

<b>Subject: Visudyne (verteporfin) Ocular Photodynamic Therapy</b>	<b>Original Effective Date: 7/10/2018</b>
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### DISCLAIMER

*This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.*

### SUMMARY OF EVIDENCE/POSITION

This policy addresses **Ocular Photodynamic Therapy utilizing Visudyne (verteporfin)** for the treatment of adult patients with **predominately classic subfoveal choroidal neovascularization associated with age-related macular degeneration, pathologic myopia, or ocular histoplasmosis** when appropriate criteria are met.

- ⌘ Choroidal neovascularization (CNV) develops when newly formed blood vessels from the choroid grow through the Bruch membrane and proliferate under the retina. This often leads to exudation and hemorrhage that ultimately damage the photoreceptors and contribute to visual loss.
  - ◆ CNV disrupts the anatomy of the retinal pigment epithelium-photoreceptor complex, leaks serum and sometimes blood, and frequently is accompanied by irreversible scar formation that is associated with loss of photoreceptors; CNV is a major cause of vision loss in developed countries.
  - ◆ Based on fluorescein angiographic assessments, choroidal neovascular lesions are defined as classic or occult. Classic CNV membranes are clearly delineated and leak fluorescein uniformly, while occult membranes are often hidden or their extent is hard to delineate, and fluorescein leakage is patchy. Some lesions may have both classic and occult components.
  - ◆ CNV is seen most often in patients with age-related macular degeneration; however, choroidal neovascularization also occurs as a consequence of pathologic myopia, the ocular histoplasmosis syndrome, angioid streaks, or idiopathic causes (Sickenberg M, Schmidt-Erfurth U, et al. 2000)
  - ◆ Available therapeutic options for CNV include photodynamic therapy, antioxidants, thermal laser photocoagulation, corticosteroids, and vascular endothelial growth factor inhibitors.
  
- ⌘ **Photodynamic therapy (PDT)** involves intravenous injection of the photosensitizing dye verteporfin just prior to treatment with a photo-activating laser applied through the eye with a specific contact lens. The activated dye forms reactive free radicals that damage the vascular endothelium and result in thrombosis of the neovascular tissue that retains dye more avidly than normal vessels. However, these vessels often reopen.<sup>UpToDate (Arroyo, JG)</sup> As an example, 33 percent of 108 eyes in one study showed evidence of recurrent choroidal neovascularization at 18 months following a course of PDT (Potter MJ). Retreatment with PDT is safe.<sup>UpToDate (Arroyo, JG)</sup> The role for PDT has decreased with the increasing use of anti-VEGF therapy. PDT (with or without intravitreal bevacizumab, aflibercept, or ranibizumab) is recommended for patients who fail to respond to initial anti-VEGF therapies.<sup>UpToDate (Arroyo, JG)</sup>

#### ⌘ **Visudyne (verteporfin for injection) therapy**

Verteporfin is a light-activated drug used in photodynamic therapy (PDT). Once verteporfin is activated by light in the presence of oxygen, highly reactive, short-lived reactive oxygen radicals are generated. Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion.

**A course of verteporfin therapy two-stage process requiring administration of both verteporfin for injection and nonthermal red light.** The first step is the intravenous infusion of verteporfin. The second step is the activation of verteporfin with light from a nonthermal diode laser. Detailed in the manufacturer's labeling.

- ◆ Verteporfin (Visudyne) was FDA approved in April 12, 2000 for the treatment of predominately classic subfoveal CNV associated with wet age-related macular degeneration, pathologic myopia, or ocular histoplasmosis.
- ◆ **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).
- ◆ Due to the potential of PDT for selective tissue injury, it offers advantages over conventional laser treatments. The potential to selectively affect CNV is attributable to preferential localization of the photosensitizer dye to the CNV complex and irradiation of the complex with light levels far lower than required for thermal injury.

