

Brimonidine Topical Gel (MIRVASO)

National Drug Monograph

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Brimonidine topical gel was FDA approved in August 2013 for the treatment of patients with the erythematotelangiectatic subtype of rosacea, which is characterized by flushing and persistent facial erythema. No other agents to date have been given FDA approval for this indication. Each gram of gel contains 5 mg (0.5%) of brimonidine tartrate, equivalent to 3.3 mg (0.33%) of brimonidine free base.
- Brimonidine is a relatively selective alpha-2 adrenergic agonist. Topical application of brimonidine gel is thought to reduce erythema through direct vasoconstriction.
- Results from the phase II trials showed reduction in facial erythema in a dose-dependent fashion (strengths evaluated, reported in terms of the tartrate salt: 0.07% once daily, 0.18% once daily or twice daily, 0.5% once daily). Brimonidine tartrate gel 0.5% (equivalent to brimonidine 0.33%) was found to have the most statistically superior success profile defined as a 2-grade improvement in CEA/PSA.
- Phase III trials evaluated use of brimonidine tartrate gel 0.5% with a treatment duration of 1 month. There was also a 4 week follow-up phase to measure for rebound, defined as worsening of erythema after treatment cessation. In both phase III study groups, brimonidine tartrate gel 0.5% was found to have a statistically superior success profile compared to vehicle. No rebound effect was observed.
- In a sub-analysis of Phase III trials, both studies showed a statistically significant improvement vs. placebo in the secondary efficacy outcome: 1 grade improvement of both CEA and PSA at 30 minutes post-dosing on day 1, day 15, and day 29.
- A long-term open-label trial including 449 subjects with moderate to severe erythema of rosacea used brimonidine tartrate 0.5% gel once daily for up to 12 months. For the efficacy outcome, mean CEA score at hour 0 reduced from 3.1 on day 1 to 2.4 at month 3, remaining stable until month 12.
- Safety: The most commonly related adverse events related to brimonidine gel are dermatological, mild and transient in nature: erythema (onset ranging from approximately 30 minutes to several hours), flushing, skin burning sensation, and dermatitis.
- There are no contraindications for use of brimonidine gel. Warnings and precautions include potentiation of vascular insufficiency, severe cardiovascular disease, ingestion of brimonidine gel, and erythema and flushing.
- As brimonidine gel is for topical use only, there are relatively few drug-drug interactions. Brimonidine topical gel may potentiate decreased blood pressure when used with antihypertensives or cardiac glycosides and may potentiate central nervous system depressant effects when used with alcohol, opioids, barbiturates, sedatives or anesthetics. Additionally, monoamine oxidase (MAO) inhibitors may reduce metabolism of brimonidine tartrate.
- Conclusions: Brimonidine tartrate gel is the only approved drug therapy for the erythematotelangiectatic subtype of rosacea, which is characterized by flushing and persistent facial erythema. There are no high-quality randomized controlled trials evaluating the use of other topical medications in the erythematotelangiectatic subtype of rosacea, but data from studies of metronidazole 1% cream or azelaic acid 15% gel in patients with papulopustular rosacea show some benefit in reduction of facial erythema. In three high-quality Phase II and Phase III randomized controlled trials involving a primarily female population, brimonidine gel 0.33% once daily was shown to have a small to medium effect size in reduction of erythema. A long-term open-label trial demonstrated that brimonidine tartrate gel 0.5%

maintained efficacy in reducing mean CEA score through month 12. No trials assessed patient satisfaction. Additionally there were no trials longer than 12 months that assessed the efficacy, safety or rebound effects of brimonidine gel. Adverse reactions mainly affected the dermatologic system and treatment was generally well tolerated. Use in Veterans with significant vascular comorbidities may need careful consideration because of the alpha-2 adrenergic agonist effects of this medication. The evidence supports a first-line place in therapy for brimonidine gel for persistent erythema associated with the erythematotelangiectatic subtype of rosacea. The evidence does not support the use of brimonidine for papulopustular rosacea.

