

Protocol

Photodynamic Therapy for Choroidal Neovascularization

(90308)

Medical Benefit		Effective Date: 10/01/18	Next Review Date: 05/23
Preauthorization	No	Review Dates: 09/13, 09/14, 09/15, 09/16, 05/17, 05/18, 05/19, 05/20, 05/21, 05/22	

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.

RELATED PROTOCOL

None

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With classic choroidal neovascularization due to age-related macular degeneration 	Interventions of interest are: <ul style="list-style-type: none"> Verteporfin photodynamic therapy 	Comparators of interest are: <ul style="list-style-type: none"> Observation only 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Functional outcomes Quality of life
Individuals: <ul style="list-style-type: none"> With choroidal neovascularization due to age-related macular degeneration 	Interventions of interest are: <ul style="list-style-type: none"> Verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy 	Comparators of interest are: <ul style="list-style-type: none"> Antivascular endothelial growth factor therapy alone 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Functional outcomes Quality of life
Individuals: <ul style="list-style-type: none"> With choroidal neovascularization due to age-related macular degeneration 	Interventions of interest are: <ul style="list-style-type: none"> Verteporfin photodynamic therapy plus corticosteroids and/or antivascular endothelial growth factor therapy 	Comparators of interest are: <ul style="list-style-type: none"> Corticosteroids and/or antivascular endothelial growth factor therapy 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Functional outcomes Quality of life
Individuals: <ul style="list-style-type: none"> With choroidal neovascularization due to pathologic myopia 	Interventions of interest are: <ul style="list-style-type: none"> Verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy 	Comparators of interest are: <ul style="list-style-type: none"> Antivascular endothelial growth factor therapy alone 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Functional outcomes Quality of life
Individuals: <ul style="list-style-type: none"> With choroidal neovascularization due to presumed ocular histoplasmosis 	Interventions of interest are: <ul style="list-style-type: none"> Verteporfin photodynamic therapy 	Comparators of interest are: <ul style="list-style-type: none"> Photocoagulation Antivascular endothelial growth factor therapies 	Relevant outcomes include: <ul style="list-style-type: none"> 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 photodynamic therapy	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 angiod 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 is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a 2-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 tissue. Patients may be retreated if leakage from choroidal neovascularization persists.

SUMMARY OF EVIDENCE**AGE-RELATED MACULAR DEGENERATION**

For individuals who have classic choroidal neovascularization due to age-related macular degeneration who receive verteporfin photodynamic therapy, the evidence includes randomized controlled trials (RCTs) and systematic reviews of controlled trials. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Multiple RCTs have supported the superiority of verteporfin photodynamic therapy 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 an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to age-related macular degeneration who receive verteporfin photodynamic therapy plus antivascular endothelial growth factor therapy, the evidence includes 2 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 anti-vascular endothelial growth factor 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 that the technology results in an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to age-related macular degeneration who receive verteporfin photodynamic therapy plus corticosteroids and/or antivascular endothelial growth factor therapy, the evidence includes 3 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 that the technology results in an improvement in the net health outcome.

Pathologic Myopia

For individuals who have choroidal neovascularization due to pathologic myopia who receive verteporfin photodynamic therapy, the evidence includes a subgroup analysis from large RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The subgroup analysis showed verteporfin photodynamic therapy 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 an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to pathologic myopia who receive verteporfin photodynamic therapy plus antivascular endothelial growth factor 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 that the technology results in an improvement in the net health outcome.

Presumed Ocular Histoplasmosis

For individuals who have choroidal neovascularization due to presumed ocular histoplasmosis who receive verteporfin photodynamic therapy, 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 that the technology results in an improvement in the net health outcome.

Central Serous Chorioretinopathy

For individuals who have choroidal neovascularization due to acute central serous chorioretinopathy who receive verteporfin photodynamic therapy, the evidence includes 2 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 verteporfin photodynamic therapy result in a small improvement in visual acuity outcomes, the improvements did not meet clinically meaningful thresholds. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to chronic central serous chorioretinopathy who receive verteporfin photodynamic therapy, 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 verteporfin photodynamic therapy yields positive functional and anatomic outcomes while, at the same time, reducing the potential adverse events associated with conventional verteporfin photodynamic therapy, data from RCTs for multiple verteporfin photodynamic therapy strategies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Polypoidal Choroidal Vasculopathy

For individuals who have choroidal neovascularization due to polypoidal choroidal vasculopathy who receive verteporfin photodynamic therapy, the evidence includes several prospective cohort studies and a meta-analysis of 2 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 verteporfin photodynamic therapy. However, RCTs comparing verteporfin photodynamic therapy with anti-vascular endothelial growth factor therapies have reported no statistically significant differences in visual acuity outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have choroidal neovascularization due to polypoidal choroidal vasculopathy who receive verteporfin photodynamic therapy plus anti-vascular endothelial growth factor therapy, the evidence includes 3 small RCTs, a meta-analysis, and 2 retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Results of the RCTs failed to demonstrate statistically significant differences in visual acuity outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Choroidal Hemangioma

For individuals who have choroidal neovascularization due to choroidal hemangioma who receive verteporfin photodynamic therapy, 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 verteporfin photodynamic therapy on various visual acuity and anatomic outcomes in patients with choroidal hemangioma, data from RCTs are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Angioid Streaks

For individuals who have choroidal neovascularization due to angioid streaks who receive verteporfin photodynamic therapy, 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 that the technology results in an improvement in the net health outcome.