- ◆ The most frequently reported adverse events in clinical trials associated with verteporfin include injection site reactions, pain inflammation, extravasation, rashes, hemorrhage, and visual disturbances which occurred in clinical trials at a rate of between 10%-30% of patients. Verteporfin is contraindicated in patients with porphyria or hypersensitivity to any component of the verteporfin preparation.
- ⌘ **The American Academy of Ophthalmology (AAO) guideline states that verteporfin is still an approved option for AMD, even though VEGF 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).
- ⌘ In the ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularisation in AMD (ANCHOR) trial, the number of patients that lost fewer than 15 letters at 12 months was achieved by 96.4% of patients treated with Lucentis 0.5 mg compared to 64.3% of patients treated with Visudyne (p<0.001). Rate of intraocular inflammation was higher for patients treated with Lucentis 0.5 mg at 15% compared to Visudyne at 2.8%.
- ⌘ **Re-treatment may be indicated as frequently as every 3 months based on the appearance of leakage on fluorescein angiography. However, the appropriate frequency of repeat treatments and how many total treatments a patient might need during the course of clinical management of their neovascular AMD is not defined. There is also no clear definition of treatment failure and, therefore, no method of determining when treatment should be terminated. The current data suggest a benefit of PDT with verteporfin for up to 2 years; however, there are no data for longer time periods.**

## FDA INDICATIONS

### Subfoveal choroidal neovascularization

Treatment of predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis.

#### *Limitations of use*

There is insufficient evidence to indicate verteporfin for the treatment of predominately occult subfoveal choroidal neovascularization.

Available As: 15 mg single-use vial

FDA Approved: April 2000

Visudyne two-step combination drug and device treatment process received new drug application (NDA) approval for use in the treatment of macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

- ◆ *This approval covered verteporfin for injection and two laser systems for photoactivation of verteporfin: the Coherent Opal Photoactivator Laser Console and LaserLink Adapter (Coherent- AMT, Ontario Canada), and the Zeiss VISULAS 690s laser and VISULINK PDT adapter (Zeiss Humphrey Systems, Dublin CA).*

August 22, 2001, the FDA granted additional approval to Visudyne for the treatment of patients with predominantly classical subfoveal choroidal neovascularization due to presumed ocular histoplasmosis syndrome or pathologic myopia.

Black Box Warnings/REMS: None at the time of this writing

CLASSIFICATION: Ophthalmic Agent; Photosensitizing Agents

## COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

**Visudyne (Verteporfin) in conjunction with Ocular Photodynamic Therapy (OPT)** may be authorized if **ALL** of the following criteria are met: **[ALL]**

### 1. Prescriber specialty **[ONE]**

- Prescribed by board-certified ophthalmologists or retinal specialist experienced in the treatment of retinal diseases. Treatment and monitoring must be retained by the Prescriber/Specialist.

### 2. Diagnosis/Indication **[ALL]**

Prescriber submit **ALL** supporting documentation and clinical rationale (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*): **[ALL]**

- Member meets **ONE (1)** of the following with documentation: **[ONE: A, B, OR C]**
  - A.** Predominantly classic subfoveal Choroidal Neovascularization (CNV) (wet macular degeneration; classic component comprises > 50% of the entire lesion area) **[ALL]**
    - Diagnosis of neovascular wet age-related macular degeneration (AMD)
      - ◆ *Photodynamic therapy with verteporfin is not recommended for use in the less severe, dry form of macular degeneration in which neovascularization is not present (AHFS 2020)*
    - Predominantly classic subfoveal CNV where the area of *classic* CNV<sup>†</sup> occupies at least 50% of the entire lesion (with a greatest linear dimension that is equal to or less than 7000-7500 microns) as demonstrated by a **fluorescein angiogram (FA)**
      - ◆ *Photodynamic therapy (PDT) with verteporfin was not associated with clinical benefit in patients in which the classic component comprised less than 50% of the area of the lesion (AHFS 2020).*

**B. Presentation of ONE (1) of the following: [1 or 2]**

1. Subfoveal occult with no classic choroidal neovascularization associated with AMD  
**OR**
2. Subfoveal minimally classic choroidal neovascularization [where the area of classic CNV occupies < 50% of the area of the entire lesion] associated with AMD

**AND BOTH of the following: [BOTH: a AND b]**

- a. Lesions are small (4 disk areas or less in size) at the time of initial treatment or within the 3 months prior to initial treatment, **AND**
- b. Lesions have shown evidence of progression within the 3 months prior to initial treatment. Evidence of progression must be documented by deterioration of visual acuity (at least 5 letters on a standard eye examination chart), lesion growth (an increase in at least 1 disk area), or the appearance of blood associated with the lesion.