Introduction

Brimonidine topical gel is a new formulation of brimonidine tartrate, which has been available in the US as single-entity and fixed-combination ophthalmic products for the treatment of ophthalmic conditions such as ocular hypertension or open-angle glaucoma with elevated intraocular pressure.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating brimonidine topical gel 0.33% for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Brimonidine is a relatively selective alpha-2 adrenergic agonist. Topical application of brimonidine gel is thought to reduce erythema through direct vasoconstriction. Absorption data was obtained in patients who applied brimonidine topical gel 1 g once daily to the entire face for 29 days. The mean plasma maximum concentration (Cmax) and area under the concentration-time curve (AUC) (\pm standard deviation) were highest on day 15 (46 ± 62 pg/mL and 417 ± 264 pg.hr/mL, respectively). Brimonidine is extensively metabolized by the liver. Urinary excretion is the major route of elimination of brimonidine and its metabolites.¹

Table 1 Pharmacokinetics of Brimonidine Gel

Absorption	Cmax 46 ± 62 pg/mL
Metabolism	Hepatic
Excretion	Urinary

FDA Approved Indication(s)

Brimonidine topical gel is FDA-approved for the topical treatment of persistent (nontransient) facial erythema of rosacea in adults 18 years and older.¹ It is the first US product approved exclusively for the treatment of the erythema of rosacea and the only approved drug therapy for the erythematotelangiectatic subtype of rosacea which is characterized by flushing and persistent facial erythema.² Telangiectasias, the presence of small dilated blood vessels near the surface of the skin or mucus membranes, may also be evident in this subtype of rosacea.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's [Guidance on "Off-label" Prescribing](#) (available on the VA PBM Intranet site only).

No evidence is currently available to support off-label uses of brimonidine topical gel.

Current Alternatives

Other products that address erythema of rosacea (not persistent / nontransient erythema per se) in their approved indications:

- Metronidazole Cream (NORITATE) 1% – for “the topical treatment of inflammatory lesions and erythema of rosacea.” [On VA National Formulary]³
- Azelaic Acid (FINACEA) Gel 15% – for “the topical treatment of the inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.” [Nonformulary]⁴

Other metronidazole formulations available as 0.75% cream, gel and lotion are approved for “topical application in the treatment of inflammatory papules and pustules of rosacea” and are not labeled to address the erythema of rosacea. There are no high-quality randomized controlled trials evaluating the use of metronidazole 1% cream or azelaic acid 15% gel in the erythematotelangiectatic subtype of rosacea, but data from studies of these drugs in patients with papulopustular rosacea show some benefit in reduction of facial erythema.⁵

Four studies have demonstrated the effectiveness of anti-inflammatory doses of doxycycline in reducing the number of lesions of patients with papulopustular rosacea, however patient satisfaction was not assessed. Further research was needed to confirm effect on erythema as evidence was not strong.⁵

The following agents have anecdotal reports of use for treating persistent erythema of rosacea: topical oxymetazoline, topical retinoids, oral isotretinoin, oral apremilast. None of these have received the FDA approval for treatment of the erythematotelangiectatic subtype of rosacea.

Dosage and Administration

Adults: Apply a pea-size amount of brimonidine topical gel, 0.33% smoothly and evenly as a thin layer once daily to each of the five areas of the face (chin, nose, central forehead, and each cheek). Each gram of gel contains 5 mg of brimonidine tartrate, equivalent to 3.3 mg of brimonidine free base. Avoid applying to eyes and lips and wash hands immediately after use.¹

Efficacy

Efficacy Measures

Phase II and Phase III randomized controlled trials use reduction in the clinician erythema assessment (CEA) and reduction in the patient’s self-assessment (PSA) as primary endpoints for establishing efficacy of brimonidine. Efficacy outcomes look for either a 1 or 2 grade improvement in both scales at different time points after application of brimonidine gel and different durations of therapy.⁶

Composite Success at Hours 3, 6, 9 and 12 on Day 29, then on Day 15 and lastly Day 1 was the primary end point. *Composite Success* was defined as a 2-grade improvement on both the CEA and PSA at each time point. The Day-29 result was used for the primary analysis. If the result showed a statistically significant treatment difference, statistical testing was to continue to Day 15 and then to Day 1. The FDA conducted post hoc modified ITT analyses which showed results that were similar to the per protocol Day-29 results conducted by the drug Sponsor.

Table 2 Erythema rating scales used in clinical trials

Scores	CEA	PSA
0, Clear	Clear skin with no signs of erythema	No redness
1, Almost clear	Almost clear, slight redness	Very mild redness
2, Mild	Mild erythema, definite redness	Mild redness
3, Moderate	Moderate erythema, marked redness	Moderate redness
4, Severe	Severe erythema; fiery redness	Severe redness

