Clinical Policy Title: Laser treatment of port-wine stains and infantile hemangiomas

Clinical Policy Number: CCP.1136

Effective Date: January 1, 2015
Initial Review Date: September 17, 2014
Most Recent Review Date: August 1, 2018
Next Review Date: August 2019

Related policies:
None.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers treatment for port-wine stains or infantile hemangiomas to be clinically proven and, therefore, medically necessary when the following criteria are met:

I. Treatment includes port-wine stains or infantile hemangioma lesions that require:
   - Emergency therapy due to life-threatening complications.
   - Urgent therapy of existing or imminent functional impairment, pain, or bleeding.
   - Evaluation to identify structural anomalies potentially associated with the disorder.
   - Elective treatment to reduce likelihood of long-term or permanent disfigurement (Darrow, 2015).

II. Treatment modalities for infantile hemangioma may include one or more of the following alone or in combination (not an all-inclusive list):
   - Systemic and intralesional steroids.
• Beta-adrenergic blockers (propranolol – oral and topical).
• Corticosteroids (systemic, intralesional, and topical).
• Chemotherapy (vincristine).
• Interferon-a.
• Imiquimod.
• Pulsed dye laser therapy.
• Surgery (Darrow, 2015).

Only pulsed dye laser therapy should be used for port-wine stains (Brightman, 2015). **Note:** Depending on the extent of the port-wine stains, several laser treatments may be required, spaced at two- to three-month intervals.

**Limitations:**

All other uses of laser therapy to treat port-wine stains and infantile hemangiomas are not medically necessary.

**Alternative covered services:**

Consultation with dermatologist.

**Background**

Port-wine stains (nevus flammeus) are red or purple marks, often on the face. Port-wine stains represent the most common vascular malformation and are commonly known as firemarks. They are caused by a localized area of abnormal blood vessels (capillaries). About three in 1,000 babies are born with port-wine stains (Minkis, 2009). Most occur on the face, but any area of the skin can be affected. Although the vast majority of port-wine stains are present at birth, they can occasionally develop later on (Children’s Hospital of Philadelphia, 2017; Cunliffe, 2012).

A modest percentage of port-wine stains located over the eye and central forehead can be associated with glaucoma and/or complications in the brain resulting in seizures or developmental disabilities. This association of facial port-wine stains and glaucoma and/or seizures is called the Sturge-Weber Syndrome. The location and the extent of the port-wine stains on one extremity can lead to enlargement of the extremity relative to an unaffected limb (Klippel-Trenaunay-Weber Syndrome).

In 2013, the cause of port-wine stains and Sturge-Weber Syndrome was discovered. A somatic activating mutation in the guanine nucleotide-binding protein was identified in 12 of 13 cases of port-wine stains and 23 of 26 cases of Sturge-Weber Syndrome, confirming a long-standing hypothesis (Shirley, 2013).

There are several types of laser systems available for port-wine stains. The Flashlamp-Pulsed Dye Laser is the gold standard for port-wine stains treatment. It emits a yellow light wave length of 595 to 600 nanometers (nm), which allow deeper penetration than the original 577 nm models introduced in the 1980s (Brightman, 2015). Pulsed dye lasers target oxyhemoglobin and deoxyhemoglobin. The pulsed dye
laser penetrates up to 2 millimeters of skin with a duration of just milliseconds. The procedure is delivered in outpatient settings, over multiple sessions, with or without anesthesia (Children’s Hospital of Philadelphia, 2017; Cunliffe, 2012).

Infantile hemangiomas are the most common (benign) childhood tumors. They develop within four to six weeks of birth, and are present in 1 percent - 3 percent of newborns, and in 10 percent - 20 percent of infants under age 1 (Darrow, 2015). In newborns under 1,000 grams, the rate can be as high as 22 percent - 30 percent (Zang, 2013). Up to 70 percent of cases lead to residual skin changes. Complications include ulceration, bleeding, feeding problems, and visual impairment (Randel, 2016).

A Mayo Clinic study of Olmsted County, Minnesota, demonstrated that the rate of infantile hemangiomas more than doubled from 1976–1980 to 2006–2010, from 0.97 to 1.97 cases per 100 person-years. A total of 999 cases was identified in the 35-year period, and the increase was correlated with declines in average gestation period (39.2 weeks to 38.3 weeks, \( P < .001 \)) and average birth weight (3,383 grams to 3,185 grams, \( P = .003 \)) (Anderson, 2016).

