Transpupillary Thermotherapy for Treatment of Choroidal Neovascular Conditions
Archived Medical Policy

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Policy # 00125
Original Effective Date: 08/26/2002
Archived Date: 10/15/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of transpupillary thermotherapy (TTT) as a treatment for retinoblastoma and small choroidal melanomas to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers transpupillary thermotherapy (TTT) as a treatment for choroidal neovascularization (CNV) secondary to ocular conditions, including but not limited to age-related macular degeneration (AMD) to be investigational.*

Background/Overview
Transpupillary thermotherapy is a technique in which low level heat is delivered through the pupil using a modified diode laser. Transpupillary thermotherapy is designed to gently heat subfoveal choroidal lesions while limiting damage to the overlying retinal pigment epithelium.

Age-related Macular Degeneration
Choroidal neovascularization is a common cause of adult-onset blindness, most commonly associated with AMD. In its earliest stages, AMD is characterized by minimal visual impairment and the presence of large drusen and other pigmentary abnormalities on ophthalmoscopic examination. As AMD progresses, 2 distinctively different forms of degeneration may be observed. The first, called the atrophic, areolar or dry form, evolves slowly. Atrophic AMD is the most common form of degeneration and is often a precursor of the second form, the more devastating exudative neovascular form, also referred to as disciform or wet degeneration. The wet form is distinguished from the atrophic form by serous or hemorrhagic detachment of the retinal pigment epithelium and the development of CNV, sometimes called neovascular membranes. Risk of developing severe irreversible loss of vision is greatly increased by the presence of CNV.

*Investigational means a procedure or service that has not been thoroughly studied or tested by scientific research, or that is still being studied and not yet proven to be safe and effective for the patient's condition.

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The pattern of CNV, as revealed by fluorescein or indocyanine angiography, is further categorized as classic or occult. For example, 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, either due to the opacity of coexisting subretinal hemorrhage or, especially in CNV associated with AMD, by a tendency for epithelial cells to proliferate and partially or completely surround the new vessels. Interestingly, lesions consisting only of classic CNV carry a worse visual prognosis than those composed of only occult CNV, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of AMD.

There is ongoing research interest in the use of TTT to treat subfoveal CNV with an “occult” angiographic pattern. Transpupillary thermotherapy is a technique in which heat is delivered to the choroid and retinal pigment epithelium through the pupil using a modified diode laser. This laser technique contrasts with the laser used in standard photocoagulation therapy in that TTT uses a lower power laser for more prolonged periods of time and is designed to gently heat the choroidal lesion, thus limiting damage to the overlying retinal pigment epithelium.

Other Treatments for Choroidal Neovascularization Secondary to Age-related Macular Degeneration

Other available therapeutic options for CNV not addressed in this policy include photodynamic therapy (PDT) and vascular endothelial growth factor (VEGF) antagonists or angiostatics. These may be administered alone or in combination. Angiostatic agents target various points in the pathway leading to new blood vessel formation (angiogenesis): messenger ribonucleic acid (RNA), Vascular endothelial growth factors, and endothelial cell proliferation, migration, and proteolysis. Pegaptanib (Macugen™, Eyetech and Pfizer), ranibizumab (Lucentis™, Genentech) and aflibercept (Eylea™, Regeneron) are approved by the U.S. Food and Drug Administration (FDA) for use in AMD. Bevacizumab (Avastin, Genentech) has been used off label to treat AMD. It is derived from the same murine monoclonal antibody precursor as ranibizumab and is approved by the FDA for the treatment of metastatic cancer of the colon or rectum. Photodynamic therapy has also been used with success in treating subfoveal CNV; the treatment has shown the greatest success in treating patients with classic CNV (as opposed to occult CNV), as defined angiographically. Photodynamic therapy as a treatment of CNV uses a nonthermal laser designed to activate verteporfin, the photosensitizing agent. Laser photocoagulation has been used to treat CNV; however, patients with subfoveal lesions are generally not candidates for this treatment due to the risk of an immediate reduction in central vision, outweighing any treatment advantage.