Summary of efficacy findings

- All studies used the CEA/PSA erythema rating scales to assess severity of facial erythema of rosacea. The phase II and III trials evaluated use of brimonidine in patients with moderate-severe erythema. The majority of subjects in all trials were female (75-80%) and average age was 45-50 years.^{6,7,8,9}
- Results from two phase II trials were published in Fowler et. al. (2012).⁷ The first study is a phase IIa trial evaluating effects of a single application of three different brimonidine strengths that were reported in terms of brimonidine tartrate * (0.07%, 0.18%, 0.5%) vs. placebo in 122 subjects. Brimonidine tartrate 0.5% was the only strength with a statistically superior success rate defined as a 2-grade improvement on CEA/PSA over 12 hours ($p<0.001$). The brimonidine tartrate 0.5% group had 55% of subjects with a 2-grade improvement on CEA/PSA vs. 12% of subjects in the vehicle group. This resulted in a treatment difference of 43% and a medium effect size (NNT=3, 95% CI 2-5). However, all strengths did show 1-grade improvement of CEA/PSA at 12 hours $p<0.001$).
- The second study was a phase IIb trial evaluating effects of different strengths/dosing regimens of brimonidine tartrate (0.18%, 0.5% or vehicle once daily; 0.18% or vehicle twice daily) vs. placebo in 269 subjects for 4 weeks (treatment phase) followed by a 4-week follow-up phase (no treatment). Results again showed that brimonidine tartrate 0.5% gel had superior success rates with a 2-grade improvement on CEA/PSA at 12 hours on day 29 ($p<0.001$). The brimonidine tartrate 0.5% group had 19% of subjects with a 2-grade improvement on CEA/PSA vs. 4% of subjects in the vehicle group. This resulted in a treatment difference of 15% and a small effect size (NNT=7, 95% CI 4-28).
- Results from two high-quality, phase III, multicenter, double-blind, vehicle-controlled, randomized clinical trials were published in Fowler et. al. (2013).⁸ Both studies assessed the efficacy of brimonidine tartrate gel 0.5% daily vs. placebo in 553 subjects for 4 weeks (treatment phase) followed by a 4-week follow-up phase (no treatment). Subjects had a clinical diagnosis of facial rosacea with CEA and PSA scores of ≥ 3 (moderate-severe) and fewer than three facial inflammatory lesions of rosacea. On day 29, the brimonidine groups in both studies showed superior success profiles ($p<0.001$). The NNTs ranged from 5 to 9, with lower confidence limits (CLs) ranging from 4 to 6 and upper CLs ranging from 9 to 36, indicating small effect sizes overall.
- A sub-analysis of the two high-quality phase III trials (Fowler et. al. 2013) was conducted and published separately in Jackson et. al (2014).⁶ Both studies showed a statistically significant ($P< 0.001 - P=0.003$) improvement vs. placebo in the secondary efficacy outcome: 1-grade improvement of both CEA and PSA at 30 minutes post-dosing on day 1, day 15, and day 29. The NNT ranged from 3 to 6 indicating medium effect sizes overall (CI not reported).
- Results from a 52 week open-label, non-placebo controlled trial are published in Moore et. al. (2014).⁹ In this trial 449 subjects with moderate to severe erythema of rosacea used brimonidine tartrate 0.5% gel once daily for up to 12 months. For the efficacy outcome, mean CEA score at hour 0 decreased by 0.7 from 3.1 (moderate-severe) on day 1 to 2.4 (mild-moderate) at month 3, remaining stable until month 12.

* According to FDA policy, drug product strength should be expressed in terms of the active moiety rather than the salt strength equivalent

