Topical Alpha Adrenergic Agonists

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Related Coverage Resources

Rosacea Procedures

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Coverage for the treatment of rosacea is dependent on benefit plan language and may be subject to the provisions of a cosmetic benefit. Please refer to the applicable benefit plan language to determine benefit availability and the terms, conditions and limitations of coverage.

The treatment of the untoward cosmetic effects associated with rosacea (for example: telangiectasia, erythema) is not covered because such treatment is considered cosmetic in nature and not medically necessary. Under many benefit plans, services are not covered when they are performed solely for the purpose of altering appearance or self-esteem, or to treat psychological symptomatology or psychosocial complaints related to one’s appearance.

Brimonidine topical gel (Mirvaso®) or oxymetazoline topical cream (Rhofade®) are NOT covered for the treatment of persistent (nontransient) erythema of rosacea because it is considered not medically necessary.

Brimonidine topical gel (Mirvaso) or oxymetazoline topical cream (Rhofade) are considered experimental, investigational or unproven for ANY other use.
**FDA Approved Indications**

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Approved Indications</th>
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<tbody>
<tr>
<td>Mirvaso (brimonidine)</td>
<td>Mirvaso gel is indicated for the topical treatment of persistent (nontransient) erythema of rosacea in adults 18 years of age or older.</td>
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<tr>
<td>Rhofade (oxymetazoline)</td>
<td>Rhofade cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.</td>
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**Recommended Dosing**

<table>
<thead>
<tr>
<th>FDA Recommended Dosing</th>
<th>Mirvaso (brimonidine)</th>
<th>Rhofade (oxymetazoline)</th>
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<tr>
<td>Mirvaso (brimonidine)</td>
<td><strong>Recommended Dosage</strong> Mirvaso is for topical use only. Not for oral, ophthalmic, or intravaginal use.  The recommended dose of Mirvaso is a pea-sized amount applied once daily to each of the five areas of the face (forehead, chin, nose, each cheek) avoiding the eyes and lips. Hands should be washed immediately after applying Mirvaso topical gel.</td>
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<tr>
<td>Rhofade (oxymetazoline)</td>
<td><strong>Recommended Dosage</strong> For topical use only. Rhofade is not for oral, ophthalmic, or intravaginal use.  The recommended dose of Rhofade is a pea-sized amount applied once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) avoiding the eyes and lips. Wash hands immediately after applying Rhofade cream. Preparation and Administration Prime the Rhofade pump before using for the first time. To do so, with the pump in the upright position, repeatedly depress the actuator until cream is dispensed and then pump three times. Discard the cream from priming actuations. It is only necessary to prime the pump before the first dose. Rhofade tubes do not require priming.</td>
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**Drug Availability**

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<tbody>
<tr>
<td>Mirvaso (brimonidine)</td>
<td>Mirvaso (brimonidine) topical gel. 0.33% is supplied in tubes containing 30 grams and pump bottles containing 30 grams. Each gram of gel contains 5 mg of brimonidine tartrate, equivalent to 3.3 mg of brimonidine free base.</td>
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<tr>
<td>Rhofade (oxymetazoline)</td>
<td>Rhofade (oxymetazoline hydrochloride) cream, 1% is supplied in tubes containing 30 grams. Each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8 mg (0.88%) of oxymetazoline free base.</td>
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**General Background**

**Disease Overview**
Rosacea is a chronic disorder affecting the facial skin and is associated with blushing. Rosacea develops slowly, starting with redness around the cheeks and worsening to additional symptoms and affecting other parts of the face. Adults, starting at 40–50 years of age, are most often affected, especially fair-skinned people. In general, treatment of rosacea is aimed at improving the untoward cosmetic effects associated with the condition. Surgery may be indicated in a selected subset of individuals with advanced nodular rhinophyma when the condition is causing a significant functional impairment. (Zager, 2012; Habif, 2009; American Academy of Dermatology [AAD], 2008)
The signs and symptoms of rosacea vary from person to person and are often intermittent. The clinical conditions of rosacea include:

- Erythema or flushing of the face/neck
- Pimples: The pimples, or papules and pustules, of rosacea, appear as small red bumps and occur as the disease progresses.
- Red lines: Some individuals with rosacea notice red lines, called telangiectasia, which appear when they flush.
- Bumps on the nose: Nasal bumps, a condition called rhinophyma, are an uncommon sign seen especially in untreated rosacea.
- Facial dryness, burning, stinging or itching