Infantile hemangiomas can also be associated with a constellation of congenital anomalies:

- Posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, ephelial cleft, and supraumbilical raphe.
- Perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag.
- Lower-body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies.

A distant subset of infantile hemangiomas consists of multiple small lesions varying in size from a few millimeters to one to two centimeters. This form of infantile hemangioma (so-called multiple neonatal hemangiomatosis) has a higher risk of visceral involvement, particularly in the liver and gastrointestinal tract; however, the prognosis for the skin lesions is usually good, as they often involute by two years of age.

After laser therapy for infantile hemangioma, the area will often turn off-white within seven to 14 days. An evaluation should be made every two to four weeks after treatment until the condition is resolved, or another treatment is needed (Zhang, 2013).

The U.S. Food and Drug Administration has approved lasers for marketing, through the 510(k) process, for a variety of dermatologic indications, including treatment of port-wine stains. Approved lasers for this indication include the Candela Vbeam® pulsed dye laser system (Candela Corp., Wayland, MA), the Cynosure Photogenica® pulsed dye laser (Cynosure Inc., Westford, MA), and the Cynosure Nd: YAG laser system (Cynosure). In addition, the Cynergy™ MultiPlex Laser™ (Cynosure), a combined Nd: YAG and pulsed dye laser, was approved by the Food and Drug Administration in 2005 for treatment of benign vascular and vascular dependent lesions, including port-wine stains. In 2003, the Lumenis® family of intense pulsed light systems was approved by the Food and Drug Administration; indications for use include dermatological
applications. Subsequently, the NannoLight™ intense pulsed light system (Sybaritic) was approved by the Food and Drug Administration in 2008 and the MDFLASH4 and STFLASH4 systems (Dermeo®) were approved in 2010 for indications specifically including treatment of port-wine stains.

No specific professional guidelines exist for treating port-wine stains. A 2015 review of the literature finds that lasers, in particular, pulsed dye lasers, are effective modes of treatment for port-wine stains, asserting that 80 percent to 90 percent improvements are common in early and optimal treatments (Brightman, 2015).

An American Academy of Pediatrics guideline notes that after 2008, systemic corticosteroids, in particular, propranolol, have been used to treat infantile hemangioma. The guideline recommends the drug, with cardiovascular monitoring every hour for two hours, with repeat monitoring for any dose increase over 5 mg/kg. If propranolol cannot be used or is ineffective, corticosteroids (usually daily oral prednisone or prednisolone) can be an alternative therapy. Laser therapy may be useful in treating early lesions (Randel, 2016).

A summary of recommended therapies for infantile hemangioma includes lasers, along with chemotherapy, Interferon alpha 2a, systemic or intralesional steroids, radio- or cryo-therapy, therapeutic embolization, and surgery (Fette, 2013). Another guideline states that laser therapy for infantile hemangioma be repeated every two to four weeks, and that it is not suitable for deep-seated hemangiomas (Zhang, 2013).

**Searches**

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on June 6, 2018. Search terms were: “Port wine stain,” “infantile hemangioma,” and “laser treatment.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**
Port-wine stains results:

One large nonrandomized study on pulsed dye laser for port-wine stains included 848 cases, using a 595 nm laser. The response rate was 69.9 percent, and the cure rate among respondents was 6.3 percent. The response for infants under age 1 was 93.3 percent, significantly greater than for patients over age 50. The temporal region had the highest clearance rate of 75.5 percent, while the rate for extremities was just 44.5 percent. Patients with lesion size of <20 cm had a higher rate of clearance than those larger than 80 cm, 73.8 percent versus 53.2 percent. Finally, early intervention was associated with higher clearance rates (Shi, 2014).

A randomized controlled trial compared (single-session) pulsed dye laser treatment with vascular-targeted photodynamic therapy in 15 port-wine stains in patients ages 11 to 36, using adjacent flat areas of lesions. For both red and purple lesions, photodynamic therapy showed equal or higher blanching improvements than did pulsed dye laser (Gao, 2013). Another randomized controlled trial compared pulsed dye laser with intense pulsed light for port-wine stains in a randomized side-by-side trial in 20 patients with port-wine stains. Both treatments resulted in clinical improvements, but were significantly better for pulsed dye laser (65 percent versus 30 percent, \( P = .0004 \)). Improvement in skin lightening was also superior for pulsed dye laser (33 percent versus 12 percent, \( P = .002 \)). All but two of the 20 patients preferred to receive continued treatment with pulsed dye laser (Faurschou, 2009). A study of 158 port-wine stains spots in pulsed dye laser patients found that intense pulsed light treatments were significantly better in clearing lesions than pulsed dye laser (Babilas, 2010).

