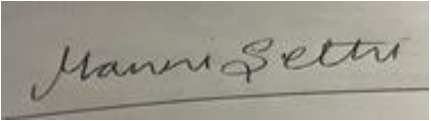


**Prior Authorization Review Panel
MCO Policy Submission**

A separate copy of this form must accompany each policy submitted for review.
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Plan: Keystone First	Submission Date: 10/1/2024
Policy Number: ccp.1136	Effective Date: 1/20215 Revision Date: September 1, 2024
Policy Name: Pulsed dye laser for port-wine stain and infantile hemangioma	
Type of Submission – Check all that apply: ☐ New Policy ☒ Revised Policy* ☐ Annual Review – No Revisions ☐ Statewide PDL	
*All revisions to the policy <u>must</u> be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below: See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual: 



Pulsed dye laser for port-wine stain and infantile hemangioma

Clinical Policy ID: CCP.1136

Recent review date: 9/2024

Next review date: 1/2026

Policy contains: Infantile hemangiomas, laser treatment; port-wine stains; propranolol.

Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First'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 Keystone First, on a case by case basis, 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. Keystone First'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. Keystone First's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First's clinical policies are not guarantees of payment.

Coverage policy

Pulsed dye laser treatment for port-wine stains and infantile hemangiomas is clinically proven and, therefore, may be medically necessary for any of the following indications (Darrow, 2015; Krowchuk, 2019; Randel, 2016; Sabeti, 2021):

- 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.

Only pulsed dye laser therapy should be used for port-wine stains (Sabeti, 2021), and it should be used for infantile hemangiomas only in refractory cases (Darrow, 2015; Krowchuk, 2019). Propranolol should be used for systemic therapy for infantile hemangiomas, at 2 – 3 mg/kg daily, for at least six months to as many as 12 months (Krowchuk, 2019).

Note: Depending on the extent of the port-wine stains, several laser treatments may be required, spaced at two- to three-month intervals.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

- Adjuvant medications (e.g., propranolol).

- Photodynamic therapy.
- Surgical debulking and excision.
- Consultation with dermatologist.

Background

A port-wine stain (nevus flammeus) is a red or purple mark, often on the face. Port-wine stains represent the most common cutaneous vascular lesions and are commonly known as fire marks. They are caused by a localized area of abnormal blood vessels (capillaries). About three in 1,000 babies are born with port-wine stains (Nguyen, 2019). 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 (Cunliffe, 2022b).

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) (Cunliffe, 2022b).

Infantile hemangiomas are the most common benign childhood tumors. They are classified according to the International Society for the Study of Vascular Anomalies as distinct from more proliferative vascular malformations with implications for care management, as most infantile hemangiomas do not require imaging for diagnosis or aggressive treatment (Wildgruber, 2019). They typically develop within four to six weeks of birth, and approximately 20% are present at birth. Infantile hemangioma may present as a superficial nevus or as a deeply set lesion in the dermis and subcutis. While most lesions require no treatment, some can grow rapidly, bleed, or ulcerate. Segmental proliferative hemangiomas present the most challenges, as they occur at a younger age, can grow up to ten times larger, and are more likely to have associated congenital anomalies (Cunliff, 2022a).

Genetic mechanisms underlying infantile hemangiomas have been implicated in certain multi-organ birth defect syndromes. These syndromes include the acronyms PHACE (**P**osterior fossa brain malformations, segmental facial **H**emangiomas, **A**rterial anomalies, **C**ardiac defects, **E**ye anomalies, and sternal clefting or supraumbilical raphe) and LUMBAR (**L**ower body hemangiomas, **U**rogenital anomalies, **M**yelopathy, **B**one deformities, **A**norectal malformations/**A**rterial anomalies, and **R**enal anomalies) (Siegel, 2018).

A distant subset of infantile hemangioma 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 (Wildgruber, 2019).

