Rosacea, a chronic and potentially life-disrupting skin condition, affects an estimated 16 million people in the United States. Although rosacea generally affects the facial area, it can also occur on the neck, ears, scalp, or chest. The manifestations of rosacea include facial erythema; visible blood vessels; swollen, red acne-like bumps; dry eyes; and swollen, reddened eyelids. Rosacea is classified into 4 major subtypes:

- Subtype 1, erythematotelangiectatic rosacea
- Subtype 2, papulopustular rosacea
- Subtype 3, phymatous rosacea
- Subtype 4, ocular rosacea.

Occurring most frequently in middle-aged women with fair skin, rosacea also affects all population segments. Individuals between the ages of 30 and 60 years, people who have a family history of rosacea, and those who tend to flush or flush easily are at increased risk for rosacea. A severe and rare complication of rosacea is rhinophyma, an enlargement of the sebaceous glands in the nose resulting in a buildup of tissue on and around the nose, which generally occurs more frequently in men and develops slowly over several years.

Factors that can trigger rosacea include spicy foods, alcohol, temperature extremes, sunlight, strenuous activity, hot baths or saunas, and emotional stress. Corticosteroids (eg, prednisone) and vasodilators, including some blood pressure medications, can also trigger rosacea. Although the pathophysiology of rosacea is not fully understood, it is thought to be an inflammatory disorder characterized by neurovascular dysregulation and inflammation that produce physiochemical and structural changes in the skin, as described by Del Rosso and colleagues. Vasculature, dermal matrix degeneration, pilosebaceous unit abnormalities, and interactions with microbial organisms are among the multiple factors that may play a role in rosacea. Contributors to inflammation may include antimicrobial peptides, processing enzymes, and toll-like receptors (a class of proteins).

The facial manifestations of rosacea have a substantial psychosocial impact on patients. Based on a survey of 502 women with rosacea, 54% of these women waited ≥7 months after symptom onset before seeking medical assistance, and the mean time from symptom onset to diagnosis was 12.9 months (median, 6 months). Overall, the survey revealed that rosacea was associated with a negative self-perception and a negative first impression by others, regardless of the observer’s own appearance.

In another survey of 801 patients with rosacea conducted in 2012 by the National Rosacea Society, 61% of patients with erythematotelangiectatic rosacea (characterized by facial redness) revealed that rosacea had inhibited their social lives; this percentage increased to 72% among patients with moderate or severe facial erythema. Moreover, 77% of patients with papulopustular rosacea and 85% of patients with phymatous rosacea reported that the condition had a negative impact on their social lives.

Although there is no known cure for rosacea, medical treatment can help control the disorder and alleviate symptoms. However, only a small portion of patients affected by rosacea are receiving treatment. Without treatment, rosacea can worsen over time—sign and symptoms may flare up for weeks to months, then recede, followed by a repeat flare-up. The clinical diagnosis of rosacea requires differentiating between rosacea and acne, because both conditions may have a similar appearance, particularly in the presence of papules or pustules.

The therapeutic goals for rosacea include managing the clinical signs and physical symptoms while addressing the patient’s emotional health and quality of life. Treatment approaches for rosacea include lifestyle changes, skin care regimens, patient education, topical treatment, and systemic pharmacologic therapy, or a combination of oral and topical therapies.

Mirvaso, a New Topical Treatment for Facial Erythema of Rosacea

In August 2013, brimonidine topical gel, 0.33% (Mirvaso; Galderma) was approved by the US Food and Drug Administration (FDA) for the topical treatment of the facial erythema of rosacea in adults aged ≥18 years. Mirvaso is the first topical agent to receive FDA approval for the treatment of facial erythema of rosacea.

According to J. Mark Jackson, MD, Clinical Professor of Medicine, University of Louisville, KY, and a principal investigator of the phase 3 clinical trials, “The FDA
approval of Mirvaso marks a turning point in rosacea treatment: we are now able to provide patients who deal with the daily frustrations caused by the redness [ie, erythema] of rosacea with an effective therapy.” Dr Jackson emphasized that facial erythema “is the most common symptom of rosacea, but until now, physicians have been without prescription treatment options to specifically address this patient need.” 9

Mechanism of Action

Brimonidine is a relatively selective alpha-2 adrenergic agonist. The topical application of brimonidine gel may reduce erythema through direct vasoconstriction. 10

Brimonidine is extensively metabolized by the liver. Urinary excretion is the major route of elimination of brimonidine and its metabolites. 10

Dosing

A pea-sized amount of brimonidine gel is applied once daily to each of the 5 areas of the face—central forehead, chin, nose, and each cheek. Brimonidine topical gel should be applied smoothly and evenly as a thin layer across the entire face, avoiding the eyes and lips. Immediately after applying brimonidine topical gel, hand washing is recommended. Brimonidine topical gel is not for oral, ophthalmic, or intravaginal use. 10