Table 3 Summary of Brimonidine Gel Studies in Erythema of Rosacea

Reference	Design, Study Population	Findings
Fowler, J et al. (2012)	<p><u>Study A:</u></p> <p>Randomized, double blind, parallel-group, phase IIa study of a single application of brimonidine tartrate 0.07%, 0.18%, 0.5% or vehicle</p> <p>Patient population included 122 subjects ≥ 18 yo with moderate-severe erythema. Majority of subjects were female (75%) and mean age was 46 yo.</p>	<p><u>Study A:</u></p> <p>Brimonidine tartrate (BT) was superior to vehicle in terms of</p> <ul style="list-style-type: none"> 2-grade improvement of both CEA and PSA at 12 hrs for BT 0.5% vs vehicle: 55% vs. 12% ($p<0.001$). NNT=3 (95% CI 2-5). 1-grade improvement of both CEA and PSA at 12 hrs: 84%, 81%, 75% for BT 0.5%, 0.18%, 0.07%, respectively, vs. 28% for vehicle ($p<0.001$). NNT=2, 2, 3 for BT 0.5%, 0.18%, 0.07%, respectively. <p>No serious adverse events; well tolerated</p>
	<p><u>Study B:</u></p> <p>8-week randomized, double-blind, parallel-group phase IIb study of brimonidine tartrate 0.5% daily, 0.18% daily, 0.18% BID or vehicle daily or twice daily</p> <p>Patient population included 269 subjects ≥ 18 yo with moderate to severe erythema. Majority of subjects were female (81%) and mean age was 44yo.</p>	<p><u>Study B:</u></p> <p>Brimonidine was superior to vehicle in terms of</p> <ul style="list-style-type: none"> 2-grade improvement of both CEA and PSA at 12 hrs on day 29 for BT 0.5% daily vs. vehicle daily: 19% vs. 4% ($p<0.001$). NNT=7 (95% CI 4-28). 1-grade improvement of both CEA and PSA at hrs 3-12 on day 29 for BT 0.5% daily vs. vehicle daily: 60-76% vs. 13-42% ($p<0.001$). <p>No serious adverse events; well tolerated</p>
Fowler J, et al. (2013)	<p><u>Study A:</u></p> <p>8-week randomized, double-blind, parallel-group, vehicle-controlled, phase III study of a brimonidine tartrate 0.5% daily vs. vehicle applied for 4 weeks with a 4-week follow-up phase</p> <p>Patient population included 260 subjects ≥ 18 yo with moderate-severe erythema. Majority of subjects were female (79%) and mean age was 49yo.</p>	<p><u>Study A:</u></p> <p>Brimonidine was superior to vehicle in terms of</p> <ul style="list-style-type: none"> 2-grade improvement of both CEA and PSA on day 29 at hrs 3, 6, 9, 12 for BT 0.5% vs. vehicle ($p<0.001$; per-protocol): <ul style="list-style-type: none"> 3 hrs: 25.4% vs. 9.2%. NNT=7 (95% CI 4-14). 6 hrs: 25.4% vs. 9.2%. NNT=7 (4-14). 9 hrs: 17.6% vs. 10.6%. (NNT not applicable) 12 hrs: 21.1% vs. 9.9%. NNT=9 (6-36). 1-grade improvement of both CEA and PSA on day 29 at hours 3, 6, 9, 12 for BT 0.5% vs. vehicle ($p<0.001$; per-protocol): <ul style="list-style-type: none"> 3 hrs: 70.9% vs. 32.8%. NNT=3. 6 hrs: 69.3% vs. 32.0%. NNT=3. 9 hrs: 53.8% vs. 29.7%. NNT=5. 12 hrs: 56.7% vs 30.5%. NNT=4. 1-grade improvement of both CEA and PSA at 30 min on day 1 for BT 0.5% vs. vehicle: 27.9% vs 6.9% ($p<0.001$). NNT=5. <p>No serious adverse events; well tolerated.</p>
	<p><u>Study B:</u></p> <p>8-week randomized, double-blind, parallel-group, vehicle-controlled, phase III study of a brimonidine tartrate 0.5% daily vs. vehicle applied for 4 weeks with a 4-week follow-up phase</p>	<p><u>Study B:</u></p> <p>Brimonidine was superior to vehicle in terms of</p> <ul style="list-style-type: none"> 2-grade improvement of both CEA and PSA on day 29 at hrs 3, 6, 9, 12 for BT 0.5% vs vehicle ($p<0.001$; per protocol):