**C. Predominantly classic subfoveal CNV [when the area of classic CNV occupies at least 50% of the area of the entire lesion] associated with macular degeneration, secondary to: [ONE]**

- Infection by *Histoplasma capsulatum*, retinitis  
or
- Pathologic myopia; Progressive high (degenerative) myopia

**NOTE: Subsequent requests require either an optical coherence tomography (OCT) report or a fluorescein angiogram (FA) to assess treatment response and should include the description of the lesion (e.g., predominantly classic), unless there is a documented history of fluorescein allergy.**

**3. Age/Gender/Restrictions [ALL]**

- 18 years of age or older
  - ◆ *Safety and efficacy not established in pediatric patients 18 years of age and younger.*

#### 4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

Documentation for ALL of the following must be submitted for review.

- Disease progression after use of an anti-vascular endothelial growth factor (VEGF) as first-line treatment (include date(s) of failed therapy or clinical event). Documentation required. [ONE]
  - bevacizumab (Avastin): PREFERRED/NO PA REQUIRED**
  - ranibizumab (Lucentis)
  - aflibercept (Eylea)
  - pegaptanib (Macugen)

**EXCEPTIONS:** Clinically significant adverse effects, labeled contraindication, or clinical rationale supporting the inappropriateness to VEGF Inhibitor therapies. Documentation required.

*Informational Note:*

- ◆ *Laser photocoagulation therapy and verteporfin are therapeutic options for selected patients that VEGF inhibition is not advisable (evidence level 1). [Reference: Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA)]*
  - ◆ *RADIANCE: A Randomized Controlled Study of Ranibizumab in Patients with Choroidal Neovascularization Secondary to Pathologic Myopia (Wolf S, et al. 2014): Ranibizumab treatment, irrespective of retreatment criteria, provided superior BCVA gains versus vPDT up to month 3. Ranibizumab treatment guided by disease activity criteria was non-inferior to VA stabilization criteria up to month 6. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV.*
- 
- Requested Visudyne (verteporfin) therapy will be used in combination with photodynamic therapy--OPT is only covered when used in conjunction with verteporfin.
  - NOT** prescribed for, or intended for concurrent or combination with/for ANY of the following treatments or conditions: [ANY]
    - Bilateral treatment **UNLESS** member had previous verteporfin therapy, with an acceptable safety profile, then treatment of both eyes concurrently (approximately 3 months after the initial treatment) may be considered. Documentation required.
      - ◆ *Use in more than one eye has not been studied; however, it is recommended that in patients requiring treatment in both eyes, initial treatment should be applied to the more aggressive lesion first, and after safe and effective treatment to the initial eye, the second eye may be treated 1 week later. After approximately 3 months and an acceptable safety profile with initial treatment, both eyes may be treated concurrently. Treat the more aggressive lesion first, followed immediately with the second eye.*

- Concurrent or combination therapy with Vascular Endothelial Growth Factor (VEGF) Inhibitors [**bevacizumab (Avastin)**; ranibizumab (Lucentis); pegaptanib (Macugen); aflibercept (Eylea)]

*Informational Note:*

- ◆ *The American Academy of Ophthalmology (AAO) guideline states that verteporfin is still an approved option for AMD, even though VEGF 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).*
- ◆ *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).*

## 5. Contraindications/Exclusions [ANY]

Authorization for Verteporfin (Visudyne) will not be authorized if ANY of the following conditions apply [ANY]

Contraindications

- Hypersensitivity to verteporfin or any component of the formulation
- Porphyria or other porphyrin sensitivity

Exclusions

- Atrophic or “dry” AMD
- Inability to obtain an adequate, legible fluorescein angiogram or OCT to document CNV (including difficulty with venous access) unless there is a documented history of fluorescein allergy as required per diagnosis criteria

Warnings/Precautions

Active hepatitis or clinically significant liver disease, should be cleared by an appropriate medical evaluation

- ◆ *A decision to use photodynamic therapy with verteporfin in patients with moderate to severe hepatic impairment or biliary obstruction should be carefully considered since there is no clinical experience with this therapy in such patients.*

## 6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member’s medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included. **NOTE:** Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

- Member has been informed about the potential adverse effects of Ocular Photodynamic Therapy (OPT) with Verteporfin
- Requested therapy for use in which affected eye: [APPLICABLE]
  - Right eye
  - Left eye
- Prescriber submit total calculated drug dose (mg) of the photodynamic therapy drug to be administered and the member’s body surface area on which the dose of the drug is based

## REAUTHORIZATION /CONTINUATION OF THERAPY

**Visudyne (Verteporfin) in conjunction with Ocular Photodynamic Therapy (OPT)** may be authorized for continuation of therapy if **ALL** of the following criteria are met: **[ALL]**

### 1. Initial Coverage Criteria **[ALL]**

- Reauthorization request is for the **same eye** as initial authorization AND 3 months since the previous Ocular Photodynamic Therapy (OPT) with Verteporfin

**NOTE:** The continuation of therapy criteria is only for the same previously treated eye. If member has developed condition in an untreated eye, a new request should be submitted and meet all initial coverage criteria.