Brimonidine topical gel, 0.33% is available as an aqueous gel containing 5 mg of brimonidine tartrate, equivalent to 3.3 mg of brimonidine-free base. 10

Clinical Trials

The efficacy of brimonidine topical gel was evaluated for the treatment of moderate-to-severe, persistent (non-transient) facial erythema of rosacea in 2 randomized, double-blind clinical trials of 553 adults who were treated once daily for 4 weeks with brimonidine topical gel or vehicle gel. The baseline disease severity was graded using a 5-point clinical erythema assessment scale and a 5-point patient self-assessment scale, on which patients scored moderate or severe on both scales. 10

In both pivotal trials, the primary efficacy end point was 2-grade composite success, defined as the proportion of patients with a 2-grade improvement on the clinical erythema assessment and patient self-assessment measures at hours 3, 6, 9, and 12 on day 29. In addition to day 29, efficacy was also evaluated on day 1 and day 15. 10

The 2-grade composite success summary from study 1 is shown in Table 1. The success summary for study 2 is shown in Table 2. In both studies, the efficacy of topical brimonidine gel 0.5% was shown to be significantly superior to the vehicle gel throughout 12 hours on days 1, 15, and 29, with significant differences observed as early as 30 minutes after the initial application on day 1 (all P <.001). 11

Safety

In controlled clinical trials with brimonidine topical gel, the most common adverse reactions (incidence, ≥1%) included erythema, flushing, skin burning sensation, and contact dermatitis. 10

In an open-label, long-term study in 276 patients with persistent (nontransient) facial erythema who applied brimonidine topical gel for at least 1 year, the most common adverse events (≥4% of patients) were flushing (10%), erythema (8%), rosacea (5%), nasopharyngitis (5%), skin burning sensation (4%), increased intraocular pressure (4%), and headache (4%). 10

Allergic contact dermatitis was reported in approximately 1% of patients in clinical studies. Of the 2 patients who underwent patch testing with individual product ingredients, 1 patient was found to be sensitive to brimonidine tartrate, and the other patient was sensitive to phenoxyethanol, a preservative. 10

Warnings and Precautions

Potentiation of vascular insufficiency. Brimonidine topical gel should be used with caution in patients with
topical gel, 0.33%.

**Severe cardiovascular disease.** Alpha-2 adrenergic agonists can lower blood pressure. Brimonidine topical gel should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease.

**Serious adverse reactions following ingestion of brimonidine topical gel.** After the accidental ingestion of brimonidine topical gel by 2 young children, 1 or both children experienced serious adverse reactions, including lethargy, respiratory distress with apneic episodes (requiring intubation), sinus bradycardia, confusion, psychomotor hyperactivity, and diaphoresis. Both children were hospitalized overnight and were discharged the next day without sequelae. Brimonidine topical gel should be kept out of the reach of children.

For the first time ever, patients with rosacea now have an efficient topical treatment option for the persistent facial erythema that is associated with rosacea, as a result of the FDA approval of brimonidine topical gel, 0.33%.

**Erythema and flushing.** In clinical trials, some individuals discontinued the use of brimonidine because of erythema or flushing. The effect of brimonidine topical gel may begin to diminish hours after application. For some individuals in the clinical trials, erythema was reported to return worse compared with the severity at baseline. Intermittent flushing occurred in some patients treated with brimonidine topical gel.

The onset of flushing relative to the application of brimonidine topical gel varies, ranging from approximately 30 minutes to several hours. Erythema and flushing resolve after the discontinuation of brimonidine topical gel.\(^\text{10}\)

**Drug Interactions**

Caution should be exercised when using beta-blockers, antihypertensive agents, and/or cardiac glycosides, because alpha-2 agonists may reduce blood pressure.\(^\text{10}\)

Although specific drug–drug interaction studies have not been conducted with brimonidine topical gel, the possibility of an additive or potentiating effect with central nervous system depressants (ie, alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Monoamine oxidase inhibitors (MAOIs) may interfere with the metabolism of brimonidine and may potentially result in an increased systemic side effect, such as hypotension. Caution is advised for patients taking MAOIs, which can affect the metabolism and uptake of circulating amines.\(^\text{10}\)

**Conclusion**

For the first time ever, patients with rosacea now have an efficient topical treatment option for the persistent facial erythema that is associated with rosacea, as a result of the FDA approval of brimonidine topical gel, 0.33% in August 2013. In 2 pivotal clinical studies of 4-week duration, brimonidine topical gel demonstrated a significantly greater improvement in the erythema of rosacea compared with the vehicle gel.

The most common adverse reactions (incidence, \(\geq 1\%\)) in controlled clinical trials included erythema, flushing, skin burning sensation, and contact dermatitis.

**References**

10. Mirvaso (brimonidine) topical gel [prescribing information]. Fort Worth, TX: Galderma Laboratories, LP; August 2013.