A literature review determined that no topical treatment currently in use is helpful as an adjunct to pulsed dye laser to treat port-wine stains (Lipner, 2018).

Combining pulsed dye laser with other treatments has been done in several studies. The most recent randomized controlled trial of pulsed dye laser treatment consisted of 23 patients that compared four groups with port-wine stains: placebo, pulsed dye laser plus placebo, rapamycin alone, and pulsed dye laser plus rapamycin. Combining pulsed dye laser and rapamycin yielded the lowest digital photographic image score and lowest percent of vessels, and a significant improvement versus other interventions (Marques, 2015). Adding imiquimod five percent cream to pulsed dye laser in 24 patients with port-wine stains resulted in greater change in erythema in combination sites versus pulsed dye laser plus placebo sites \( (P < .03) \), and greater change in color in combination sites \( (P < .04) \) (Tremaine, 2012).

In 26 patients with port-wine stains treated with a minimum of three double-pass pulsed dye laser treatments alone, or in combination with single-pass conventional pulsed dye laser, 12 showed a moderate or significant improvement, and another 12 a mild improvement, in fading, compared to pretreatment photographs with the double-pass technique. Many patients developed mild side effects, including blisters \( (n = 5) \), dry scabs \( (n = 11) \), and transient hyperpigmentation \( (n = 4) \) (Rajaratnam, 2011).

Pain is a common side effect after laser therapy for dermatological procedures for conditions such as port-wine stains. A review of 32 randomized and nonrandomized controlled studies showed that noninvasive techniques including pulsed dye laser resulted in less pain than placebo, and topical anesthesia had better outcomes than skin cooling (Greveling, 2017).
Infantile hemangioma results:

A Cochrane review of five studies (n = 103) of infantile hemangioma treatment with various laser therapies showed subjects marginally preferred yttrium-aluminum garnet lasers to pulsed dye therapy. However, one to three pulsed dye laser treatments over four to six months produced a reduction of at least 25 percent in redness, described by the authors as “clinically relevant clearance” (Faurschou, 2011). Another Cochrane review of four studies (n = 271) included a single randomized controlled trial that observed pulsed dye laser was (significantly) more likely to result in complete resolution of pulsed dye laser than a “wait and see” approach; pulsed dye laser patients experienced less redness, but had higher increases in atrophy and skin hypopigmentation. Authors concluded that more randomized controlled trials were needed to confirm results such as this (Leonardi-Bee, 2011).

A meta-analysis of 13 studies (n = 1,580) showed an 89.1 percent resolution rate and a 6.28 percent adverse effect rate of pulsed dye laser on infantile hemangioma (Shen, 2015). A systematic review of 76 studies (n = 1,239) showed no significant advantages in outcomes between various treatment modes for ulcerated infantile hemangiomas; oral propranolol was associated with a 97.0 percent complete ulcer healing in 197 cases (Wang, 2018).

An Agency for Healthcare Quality and Research review of 148 studies of infantile hemangioma outcomes indicated that longer-pulse pulsed dye laser was generally more effective than observation (Chinnadurai, 2016a). This finding was consistent with a review of 29 studies, which also concluded that pulsed dye laser worked better than other laser therapies (Chinnadurai, 2016b).

A meta-analysis of 61 studies (n = 5,130) found propranolol was more effective in treating infantile hemangioma than other modalities (Odds Ratio = 0.92), and was especially effective at daily doses greater than 2 mg/kg. Propranolol also had significantly fewer complications than systemic steroids (Odds Ratio = 0.68), laser ablation (Odds Ratio = 0.55), other beta-adrenergic blockers (Odds Ratio = 0.56), and surgery (Odds Ratio = 0.55) (Liu, 2015).

A meta-analysis of 35 studies (n = 572) of infantile hemangioma patients revealed that propranolol (n = 324) was significantly more effective than other therapies (P < .001). Propranolol effectiveness was greater versus steroids (P < .001), vincristine (P = .003), and laser treatment (P = .02) in treating cutaneous (P < .001), peri-ocular (P < .001), infantile airway (P < .001), and hepatic (P = .033) hemangioma (Lou, 2014).

A systematic review of periorbital infantile hemangiomas of 31 studies (n = 425) compared outcomes after propranolol and corticosteroid treatment. Propranolol had significantly better outcomes for response rate (94.0 percent versus 82.3 percent, P = .001), reduction in spherical power (P = .005), and postoperative amblyopia (16.7 percent versus 31.1 percent, P = .04), Corticosteroids were associated with significantly fewer temporary adverse events (9.5 percent versus 24.0 percent, P = .006) (Xu, 2014).