Central Serous Chorioretinopathy

Central serous chorioretinopathy (CSC) is the fourth most common retinopathy after AMD, diabetic retinopathy, and branch retinal vein occlusion. 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. Central serous chorioretinopathy can be divided into acute, recurrent, and chronic conditions. Usually, serous retinal detachments have spontaneous resolution with
Recovery of visual function; however, a subset of patients may experience permanent deterioration of visual function attributable to chronic CSC or multiple recurrences of CSC. The pathogenesis of CSC is believed to be ischemia and inflammation, which lead to abnormal permeability of the inner choroid and elevation of the retinal pigment epithelium, causing serous epithelial detachments. The separated retinal pigment epithelium can then undergo tiny rips (blowouts) with a break in continuity. The change in permeability of the retinal pigment epithelium results in focal leakage and retinal detachment. Neovascularization can occur as a secondary complication. In about 90% of cases, CSC resolves spontaneously with detachment resolution within 3 months. The traditional management of acute CSC is observation. Recurring or chronic CSC can be treated with focal laser photocoagulation if the leaks are extrafoveal. Although laser may shorten the duration of symptoms, it does not have any impact on the final vision or the recurrence rate of CSC. In addition, laser photocoagulation causes collateral damage creating symptomatic scotomas and a risk of triggering secondary CNV. Photodynamic therapy is not a standard treatment for CSC due to complications that may include CNV, although low-fluence PDT is being evaluated.

Other Choroidal Neovascular Conditions
Other choroidal neovascular conditions include pathologic myopia, presumed ocular histoplasmosis syndrome, angioid streaks, idiopathic CNV, uveitis, choroidal rupture or trauma, and chorioretinal scars. Treatments that have been evaluated for CNV not related to AMD include submacular surgery, laser photocoagulation, and PDT. Efficacy of these treatment modalities is limited.

FDA or Other Governmental Regulatory Approval
Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination.

Rationale/Source
At the time this policy was created in 2002, there were minimal published data regarding TTT. Published evidence through 2005 consisted primarily of uncontrolled case series and in 2005, a Technology Evaluation Center (TEC) Special Report on the treatment of AMD noted that TTT, when used alone, had not been shown to be efficacious. Subsequently, this policy has been updated periodically with literature searches. Following is a summary of key studies to date.

Transpupillary Thermotherapy versus Sham
In a presentation at the American Academy of Ophthalmology meeting in October 2004, in New Orleans, Iridex Corporation announced preliminary results of the TTT4 CNV study. The TTT4 CNV study is a nationwide study involving 22 centers that was started in March 2000. A total of 336 patients with symptomatic occult CNV that show signs of exudation were to be recruited. Two-thirds of eyes would be treated and one-third would receive sham treatment. Patients would be followed up for 2 years. Iridex-reported preliminary results did not show TTT for CNV resulted in significant benefit over sham treatment.
Forty-seven percent of 303 patients who received TTT for CNV had modest or severe visual loss after 2 years, compared with 43% in those who received sham treatment. To date, results of this trial have not been published.

Two small randomized trials (28 and 25 patients) from 2005 and 2006 reported no benefit of TTT in preventing further visual loss in patients with occult CNV who were not candidates for PDT.

**Transpupillary Thermotherapy versus Photodynamic Therapy**

The largest published controlled trial randomly assigned 98 patients with occult CNV to TTT (136 mW/mm) with sham PDT (n=52), or to PDT with sham TTT (n=46). Retreatment was given if leakage was documented by fluorescein angiography (follow-up of 6, 12, 18, 24, 36, and 48 weeks). With a mean of 3.0 treatments in the TTT group and 2.3 treatments in the PDT group, a similar percentage of patients had lost fewer than 15 letters at 12 months (75% for TTT and 74% for PDT). There were non-significant trends for a larger percentage of patients to have preserved or improved best corrected visual acuity (BCVA) in the TTT group (37%) than in the PDT group (24%) and to have less of a decrease in foveal thickness (15% vs. 24%). Patient-reported visual function from this trial was reported in 2010. Outcomes on the National Eye Institute Visual Function Questionnaire 25 were similar in patients treated with TTT (change of +1.2) or PDT (change of +0.7) at 12 months, but the study was underpowered to detect differences in this outcome measure.

In a controlled trial from Asia, patients chose PDT or TTT after an explanation of the costs, benefits, and risks of each treatment. Sixteen patients (16 eyes) selected PDT, and 14 patients (16 eyes) selected TTT; treatments were repeated if dye leakage was evident at follow-up. The average pre-treatment visual acuity was similar in the 2 groups. At 6 months’ follow-up, loss of visual acuity was 15 letters or less in 14 (87%) eyes treated with TTT and in 13 (81%) eyes treated with PDT; however, more patients with good initial visual acuity (20/63 or greater) had a loss of 2 or more lines following TTT (4 of 4), than following PDT (1 of 6). Although the authors concluded that patients with good initial visual acuity should be treated with PDT, the study is limited by selection bias and small subject number. The authors of this study and another report from Asia indicated that the rationale for using TTT was the lower cost of this treatment in comparison with PDT.