Reference	Design, Study Population	Findings
	Patient population included 293 subjects ≥ 18 yo with moderate-severe erythema. Majority of subjects were female (73%) and mean age was 48yo	<ul style="list-style-type: none"> - 3 hrs: 31.5% vs. 10.9%. NNT=5 (95% CI 4–10). - 6 hrs: 30.7% vs. 9.4%. NNT=5 (4–9). - 9 hrs: 26% vs. 10.2%. NNT=7 (4–16). - 12 hrs: 22.8% vs. 8.6%. NNT=7 (5–19). • 1-grade improvement of both CEA and PSA on day 29 at hours 3, 6, 9, 12 for BT 0.5% vs. vehicle ($p<0.001$; per protocol): <ul style="list-style-type: none"> - 3 hrs: 71.1% vs. 40.1%. NNT=4. - 6 hrs: 64.8% vs. 43.0%. NNT=5. - 9 hrs: 66.9% vs. 39.4%. NNT=4. - 12 hrs: 53.5% vs 40.1%. NNT=8. • 1-grade improvement of both CEA and PSA at 30 min on day 1 for BT 0.5% vs vehicle: 28.4% vs 4.8% ($p<0.001$). NNT=5. <p>No serious adverse events; well tolerated</p>
Jackson JM, et al. (2014)	Sub analysis; obtained from the two 8-week Phase III, multi-center, randomized double-blind, brimonidine tartrate 0.5% daily vs vehicle applied for 4 weeks with a 4-week follow-up phase comparison studies of identical design and duration (see Fowler J, et al. 2013 above)	<p><u>Study A:</u></p> <p>Brimonidine was superior to vehicle in terms of</p> <ul style="list-style-type: none"> • Secondary efficacy outcome: 1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 1: BT gel 0.5% vs vehicle 27.9% vs. 6.9% ($P <0.001$); NNT= 5 (CI not reported). • 1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 15: BT gel 0.5% vs vehicle 55.9% vs. 21.1% ($P <0.001$); NNT= 3 (CI not reported). • 1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 29: BT gel 0.5% vs vehicle 58.3% vs. 32.0% ($P <0.001$); NNT= 4 (CI not reported). <p><u>Study B:</u></p> <p>Brimonidine was superior to vehicle in terms of</p> <ul style="list-style-type: none"> • Secondary efficacy outcome: 1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 1: BT gel 0.5% vs vehicle 28.4% vs. 4.8% ($P <0.001$); difference. NNT= 5 (CI not reported). • 1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 15: BT gel 0.5% vs vehicle 45.5% vs. 28.4% ($P=0.003$); difference. NNT= 6 (CI not reported). • 1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 29: BT gel 0.5% vs vehicle 53.5% vs. 34.5% ($P =0.001$); difference. NNT= 5 (CI not reported).
		No adverse event data mentioned for study A or B
Moore A, et al. (2014)	52-week Open-Label Study, non-placebo controlled 449 subjects with moderate to severe erythema of rosacea at 27 US centers used brimonidine tartrate	<p>Brimonidine</p> <ul style="list-style-type: none"> • Efficacy: mean CEA score at hour 0 decreased from 3.1 on day 1 to 2.4 at month 3, remaining stable until month 12.

Reference	Design, Study Population	Findings
	<p>0.5% gel once daily.</p> <p>Patient population: 74.8% of subjects were female, 97.6% were Caucasian/white, and median age was 50.9yo</p> <p>131 subjects (29.2%) received concomitant therapies for inflammatory lesions of rosacea including metronidazole, azelaic acid, or tetracycline products. 70 subjects (15.6%) received topical metronidazole specifically. No subgroup analysis of the patients treated with concomitant medications was conducted.</p>	<ul style="list-style-type: none"> Safety: 139 subjects (31.0%) reported 238 related AEs during the course of the study No serious adverse events were deemed related to the study drug; well tolerated

Table 4: Assessment of Evidence Base

Category	Summary
Overall Quality of Studies (GRADE) (Internal validity or risk of bias)	GRADE: High. Three studies were rated high because of their randomized, placebo-controlled design and minimal bias. One study was an open-label label trial showing longer-term effects of brimonidine tartrate gel 0.5%.
Consistency of Results (Within and among studies)	3 of 4 studies showed significant benefit in reducing symptoms of erythema of rosacea. The open-label trial demonstrated durability of reduction in symptoms of erythema but was not placebo controlled.
Directness of Evidence	Direct evidence for all 4 studies: all used the same clinician and patient assessment of erythema for efficacy outcomes, which is a measure of the clinically important outcome of interest. The trials did not assess patient satisfaction.
Precision of Results	The 95% CIs for NNTs were relatively narrow at Hours 3, 6 and 9, and were wider for Hour 12.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 12).

Safety

Of 2174 subjects evaluated during the clinical development program, 1619 subjects were exposed to brimonidine gel including 1210 subjects exposed to BT 0.5% gel once daily. In the long-term observational study, 333 subjects were treated for >180 days, and of these subjects, 276 were treated for ≥365 days. In the pivotal trials, the mean daily dose was 0.8 g of brimonidine tartrate 0.5% gel and the mean duration of treatment was 28.6 days. In the long-term observational study, the corresponding amounts were 0.5 g and 277.9 days, respectively.