A systematic review of 83 studies, three pooled clinical trials, and one compassionate use program (n = 5,862) of infantile hemangioma patients treated with propranolol documented an adverse event in about one-third (1,945 of 5,862). Most frequent events were sleep disturbances, peripheral coldness, and agitation. The most serious events (atrioventricular block, bradycardia, hypotension,
bronchospasm/bronchial hyperreactivity, and hypoglycemia-related seizures) were controlled by decreasing doses or discontinuing propranolol temporarily or permanently (Leaute-Labreze, 2016).

Despite the proliferation of meta-analyses and systematic reviews, many studies suffer from low quality. Thus, a 2018 Cochrane review of infantile hemangioma effectiveness in 28 studies concluded that only limited conclusions can presently be made, and that future studies should include more randomized controlled trials (Novoa, 2018).

A 2016 study of 647 patients with a variety of diseases, including infantile hemangioma, found use of the relatively new potassium-titanyl phosphate laser resulted in only 5.8 percent of patients with adverse effects, and only one patient with bruising rates lower than for pulsed dye laser (Becher, 2014).

**Policy updates:**

A total of nine peer-reviewed references were added to and four peer-reviewed references were removed from this policy in June 2018.

A total of 5 guidelines/other and 18 peer-reviewed references were added to this policy in 2017, and 1 guidelines

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td><strong>Leaute-Labreze (2016)</strong></td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Adverse events in infantile hemangiomas treated with propranolol</td>
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</table>
    - Systematic review of 83 studies, three pooled clinical trials, and one compassionate use program (n = 5,862) of infantile hemangioma patients treated with propranolol.  
    - Adverse events were reported in about one-third (1,945 of 5,862) of cases.  
    - Most common adverse events were sleep disturbances, peripheral coldness, and agitation.  
    - Most serious events (atrioventricular block, bradycardia, hypotension, bronchospasm/bronchial hyperreactivity, and hypoglycemia-related seizures) were controlled by decreasing doses or discontinuing propranolol. |
| **Liu (2015)** | **Key points:** |
| Comparison of effectiveness of treatments for infantile hemangiomas |  
    - Meta-analysis of 61 studies (n = 5,130).  
    - Propranolol was more effective in treating infantile hemangioma than other modalities (Odds Ratio (OR) = 0.92).  
    - Propranolol was especially effective at daily doses greater than 2 mg/kg.  
    - Propranolol had significantly fewer complications than systemic steroids (ORs = 0.68), laser ablation (ORs = 0.55), other beta-adrenergic blockers (ORs = 0.56), and surgery (ORs = 0.55). |
| **Shen (2015)** | **Key points:** |
| Pulsed dye laser for infantile hemangioma |  
    - Systematic review and meta-analysis for infantile hemangioma, included 13 articles (n = 1,529).  
    - Overall resolution rate was 89.1 percent (%).  
    - Incidence of adverse effects was 6.28%. |
<table>
<thead>
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<td>Lou (2014)</td>
<td><strong>Key points:</strong></td>
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| **Effectiveness of propranolol versus other therapies for infantile hemangiomas** | • Meta-analysis of 35 studies (n = 572) of infantile hemangioma patients.  
• Propranolol (n = 324) was more effective than other therapies ($P < .001$).  
• Propranolol was more effective than steroids ($P < .001$), vincristine ($P = .003$), and laser treatment ($P = .02$).  
• Propranolol was more effective in treating cutaneous ($P < .001$), peri-ocular ($P < .001$), infantile airway ($P < .001$), and hepatic ($P = .033$) hemangiomas. |
| Shi (2014)   | **Key points:**                    |
| **Outcomes of port wine stains treatment with pulsed dye laser** | • Descriptive study of 848 port-wine stains patients in China.  
• Response rate of patients = 69.9%, of which 6.3% were cured.  
• Rate higher for age <1 (93.9% versus age >50.  
• Rate highest for temporal region (75.3%) versus extremities (44.5%).  
• Rate highest for small lesions <20 cm (73.8%) versus >80 cm (53.2%). |

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


**Centers for Medicare & Medicaid National Coverage Determinations:**


**Local Coverage Determinations:**


**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>17108</td>
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<td>D18.09</td>
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Appendix A

PerformRx

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No PerformRx policy identified as of the writing of this policy.