The diagnosis of rosacea is made clinically. A skin biopsy is sometimes performed to exclude diseases such as lupus or sarcoidosis. The most commonly used classification system is based on predominant lesion morphology and was developed by a committee of the National Rosacea Society. Patients are classified as having one of four types of rosacea: erythematotelangiectatic, papulopustular, phymatous, or ocular with a variant form referred to as granulomatous. Individual patients may overlap one or more subtypes, but this system allows physicians to determine therapy based on similar lesion types. Therapeutic options for the various lesion types are easily categorized, and there are few medications or modalities that are significantly effective in more than one category. (Ferri, 2015; Baldwin, 2007)

**Treatments**

Rosacea can be treated and controlled, but there is no cure. Since the pathophysiology of rosacea is unknown, the treatments or therapies of rosacea empirically target the signs and symptoms of the disease. As previously stated, treatment for rosacea is usually performed solely for cosmesis, with the primary purpose being to improve appearance of the skin. However, in certain rare cases of advanced nodular rhinophyma, the condition causes a functional impairment such as airway obstruction, and thus surgical therapy may be indicated. In most patients who receive treatment, a stable state is reached with variable residual symptomatology.

Prior to initiating therapy, identification of any trigger factors are considered. Triggers are both exposures and situations that can cause a flare-up of the flushing and skin changes in rosacea. Trigger factors are specific for each patient and do not affect every patient. Common triggers include: hot or cold temperature, wind, hot drinks, exercise, spicy food, alcohol, emotions, topical products that irritate the skin or impair barrier function, menopausal flushing, and medications that promote flushing. It is recommended that those trigger factors that induce flushing be avoided. Patients are recommended to use a broad-spectrum, gentle sunscreen daily; avoid midday sun, and use protective clothing when in the sun. The untoward cosmetic signs of rosacea may be camouflaged with nonirritating concealers and cosmetics. A combination of treatments is often prescribed, depending on the individual patient’s needs. Sometimes both an oral antibiotic and a topical medication are prescribed. (Kupiec-Banasikowska, 2014; Pelle, 2004)

**Erythema or Flushing:** Topical brimonidine gel (Mirvaso) and topical oxymetazoline cream (Rhofade) are alpha adrenergic agonists FDA approved for the treatment of persistent erythema. Oral and other topical therapies do not clear the redness or reduce the appearance of dilated blood vessels. Anti-inflammatory medication may be used to treat the erythema. Electrosurgery, intense pulse light (IPL) and laser surgery or vascular lasers are often used to destroy the visible blood vessels below the skin. Multiple IPL or laser therapy treatments may be needed to achieve the optimum results. Anecdotal evidence indicates treatment of rosacea with medications that reduce flushing may include anticholinergic medications (for example: glycopyrrolate), beta-blockers, clonidine, and psychotropic medications. These medications can have serious side effects that should be weighed against potential benefits. These therapies or treatments do not treat the underlying cause of rosacea but rather the red appearance of the skin which is associated with rosacea; therefore, these treatments are cosmetic in nature. Unlike agents such as metronidazole and azelaic acid, which can reduce inflammatory lesions and perilesional/infammatory erythema, the therapeutic role of topical alpha-agonists is to reduce the persistent background erythema of rosacea. (Del Rosso, 2013)
Pharmacology

<table>
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<tr>
<td>Mirvaso (brimonidine)</td>
<td>Brimonidine is a relatively selective alpha-2 adrenergic agonist. Topical application of Mirvaso topical gel may reduce erythema through direct vasoconstriction.</td>
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<tr>
<td>Rhofade (oxymetazoline)</td>
<td>Oxymetazoline is an alpha-1A adrenoceptor agonist. Oxymetazoline acts as a vasoconstrictor.</td>
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Professional Societies/Organizations

National Rosacea Society Expert Committee on the Classification and Staging of Rosacea

In 2009 the National Rosacea Society provided management options for rosacea according to the individual’s subtype. Alpha-agonists, such as clonidine, are considered part of a therapeutic approach for severe erythematotelangiectatic rosacea (subtype 1), which is primarily characterized by flushing and persistent erythema of the central face. (Odom, 2009) Topical brimonidine gel and topical oxymetazoline cream were not commercially available when this guideline was published and alpha agonists are not recommended for any other subtype of rosacea.

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for Mirvaso or Rhofade.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for Mirvaso or Rhofade.

Off Label Uses

AHFS Drug Information 2019 Edition does not support any off-label uses of Mirvaso or Rhofade.

Experimental, Investigational, Unproven Uses

Brimonidine topical gel has also been studied preoperatively in a limited number of patients for treating hemostasis in Mohs micrographic surgery. (Chen, 2017) Topical oxymetazoline has also been studied in a limited number of patients for treating fecal incontinence in patients with spinal cord injury. (Barak, 2019) At this time there is insufficient evidence to support use of brimonidine topical gel and oxymetazoline topical cream in these conditions.

Coding/ Billing Information

Note: Brimonidine topical gel and oxymetazoline topical cream are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

References