**NOTE:** Use in more than one eye has not been studied; however, it is recommended that in patients requiring treatment in both eyes, initial treatment should be applied to the more aggressive lesion first, and after safe and effective treatment to the initial eye, the second eye may be treated 1 week later. After approximately 3 months and an acceptable safety profile with initial treatment, both eyes may be treated concurrently.

- Member continues to meet initial coverage criteria AND member's continued need for treatment has been formally assessed and documentation submitted for review

### 2. Compliance: N/A

### 3. Labs/Reports/Documentation required **[ALL APPLICABLE]**

Prescriber submit ALL supporting documentation and clinical rationale **[ALL APPLICABLE]**

- Clinical evidence of deterioration as demonstrated by persistent fluorescein leakage from CNV: Recurrent or persistent choroidal neovascular leakage indicated by a **recent fluorescein angiography**, conducted at least 3 months after the last treatment

**NOTE:** Re-treatment is necessary if fluorescein angiograms or OCT show any signs of recurrence or persistence of leakage.

- Member is likely to benefit from re-treatment without being exposed to significant risk according to Prescriber



#### 4. Discontinuation of Treatment [ANY]

Authorization for Ocular Photodynamic Therapy (OPT) with Verteporfin will not be authorized if ANY of the following conditions apply [ANY]

- Atrophic or “dry” AMD
- Inability to obtain an adequate, legible fluorescein angiogram or OCT to document CNV (*including difficulty with venous access*) unless there is a documented history of fluorescein allergy
- No evidence of CNV leakage (as determined by fluorescein angiography or OCT)
- Contraindications/Exclusions to therapy

Ocular Photodynamic Therapy (OPT) with Verteporfin will not be authorized if ANY of the following conditions apply [ANY]

- Hypersensitivity to verteporfin or any component of the formulation
- Porphyria or other porphyrin sensitivity.

- EXCEPTIONS** to the above criteria may be reviewed on a case-by-case basis with relevant, supporting documentation from Prescriber

### ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

*Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.*

#### 1. Recommended Dosage [ONE]

- Subfoveal choroidal neovascularization (Adults): 6 mg/m<sup>2</sup> IV every 3 months as needed; administer light delivery 15 minutes after the start of the infusion
  - IV infusion: 6 mg/m<sup>2</sup> body surface area (BSA) administered IV over 10 minutes at a rate of 3 mL/min.
  - Light: 50 J/cm<sup>2</sup> of neovascular lesion administered at an intensity of 600 mW/cm<sup>2</sup>. This dose is administered over 83 seconds.
  - Duration of therapy: The health care provider should reevaluate the patient every 3 months and if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated.
- Pediatrics: Safety and efficacy in pediatric patients have not been established for Verteporfin

## 2. Authorization Limit [ALL]

- Quantity Limit: [ALL]
  - Total calculated drug dose (mg) of the photodynamic therapy drug to be administered and the member's body surface area on which the dose of the drug is based does **not** exceed **6 mg/m<sup>2</sup> BSA administered every three months PER EYE**
  - Up to four treatments per eye (every 3 months) per year **AND** NOT TO EXCEED TWO (2) YEARS  
*Informational Note: Safety and efficacy have not been established of use for longer than 2 years*

## 3. Route of Administration [ALL]

- Visudyne (Verteporfin) Photodynamic Therapy is considered a **provider-administered** procedure to be performed in a **provider office, outpatient setting** by a qualified ophthalmologist experienced in intravitreal injections.
- Administration of Visudyne (Verteporfin) Photodynamic Therapy (*record in the procedure or post-procedure note following the completion of treatments*). Documentation of the following information required for review and submission of requests for subsequent treatment(s):
  - Dose and frequency
  - Treated eye: right eye, left eye, or both eyes
- Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

## COVERAGE EXCLUSIONS

This policy addresses **Ocular Photodynamic Therapy utilizing Visudyne (verteporfin)** for the treatment of adult patients with **predominately classic subfoveal choroidal neovascularization associated with age-related macular degeneration, pathologic myopia, or ocular histoplasmosis** when appropriate criteria are met.