Inflammatory Chorioretinal Conditions

For individuals who have choroidal neovascularization due to inflammatory chorioretinal conditions who receive verteporfin photodynamic therapy, 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 that the technology results in an improvement in the net health outcome.

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 two 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 by fluorescein angiography, it 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 **not medically necessary** 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 age-related macular degeneration.

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration 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 as 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 choroidal neovascularization, which greatly increases the risk of developing severe irreversible loss of vision. Choroidal neovascularization is categorized as classic or occult. Classic choroidal neovascularization appears as an initial lacy pattern of hyperfluorescence followed by more irregular patterns as the dye leaks into the subretinal space. Occult choroidal neovascularization lacks the characteristic angiographic pattern. Classic choroidal neovascularization carries a worse prognosis for vision than occult choroidal neovascularization, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of age-related macular degeneration.

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 choroidal neovascularization. Verteporfin photodynamic therapy has also been investigated in patients with choroidal neovascularization related to pathologic myopia. Antivascular endo-

thelial growth factor therapy is now considered a first-line intervention in patients with myopic choroidal neovascularization.

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 choroidal neovascularization lesions, which may develop many years after chorioretinal scarring has taken place, affect the macula.

CENTRAL SEROUS CHORIORETINOPATHY

Central serous chorioretinopathy 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, central serous chorioretinopathy resolves spontaneously in 3 to 4 months. However, in a few cases, chronic progression or recurrence can lead to the progressive decline of visual acuity. Central serous chorioretinopathy has been treated with medication and laser photocoagulation, but these treatments have limited efficacy. Multiple definitions have been used in the literature to classify central serous chorioretinopathy as acute or chronic based cutoff time points (e.g., persistent fluid for <3, 4 or 6 months) or less frequently based on the timing of treatment. For example, acute central serous chorioretinopathy defined as the first attempted treatment to improve visual acuity, and chronic central serous chorioretinopathy is defined as being refractory to treatment. Further, multiple verteporfin photodynamic therapy strategies that use either reduced-dose or half-fluency have been evaluated for the treatment of central serous chorioretinopathy because full-dose verteporfin photodynamic therapy used in age-related macular degeneration 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 choroidal neovascularization, and it may be considered a subtype of age-related macular degeneration. 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 choroidal neovascularization.

Treatment

Available therapeutic options for choroidal neovascularization include antivascular endothelial growth factor inhibitors, verteporfin photodynamic therapy, antioxidants, thermal laser photocoagulation, and corticosteroids. The safety and efficacy of each treatment depends on the form and location of the neovascularization.

Verteporfin photodynamic therapy is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a 2-step process, consisting of an injection of the photosensitizer verteporfin, fol-

lowed 15 minutes later by laser treatment to the targeted sites of retinal neovascularization. The laser treatment selectively damages the vascular endothelium and occludes the neovascularized tissue. Patients may be retreated if leakage from choroidal neovascularization persists.

Monotherapy with vascular endothelial growth factor inhibitors is now standard treatment of choroidal neovascularization due to age-related macular degeneration and pathologic myopia. Combining verteporfin photodynamic therapy with antivascular endothelial growth factor inhibitors, concurrently or sequentially, has a biologic basis and has been investigated in multiple trials particularly in the treatment of choroidal neovascularization due to age-related macular degeneration and pathologic myopia.

The use of verteporfin photodynamic therapy in choroidal neovascularization has decreased substantially with the availability of antivascular endothelial growth factor therapy. Subsequent to U.S. Food and Drug Administration (FDA) approval of verteporfin photodynamic therapy in 2000, the FDA approved pegaptanib in 2004 and ranibizumab in 2006 for treatment of age-related macular degeneration related choroidal neovascularization. The approval of pegaptanib was based on a sham-controlled RCT^{1,2} while ranibizumab was approved based on a head-to-head comparison with verteporfin photodynamic therapy in the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trial.³ Intravitreal injections of antivascular endothelial growth factor drugs such as ranibizumab and bevacizumab have shown superior efficacy compared with verteporfin photodynamic therapy in multiple head-to-head trials. Currently, verteporfin photodynamic therapy is used for patients in whom vascular endothelial growth factor inhibitors are contraindicated or for those who fail to benefit from vascular endothelial growth factor inhibitors.

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 age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization. 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 and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services 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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70. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Determination (LCD): Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394), Revision Effective Date for services performed on or after 11/07/2019.