Pulsed dye lasers target oxyhemoglobin and deoxyhemoglobin. They penetrate up to two millimeters of skin with a duration of just milliseconds. The procedure is delivered in outpatient settings, over multiple sessions, with or without anesthesia. The U.S. Food and Drug Administration has approved a variety of lasers for marketing, through the 510(k) process, for a variety of dermatologic indications, including treatment of port-wine stains and infantile hemangiomas. The flashlamp-pulsed dye laser emits a yellow light wave length of 595 to 600 nanometers, which allows deeper penetration than the original 577 nanometer models introduced in the 1980s (Brightman, 2015).

Findings

Guidelines

A consensus statement from dermatological experts in the United States recommends pulsed dye laser as the standard treatment for port-wine stains regardless of lesion size, location, or color. Laser treatment is safe for people of all ages when performed by experienced physicians to minimize the psychosocial impact and to diminish nodularity and potential tissue hypertrophy. Treatment efficacy is higher in patients with lighter skin types. In patients with skin of color (e.g., Fitzpatrick skin types V and VI), higher rates of side effects, mainly dyspigmentation and atrophic scarring, may be observed, but moderate energy densities, less pulse overlap, and increased cooling may minimize these risks. Starting treatment at an earlier age may achieve better outcomes, and the use of general anesthesia in young patients should be considered on a case-by-case basis (Sabeti, 2021).

An American Academy of Pediatrics guideline notes that since 2008, propranolol has 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 five 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 2015 report from the American Academy of Pediatrics provided updates on the pathogenesis, treatment, and clinical associations of infantile hemangiomas, including the use of pulsed dye laser for refractory cases (Darrow, 2015).

The most recent American Academy of Pediatrics guideline on infantile hemangiomas declares that pulsed dye laser is safe and effective, and evidence has demonstrated that pulsed dye is more effective than other laser therapies, although acknowledging there is controversy over using the technique in infants. The guideline also recommends using propranolol for systemic treatment of infantile hemangiomas (Krowchuk, 2019).

Evidence reviews

Port-wine stains

The optimal treatment of port-wine stains is pulsed dye laser for its ability to improve redness. Early intervention appears to improve outcomes. No determination of the optimal treatment protocol can be established.

A review of 65 studies (n = 6,207) revealed that just 21% of patients with port-wine stains treated with pulsed dye laser achieved 75% to 100% clearance. The authors observed no improvement in outcomes over the past three decades despite technological improvements and changes in patient selection, indicating the need for further research of novel therapies (van Raath, 2019). Newer generations of pulsed dye laser, such as large spot pulsed dye laser, may offer improved effectiveness and efficiency but require higher quality studies to confirm improvement in outcomes (Sodha, 2023). Protocol changes such as varying interval time between pulsed dye laser treatments appears to have no effect on patient outcomes (Snast, 2021).

Shi's systematic review and meta-analysis identified several acute and long-term complications associated with pulsed dye laser. The pooled complication rates were purpura (98.3%), edema (97.6%), crusting (21.5%), blistering (8.7%), hyperpigmentation (12.8%), hypopigmentation (0.9%), and scarring (0.2%). Long-term permanent complications occur infrequently, suggesting the importance of protective measures after treatment in preventing scar formation (Shi, 2023).

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).

The effectiveness of pulsed dye laser has been examined in several subtypes. Eckembrecher (2023) summarized nine observational studies (n = 241) on pulsed dye laser for treating port-wine stains in patients with

Fitzpatrick skin type IV–VI. While preliminary evidence suggests pulsed dye laser can be effective in patients with darker skin color, larger studies with diverse populations are needed to inform clinical practice, including use of adjunct treatments to mitigate adverse effects.

For treating hypertrophic or resistant port-wine stains, a network meta-analysis of eight comparative studies (comprising 308 difficult-to-treat port-wine stains) found intense pulsed light (odds ratio 11.81, 95% confidence interval 2.15 to 64.89) and 585 nanometer long-pulsed dye laser (odds ratio 9.95, 95% confidence interval 1.75 to 56.62) were likely more effective than 585 nanometer short pulsed dye laser in further clearing lesions by more than 25%. Where reported, side effects were rare with scarring and hypopigmentation or hyperpigmentation in varying degrees of severity were the most common. The evidence was rated as having low certainty in the findings, and the authors call for well-designed trials to confirm these findings (Jamjanya, 2023).