**Transpupillary Thermotherapy Combined with Intravitreal Ranibizumab**

In a 2012 report, Soderberg et al. randomized 100 patients with neovascular AMD to low-dose TTT and intravitreal ranibizumab or to sham TTT and intravitreal ranibizumab. At 24-month follow-up (78 patients), quarterly TTT was found to decrease the mean number of ranibizumab injections from 8.0 to 6.3 with no significant difference between the sham and active TTT groups in BCVA (+4.0 vs. +0.9, respectively). Thus, 7 quarterly treatments with TTT resulted in a mean reduction of 1.7 ranibizumab injections. It was not described whether the investigator who determined if the patient met retreatment criteria was masked to
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treatment allocation. Masked evaluation found no significant difference between the sham and active TTT groups in central retinal thickness (-49.9% vs. -36.4%) or lesion area (-0.3% vs. -10.6%, both respectively).

Other
One randomized (not masked) study of 26 patients from 2005 did not find a statistically significant improvement for combination treatment with triamcinolone and TTT in comparison with TTT alone.

Four nonrandomized studies of TTT in eyes with CNV related to AMD were identified from 2003 and 2004. The largest series is from Nagpal and colleagues, who reported on TTT for CNV in 160 eyes (99 classic and 61 occult) of patients of Indian descent. The authors reported that in eyes with classic CNV, 29.3% improved, 39.4% stabilized, and 31.3% deteriorated at 12 month follow-up. In occult CNV, 19.6% improved, 57.4% stabilized, and 22.9% deteriorated. Nagpal and colleagues concluded that there was effectiveness with TTT in Indian eyes, which responded to lower energy levels than did Caucasian eyes in their experience.

In 2011, Peyman and colleagues reported treatment of a small series of patients (n=4) with peripapillary CNV that was recalcitrant to other treatments, including intravitreal angiostatic agents. These investigators used a variation of TTT with indocyanine green dye as a thermal enhancing agent, which permitted use of a lower energy level (oscillatory thermotherapy). The photodynamic treatment was combined with bevacizumab and intravitreal dexamethasone, and visual acuity was found to remain stable (1 of 4 improved visual acuity) at a mean 12-month follow-up.

Small case series from Asia describe the use of TTT for CSC and choroidal hemangioma.

Adverse Events
A case series reported macular burn as a complication of TTT in 8.6% of 35 patients available for follow-up.

Questions have been raised about the potential harms of this treatment if given at higher intensity, while Peyman and colleagues note that a major limitation of TTT is the inability to titrate the energy level and subsequently control both the rate and the total amount of temperature rise during the procedure.

Summary
Transpupillary thermotherapy is a technique in which low-level heat is delivered through the pupil using a modified diode laser. Transpupillary thermotherapy is designed to gently heat subfoveal choroidal lesions while limiting damage to the overlying retinal pigment epithelium. Evidence on TTT is limited. The available studies comparing TTT to sham have not shown a benefit of this procedure. Although trials comparing TTT to PDT show similar outcomes for the 2 treatments, there may be an increase in adverse events with TTT. Transpupillary thermotherapy has not been compared with angiogenesis inhibitors. Evidence is insufficient
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to determine whether TTT is as beneficial as the established alternative; this procedure is considered investigational.

References
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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Policy History
Original Effective Date: 08/26/2012
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07/18/2002 Medical Policy Committee review
08/26/2002 Managed Care Advisory Council approval
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09/21/2004 Medical Policy Committee review Format revision. No substance change to policy.
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08/03/2005 Medical Director review
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08/16/2005 Medical Policy Committee review Coverage eligibility statement revised: “treatment for retinoblastoma and small choroidal melanomas may be considered eligible for coverage”
08/24/2005 Managed Care Advisory Council approval
06/07/2006 Medical Director review
06/21/2006 Medical Policy Committee approval. Format revision; FDA/Governmental regulations. No change to policy statement. Preparation for posting to intranet.
08/02/2006 Medical Director Review
08/09/2006 Medical Policy Committee approval. Scheduled review, No changes to policy statement.
06/13/2007 Medical Director Review
06/20/2007 Medical Policy Committee approval. No change to coverage eligibility.
07/02/2008 Medical Director Review
07/16/2008 Medical Policy Committee approval. No change to coverage eligibility.
07/02/2009 Medical Director Review
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09/09/2010 Medical Policy Committee review
12/31/2010 Coding updated
09/01/2011 Medical Policy Committee review
09/14/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/11/2012 Medical Policy Committee review
10/31/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Title changed. Age related macular degeneration added as investigational indication.
10/02/2014 Medical Policy Committee review. Recommend archiving policy.

Next Scheduled Review Date: Archived medical policy.

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.
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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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