During the Fowler, J et al. 2012 and 2013 clinical trials,^{7,8} a total of 330 subjects were treated with brimonidine tartrate 0.5% topical gel for 29 days for persistent (nontransient) erythema associated with rosacea. Adverse reactions that occurred in at least 1% of subjects include:

Table 5: Adverse Reactions in RCTs, Pooled Results

Adverse Reaction	Brimonidine Tartrate 0.5% topical gel (n=330) n (%)	Vehicle Gel (n=331) n (%)
Erythema	12 (4%)	3 (1%)
Flushing	9 (3%)	0
Skin burning sensation	5 (2%)	2 (1%)
Dermatitis contact	3 (1%)	1 (<1%)
Dermatitis	3 (1%)	1 (<1%)
Skin warm	3 (1%)	0
Paresthesia	2 (1%)	1 (<1%)
Acne	2 (1%)	1 (<1%)
Pain of skin	2 (1%)	0
Vision blurred	2 (1%)	0
Nasal congestion	2 (1%)	0

Sources: References 1, 7, 8

During the Moore et al. 2014 open-label study, 449 subjects were included in the safety population. 335 subjects (74.6%) completed 6 months of daily treatment with brimonidine tartrate 0.5% topical gel, and 279 (62.1%) completed the study up to the 12 month visit. Adverse reactions that occurred in at least 1% of subjects:

Table 6: Adverse reactions associated with brimonidine gel in long-term open label trial

Flushing	Worsening of Erythema	Worsening of Rosacea	Skin Burning Sensation	Skin Irritation	Contact Dermatitis	Pruritus
9.1 %	6.5%	3.6%	3.3%	3.1%	2.2%	2.0%

Source: Reference 9

Deaths and Other Serious Adverse Events

Published literature reported no deaths or serious adverse events related to topical application of brimonidine gel. There were two serious but unrelated adverse event (AEs) reported in Fowler J, et al. (2012)⁷—one gastric reflux in the brimonidine tartrate 0.18% once daily group and one deep vein thrombosis in the vehicle once daily group.

The FDA Medical Review noted 2 subjects reporting 8 serious adverse events in the brimonidine group. One subject reported appendicitis. The other subject had serious adverse events attributed to her; however, they occurred in her two young children who mistook the medication for toothpaste.¹⁰ See: **Serious Adverse Reactions Following Ingestion of Brimonidine Topical Gel.**

Common Adverse Reactions

The most commonly related adverse events to brimonidine gel were dermatological, and were mild and transient:

- Erythema (onset ranging from approximately 30 minutes to several hours), 4%
- Flushing, 3%
- Skin burning sensation 2%
- Dermatitis, 1%

Other Notable Adverse Events

Two cases of transient, mild and reversible decreases in intra-ocular pressure were observed in the study by Fowler et al. (2012).⁷

Allergic Contact Dermatitis – occurred in about 1% of subjects across clinical trials. Patch testing of 2 subjects revealed sensitivity to brimonidine tartrate in one subject and sensitivity to the preservative phenoxyethanol in the other subject.

Tolerability

Phase II studies (Fowler et al. 2012) – 0 patients discontinued because of adverse events.⁷

Phase III trials (Fowler et al. 2013) – 2 patients (1.6%) discontinued the study because of adverse events (severe skin irritation in one subject and “intermittent rebound erythema” in the other subject).⁸

Long-term open-label study (Moore et al. 2014) – 75 patients (16.7%) discontinued the study because of adverse events.⁹

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 12).

Contraindications

None¹

Warnings and Precautions

Potentiation of Vascular Insufficiency

Brimonidine tartrate topical gel should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud’s phenomenon, orthostatic hypotension, thrombangiitis obliterans, scleroderma, or Sjögren’s syndrome.¹

Severe Cardiovascular Disease

Alpha-2 adrenergic agonists can cause hypotension. Brimonidine tartrate topical gel should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease.¹

Serious Adverse Reactions Following Ingestion of Brimonidine Topical Gel

During clinical trials two young children of a subject accidentally ingested brimonidine tartrate topical gel and experienced adverse reactions: lethargy, respiratory distress with apneic episodes (requiring intubation), sinus bradycardia, confusion, psychomotor hyperactivity, and diaphoresis. Both children were hospitalized overnight and discharged the following day without sequelae. Keep brimonidine tartrate topical gel out of reach of children.¹

Erythema and Flushing

During clinical trials, some subjects discontinued use of brimonidine topical gel because of erythema or flushing. Onset of flushing ranged from 30 minutes to several hours after application and disappeared after discontinuation of brimonidine tartrate. For some subjects the new onset erythema was worse compared to the severity at baseline. Intermittent flushing occurred in some subjects treated with brimonidine tartrate topical gel.¹

Special Populations

Pregnancy: Pregnancy Category B¹

Nursing Mothers: It is unknown whether brimonidine gel is excreted into human breast milk. Animal studies have shown evidence that brimonidine may be excreted in breast milk.¹

Geriatric Use: Clinical trials of brimonidine gel have not included enough subjects ≥65 years of age and older to determine differences in response compared to younger subjects. To date, no overall differences in efficacy or safety have been reported between geriatric and younger populations.¹