All other uses of Visudyne (verteporfin) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

### ❑ Central Serous Chorioretinopathy (CSCR)

- Currently, there are no FDA approved therapeutic options for managing this condition. Although half-fluence PDT has been considered as a viable option for treatment, there is no general consensus in regard to the use of this option for managing chronic CSCR.
- Lai et al. investigated the long-term efficacy and prognostic factors of half-dose photodynamic therapy (PDT) in chronic central serous chorioretinopathy (CSCR); however, the study was based on a retrospective evaluation of past data (Lai FH, et al 2016). A review of the PubMed database yields mostly retrospective studies and case series. There is currently not enough evidence to support the use of Visudyne/PDT for this indication. [AMR Review 2018](#)

- ❑ Simultaneous use of Visudyne (verteporfin) in **combination with anti-angiogenic agents** for the treatment of CNV due to AMD experimental and investigational because the safety and effectiveness of such combination therapy has not been established.

\*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

*\*FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

**Choroidal neovascularization** is seen most often in patients with age-related macular degeneration; however, choroidal neovascularization also occurs as a consequence of pathologic myopia, the ocular histoplasmosis syndrome, angioid streaks, or idiopathic causes. Choroidal neovascularization disrupts the anatomy of the retinal pigment epithelium-photoreceptor complex, leaks serum and sometimes blood, and frequently is accompanied by irreversible scar formation that is associated with loss of photoreceptors; choroidal neovascularization is a major cause of vision loss in developed countries. Based on fluorescein angiographic assessments, choroidal neovascular lesions are defined as classic or occult. (AHFS 2018)

**Age-related macular degeneration (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).

- 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 ocular photodynamic therapy (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.
- 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).

Photodynamic therapy with verteporfin has been evaluated in 2 double-blind, placebo-controlled studies in patients with classic-containing subfoveal choroidal neovascularization secondary to age-related macular degeneration (AHFS 2018). Patients enrolled in these studies were randomized (2:1 randomization) to receive verteporfin or placebo followed by activation with non-thermal laser light; treatment with the same regimen was repeated every 3 months in patients with leakage from classic or occult lesions as determined by fluorescein angiogram. Results of these studies at 12 and 24 months indicate that multiple treatments with photodynamic therapy that includes verteporfin improved or maintained visual acuity, contrast sensitivity, and fluorescein angiographic outcomes in patients with predominantly classic choroidal neovascular lesions (classic component comprised 50% or more of the area of the entire lesion). At 12 or 24 months, 67 or 59% of verteporfin-treated patients with predominantly classic choroidal neovascular lesions had lost less than 3 lines (15 letters on the Early Treatment of Diabetic Retinopathy Study chart) of visual acuity compared with 40 or 31% of placebo-treated patients, respectively. Visual acuity loss of 6 lines or more was experienced by 12 or 15% of verteporfin-treated patients versus 34 or 36% of placebo-treated patients at 12 or 24 months, respectively. Approximately 77 or 27% of verteporfin- or placebo-treated patients, respectively, with classic lesions (no occult lesions) had lost less than 3 lines of visual acuity at 12 months (AHFS 2018).

#### **RADIANCE: A Randomized Controlled Study of Ranibizumab in Patients with Choroidal Neovascularization Secondary to Pathologic Myopia (Wolf S, et al. 2014)**

