveal occult with no classic CNV associated with AMD; and
- Subfoveal minimally classic CNV (where the area of classic CNV occupies less than 50% of the area of the entire lesion) associated with AMD.

The above two indications are considered **medically necessary** only when:

1. The lesions are small (four disk areas or less in size) at the time of initial treatment or within the three months prior to initial treatment; and
2. The lesions have shown evidence of progression within the three months prior to initial treatment. Evidence of progression must be documented by deterioration of visual acuity (at least five letters on a standard eye examination chart), lesion growth (an increase in at least one disk area), or the appearance of blood associated with the lesion.

Use of OPT with verteporfin for other types of AMD is **investigational** for the following:

- a diagnosis of AMD with occult and no classic CNV lesions;
- minimally classic CNV lesions;

- juxtafoveal or extrafoveal CNV lesions (lesions outside the fovea);
- inability to obtain an FA; or
- atrophic or "dry" AMD.

BACKGROUND

VISION LOSS

Severe vision loss can occur with ocular neovascularization, the growth of abnormal blood vessels in the retina or choroid. Neovascularization occurs in a number of ocular diseases, including AMD.

Age-Related Macular Degeneration

AMD is a degenerative disease of the retina that results in loss of central vision. Two distinctive forms, known as dry and wet degeneration, may be observed. The dry form (also known atrophic or areolar) is more common and is often a precursor of the wet form (also known as exudative neovascular or disciform). The wet form is more devastating and characterized by serous or hemorrhagic detachment of the retinal pigment epithelium and development of CNV, which greatly increases the risk of developing severe irreversible loss of vision. CNV is categorized as classic or occult. Classic CNV appears as an initial lacy pattern of hyperfluorescence followed by more irregular patterns as the dye leaks into the subretinal space. Occult CNV lacks the characteristic angiographic pattern. Classic CNV carries a worse prognosis for vision than occult CNV, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of AMD.

Pathologic Myopia

Pathologic myopia refers to an abnormal elongation of the eye associated with severe near-sightedness. It generally occurs among people older than 30 years of age and can result in a progressive, severe loss of vision, frequently related to the development of CNV. VPDT has also been investigated in patients with CNV related to pathologic myopia. Antivascular endothelial growth factor (anti-VEGF) therapy is now considered a first-line intervention in patients with myopic CNV.

Presumed Ocular Histoplasmosis

Presumed ocular histoplasmosis may be the second most common cause of blindness in patients younger than 50 years of age in certain endemic areas (Ohio and Mississippi River Valleys in the United States). This condition is characterized by a positive skin test for histoplasmosis, miliary opacities of the lungs, tiny choroidal scars, peripapillary disruption of the choriocapillaris, and exudation or hemorrhage from choroidal lesions in or near the macula. The condition is asymptomatic and benign, unless the CNV lesions, which may develop many years after chorioretinal scarring has taken place, affect the macula.

Central Serous Chorioretinopathy

Central serous chorioretinopathy (CSC) refers to an idiopathic disease in which there is a serous detachment of the macula due to leakage of fluid from the choriocapillaris through the retinal pigment epithelium. This condition is avascular; however, neovascularization can occur as a secondary complication. In most cases, CSC resolves spontaneously in three to four months. However, in a few cases, chronic progression or recurrence can lead to the progressive decline of visual acuity. CSC has been treated with medication and laser photocoagulation, but these treatments have limited efficacy. Multiple definitions have been used in the literature to classify CSC as acute or chronic based cutoff time points (e.g., persistent fluid for less than three, four or six months) or less frequently based on the timing of treatment. For example, acute CSC defined as the first attempted treatment to improve visual acuity, and chronic CSC is defined as being refractory to treatment. Further, multiple VPDT strategies that use either reduced-dose or half-fluency have been evaluated for the treatment of CSC

because full-dose VPDT used in AMD has shown a potentially higher risk of developing choroidal ischemia and retinal atrophic changes.

Polypoidal Choroidal Vasculopathy

Polypoidal choroidal vasculopathy arises primarily from abnormal choroidal circulation, resulting in characteristic lesions comprising well-defined vascular networks of vessels ending in polyp-like structures. A less common subtype is polypoidal CNV, and it may be considered a subtype of AMD. Eyes that develop a cluster of grape-like polypoidal dilations are at high risk for severe vision loss.

Choroidal Hemangioma

Choroidal hemangioma is an uncommon, benign vascular tumor, manifesting as an orange-red mass in the posterior pole of the eye. Visual loss may be progressive and irreversible because of chronic foveal detachment.

Angioid Streaks

Angioid streaks result from crack-like breaks in the Bruch membrane (the innermost layer of the choroid) and occur in patients spontaneously or due to blunt trauma or associated with some systemic diseases such as pseudoxanthoma elasticum, Paget disease of bone, or sickle hemoglobinopathy. Vision loss in eyes with angioid streaks occurs most frequently as a result of CNV.

Treatment

Available therapeutic options for CNV include anti-VEGF inhibitors, VPDT, antioxidants, thermal laser photocoagulation, and corticosteroids. The safety and efficacy of each treatment depends on the form and location of the neovascularization.

VPDT is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a two-step process, consisting of an injection of the photosensitizer verteporfin, followed 15 minutes later by laser treatment to the targeted sites of retinal neovascularization. The laser treatment selectively damages the vascular endothelium and occludes the neovacularized tissue. Patients may be retreated if leakage from CNV persists.

Monotherapy with VEGF inhibitors is now standard treatment of CNV due to AMD and pathologic myopia. Combining VPDT with anti-VEGF inhibitors, concurrently or sequentially, has a biologic basis and has been investigated in multiple trials particularly in the treatment of CNV due to AMD and pathologic myopia.

REGULATORY STATUS

In 2000, verteporfin (Visudyne®; Novartis), an intravenous photodynamic therapy agent, was approved by the U.S. Food and Drug Administration for the treatment of AMD in patients with predominantly classic subfoveal CNV. Subsequently, in 2001, the indication was expanded to include presumed ocular histoplasmosis and pathologic myopia.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced

procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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