Sentinel Events

None/No data

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Table 7: Results of LASA search

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Brimonidine topical gel, 0.33%	Bromocriptine	None	None	Bimatoprost Brimonidine ophthalmic Brinzolamide
Mirvaso	None	None	None	Tyvaso Mirapex Miralax

Drug Interactions

Drug-Drug Interactions

- Antihypertensives: The effects of anti-hypertensives such as beta-blockers, calcium channel blockers, etc. may be enhanced by alpha-2 agonists such as brimonidine tartrate (topical); use caution.¹
- Cardiac Glycosides: Brimonidine topical gel may potentiate decreased blood pressure when used concomitantly with cardiac glycosides; use caution.¹
- CNS depressants: Brimonidine topical may potentiate the CNS depressant effect of CNS depressants such as alcohol, opioids, barbiturates, sedatives or anesthetics; consider this possibility.¹
- Monoamine oxidase (MAO) inhibitors: The metabolism of brimonidine tartrate (topical) may be theoretically reduced by MAO inhibitors resulting in increases systemic side-effects such as hypotension; use caution.¹

Drug-Lab Interactions

None¹

Pharmacoeconomic Analysis

None

Conclusions

Brimonidine tartrate gel is the only approved drug therapy for the erythematotelangiectatic subtype of rosacea, which is characterized by flushing and persistent facial erythema. There are no high-quality randomized controlled trials evaluating the use of other topical medications in the erythematotelangiectatic subtype of rosacea, but data from studies of metronidazole 1% cream or azelaic acid 15% gel in patients with papulopustular rosacea show some benefit in reduction of facial erythema. In three high-quality Phase II and Phase III randomized controlled trials involving a primarily female population, brimonidine gel 0.33% once daily was shown to have a small to medium effect size in reduction of erythema. A long-term open-label trial demonstrated that brimonidine tartrate gel 0.5% maintained efficacy in reducing mean CEA score through month 12. No trials assessed patient satisfaction. Additionally there were no trials longer than 12 months that assessed the efficacy, safety or rebound effects of brimonidine gel. Adverse reactions mainly affected the dermatologic system and treatment was generally well tolerated. Use in Veterans with significant vascular comorbidities may need careful consideration because of the alpha-2 adrenergic agonist effects of this medication. The evidence supports a first-line place in therapy for brimonidine gel for persistent erythema associated with the erythematotelangiectatic subtype of rosacea. The evidence does not support the use of brimonidine for papulopustular rosacea.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2014) using the search terms <brimonidine> and <Mirvaso>. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Table 8: Study Methods: Brimonidine Tartrate in Erythema of Rosacea

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
<p>Fowler J, Jarratt M, Moore A, Meadows K, Pollack A, Steinhoff M, et al. Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicenter, randomized and vehicle-controlled studies. <i>Br J Dermatol.</i> 2012 Mar;166(3):633-41. (STUDY A)</p>				
<p>Design: Randomized, double blind, parallel-group, phase IIa study of a single application of brimonidine tartrate 0.07%, 0.18%, 0.5% or vehicle</p> <p>Inclusion: age ≥ 18yo, mod-sev erythema according to both CEA and PSA, <3 facial inflammatory lesions</p> <p>Efficacy assessed at baseline, 30min and every hour up to 12hrs after application</p> <p>Blinding: packaged in identical tubes, required 3rd party to dispense medication</p> <p>ITT population included all subjects randomized, safety population included all subjects receiving the study medication</p>	<p>122 subjects randomized (mean age 46yo, age range 18-74yo, 75% female, 76.2% had moderate CEA, 72% had moderate PSA, 100% completed study)</p>	<p>Subjects randomized 1:1:1:1 to receive single application of gel containing BT 0.5%, BT 0.17%, BT 0.07% or vehicle to the entire face</p>	<p>Efficacy</p> <p>Primary: Change in erythema measured by a 1 or 2-point improvement CEA and PSA over 12hrs</p> <ul style="list-style-type: none"> -1-grade improvement significant for all active treatments: 84% (BT 0.5%), 81% (BT 0.18%), 75% (BT 0.07%) vs. 28% (vehicle), p<0.001. -2-grade improvement significant only for BT 0.5%: 55% (BT 0.5%) vs. 12% (vehicle), p <0.001. <p>Secondary: Chroma Meter a* parameter, inflammatory lesions counts, severity of telangiectasia</p> <ul style="list-style-type: none"> -Chroma Meter a* values significantly reduced at all time measurements (p<0.001) for BT 0.5% only. Maximal effect had duration of 4-6hrs observed between 2-8hrs after application. After 8hrs, redness started to reappear but never returned to baseline. -No aggravations in telangiectasia or inflammatory lesions <p>Safety: AEs, vital signs, IOP</p> <ul style="list-style-type: none"> -All 3 concentrations were safe and well-tolerated. AEs were transient, dermatologic in nature and mild in intensity. AEs related to active drug ranged from 6% (BT 0.5%, 2 subjects) to 14% (0.07%, 4 subjects). 19% of subjects in the vehicle group reported AEs. 2 cases of mild, transient decreases on IOP observed (1 in BT 	<p>Sponsor: Galderma R&D</p> <p>GRADE: High</p> <p>Notes: BT gel was effective in dose-dependent fashion in reducing erythema for 12 hours after single application. Largest effect found with BT 0.5%. Onset of effect evident as early as 30 min after application.</p> <p>External Validity to VA: Possible (majority of subjects Caucasian, female)</p>