- This study compared the efficacy and safety of ranibizumab 0.5 mg, guided by visual acuity (VA) stabilization or disease activity criteria, versus verteporfin photodynamic therapy (vPDT) in patients with visual impairment due to myopic choroidal neovascularization (CNV)
- Phase III, 12-month, randomized, double-masked, multicenter, active-controlled study
- Participants: Patients (N=277) with visual impairment due to myopic CNV
- Patients were randomized to receive ranibizumab on day 1, month 1, and thereafter as needed guided by VA stabilization criteria (group I, n=106); ranibizumab on day 1 and thereafter as needed guided by disease activity criteria (group II, n=116); or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (group III, n=55).
- Main Outcome Measures: Ranibizumab treatment in groups I and II was superior to vPDT based on mean average BCVA change from baseline to month 1 through month 3 (group I: +10.5, group II: +10.6 vs. group III: +2.2 Early Treatment Diabetic Retinopathy Study [ETDRS] letters; both  $P < 0.0001$ ). Ranibizumab treatment guided by disease activity was noninferior to VA stabilization-guided retreatment based on mean average BCVA change from baseline to month 1 through month 6 (group II: +11.7 vs. group I: +11.9 ETDRS letters;  $P < 0.00001$ ). Mean BCVA change from baseline to month 12 was +13.8 (group I), +14.4 (group II), and +9.3 ETDRS letters (group III). At month 12, 63.8% to 65.7% of patients showed resolution of myopic CNV leakage. Patients received a median of 4.0 (group I) and 2.0 (groups II and III) ranibizumab injections over 12 months. No deaths or cases of endophthalmitis and myocardial infarction occurred. No deaths or cases of endophthalmitis and myocardial infarction occurred.
- **Conclusions: Ranibizumab treatment, irrespective of retreatment criteria, provided superior BCVA gains versus vPDT up to month 3.** Ranibizumab treatment guided by disease activity criteria was non-inferior to VA stabilization criteria up to month 6. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV.

ClinicalTrials.gov NCT01217944.

### Combining anti-angiogenic treatment with Visudyne PDT in the management of CNV due to AMD

- ◆ Treatments for CNV due to AMD can be directed at either the vascular component of CNV or the angiogenic component that leads to the development of the condition. Verteporfin targets the vascular component, whereas anti-angiogenic agents (such as pegaptanib and ranibizumab) target key mediators of the angiogenic cascade. The different mechanisms of action of these approaches offer the potential for additive or synergistic effects with combination therapy. In addition, anti-angiogenic agents might counteract up-regulation of angiogenic factors (including VEGF) that occur after verteporfin PDT.
- ◆ Kaiser (2007) discussed the rationale for combining anti-angiogenic treatment with Visudyne PDT in the management of CNV due to AMD and evaluated available evidence for the therapeutic benefits of such approaches.
  - Phase III trial comparing number of patients losing at least 15 lines, gaining at least 15 lines, and overall visual acuity after 12 months found ranibizumab superior to verteporfin in all three categories 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)
  - Results consistent at 24 months
  - The author concluded that the use of anti-angiogenic agents in combination with verteporfin may have the potential to improve visual outcomes and reduce the number of treatments in eyes with CNV due to AMD, and **requires further evaluation in randomized, controlled clinical trials.**

### Meta-analyses and Systematic Reviews

- 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).
- 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 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).

## DEFINITIONS

**Age-Related Macular Degeneration (AMD):** A medical condition which usually affects older adults and results in a loss of vision in the center of the visual field (the macula) because of damage to the retina. It occurs in "dry" and "wet" forms. It is a major cause of blindness and visual impairment in older adults (>50 years). 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).

**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.

- **Classic Subfoveal CNV Lesions:** In classic CNV there is a very rapid leakage of blood and fluid under the retina, causing the surface of the retina to become elevated and uneven. The leakage may even break through some of the layers of the retinal tissue, damaging the retina and leaving blind spots in vision.
- **Occult Subfoveal CNV Lesions:** The blood vessels with this type are "hidden" beneath the fovea and are not readily defined. This type involves a slower blood leak under the retina. Because it is more gradual and there is less fluid, the retina does not become as elevated and uneven as it does with classic CNV. The vision loss with this type is slower. The vast majority of wet cases are mainly occult or a mix of occult and classic.

## APPENDIX

N/A

**CODING INFORMATION:** THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description
67221	Destruction of localized lesion of choroid (e.g., choroidal neovascularization); photodynamic therapy (includes intravenous infusion)
67225	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)
92235	Fluorescein angiography (includes multiframe imaging) with interpretation and report

HCPCS	Description
J3396	Injection, verteporfin, 0.1 mg [not covered in combination with intravitreal anti-hyphenangiogenic agents]

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Policy History	Approval
<u>Policy Developed</u> Peer Review: AMR Peer Review Network. 5/18/2018. Practicing Physician. Board certified in Ophthalmology Reviewed: Q4 2019	MCPC 7/10/2018
<u>Annual Review*</u> No coverage criteria changes or notable revisions with this annual review	P&T Q4 2019
No coverage criteria changes or notable revisions with this annual review	P&T Q4 2020

*\*NOTE: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.*