Infantile hemangioma

Propranolol remains the best option for infantile hemangiomas. Pulsed dye laser alone or in combination with propranolol is effective for treating infantile hemangiomas, especially refractory cases. Its superiority to propranolol or other pharmaceutical options cannot be determined. Treatment protocols will depend on several factors such as the laser pulse width, patient age, anatomical location of the infantile hemangioma, cooling materials, and tumor size.

A multicenter retrospective cohort study examined 117 children with nonulcerated infantile hemangioma treated with pulsed dye laser. In the 99 (84.6%) participants who had late intervention (≥ 12 months of life), there was a mean 85% overall improvement compared to baseline (range 18% to 100%) measured by visual analog scale, mostly in erythema or telangiectasias, with a low incidence of adverse effects (6.1%) (Shah, 2023).

A systematic review and network meta-analysis of 30 randomized trials assessing treatment for infantile hemangioma found laser with topical beta blockers had the greatest efficiency, and long-pulsed dye laser was the most effective. A higher dose and a longer treatment duration of oral propranolol achieved a higher success rate and increased side effects, while pulse dye laser with propranolol had the lowest incidence of adverse reactions (Fei, 2020).

A meta-analysis analyzed efficacy of combined therapy with adrenergic beta-antagonist and lasers for infantile hemangiomas. Combined therapy with oral propranolol and lasers was superior to propranolol or lasers alone (both $P < .00001$). Combined therapy with topical timolol and lasers was superior to topical timolol ($P < .00001$) or lasers ($P = .007$) alone. Authors observed no differences in adverse effects (Chen, 2020).

A Cochrane review of 28 studies ($n = 1,728$) found that compared with placebo, oral propranolol (3 milligrams per kilograms daily) for infantile hemangiomas probably improves clinician-assessed clearance with no difference in rates of serious adverse events, including no instances of bradycardia or hypotension. In two trials of children with superficial early hemangiomas in the pre-proliferative or early proliferative growth phase ($n = 143$); there were no differences in clearance outcomes, aesthetic appearance, or requirements for surgical correction when comparing pulsed dye laser to wait-and-see, although fewer adverse events were reported in the wait-and-see group (Novoa, 2019).

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, 2016b). This finding was consistent with a review of 29 studies, which also concluded that pulsed dye laser worked better than other laser therapies (Chinnadurai, 2016a). Reported side effects of laser treatment include purpura, swelling, blisters, hypopigmentation, bleeding, infection, and atrophic or hypertrophic scarring. Limitations of the evidence include small sample size, lack of comparative studies, and protocol variations. Nonetheless, laser treatment can be considered if there is a contraindication to systemic treatment (Chinnadurai, 2016a, 2016b).

In 2022, we updated the references and added a consensus statement on the treatment of Sturge-Weber syndrome port-wine stains (Sabeti, 2021). No policy changes are warranted.

In 2023, we added one review (Eckembrecher, 2023) and one cohort study (Shah, 2023) to the policy with no policy changes warranted.

In 2024, we removed older references, reorganized the findings, and added three analyses to policy (Jamjanya, 2023; Shi, 2023; Sodha, 2023). No policy changes are warranted.

References

On July 24, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were (“port wine stain (MeSH),” “hemangioma (MeSH),” “dye laser, pulsed (MeSH),” “port wine stain,” “propranolol,” “infantile hemangioma,” and “laser treatment.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

9/2014: initial review date and clinical policy effective date: 1/2015

9/2015: Policy references updated.

9/2016: Policy references updated.

9/2017: Policy references updated.

9/2018: Policy references updated.

9/2019: Policy references updated. Policy ID changed to CCP.1136.

9/2020: Policy references updated. Title changed.

9/2021: Policy references updated.

9/2022: Policy references updated. Title changed.

9/2023: Policy references updated.

9/2024: Policy references updated.