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
<p>Design: 8-week randomized, double-blind, parallel-group phase IIb study of brimonidine tartrate 0.5% daily, 0.18% daily, 0.18% twice daily or vehicle daily or twice daily</p> <p>Inclusion: ≥ 18yo, clinical diagnosis of rosacea, <3 facial inflammatory lesions, mod-sev erythema according to both CEA and PSA</p> <p>Treatment phase:</p> <ul style="list-style-type: none"> -CEA, PSA, telangiectasia assessed on days 1, 15, 29 at hrs 0, 3, 6, 9, 12hrs -Inflammatory lesion counts and IGA of lesions assessed at baseline and day 29 at 12hrs <p>Follow-up phase:</p> <ul style="list-style-type: none"> -CEA, PSA, telangiectasia, inflammatory lesions and IGA assess on day 30 and weeks 5, 6, 8 <p>Blinding: packaged in identical tubes, required 3rd party to dispense medication</p> <p>ITT population included all subjects randomized, safety population included all subjects receiving the study medication</p>	<p>269 subjects randomized (mean age 44yo, age range 18-74yo, 81% female, 84% had moderate CEA, 84% had moderate PSA, 96.7% completed study)</p>	<p>Subjects randomized in a 1:1:1:1 ratio to BT 0.5% daily, BT 0.18% daily, BT 0.18% BID, vehicle BID, vehicle daily x4weeks. Once daily applications were applied in the morning. Twice daily applications were applied 6hrs after the first application. During the 4-week follow-up period, no medication application was performed.</p>	<p>0.5%, 1 in BT 0.18%)</p> <p>Efficacy:</p> <p>Primary: Treatment success defined as 2-grade improvement on both CEA and PSA over 12hrs on days 29, 15, 1.</p> <ul style="list-style-type: none"> -Significantly greater success with BT 0.5% on day 29 at 3, 6, 9, 12 hr ($p<0.001$): 30%, 28%, 32%, 19% (BT 0.5%) vs. 4%, 7%, 4%, 4% (vehicle), respectively Secondary: 1-grade improvement on both CEA and PSA over 12 hrs on days 29, 15, 1; rebound defined as worsening of erythema using CEA and PSA after treatment cessation; telangiectasia, inflammatory lesions -1-grade improvement: Significantly greater responder rate of BT 0.5% vs vehicle daily on day 29 (60-76% with BT vs. 31-42% with vehicle, $p<0.001$) as well as days 1 and 15 (no data available) -Rebound: no clinically meaningful aggravation of facial erythema; few isolated cases observed -No aggravations of telangiectasia or inflammatory lesions <p>Safety: AEs, vitals, IOP</p> <ul style="list-style-type: none"> -1 related AE of mild skin burning leading to discontinuation in BT 0.18% BID group. A lower incidence of related AEs observed for vehicle BID (2%) than active drug (range 11-19%). Majority of AEs were dermatological, transient and 	<p>Sponsor: Galderma R&D</p> <p>GRADE: High</p> <p>Notes: Similar to study A, BT 0.5% gel was significantly more efficacious than vehicle throughout the study.</p> <p>External Validity to VA: Possible (majority of subjects Caucasian, female)</p>

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
<p>Fowler J, Jackson JM, Moore A, Jarratt M, Jones, T, Meadows K, et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized double-blind, vehicle-controlled pivotal studies. <i>J Drugs Dermatol.</i> 2013;12(6):650-6. (STUDY A)</p>				
<p>Design: 8-week randomized, double-blind, parallel-group, vehicle-controlled, phase III study</p> <p>Inclusion: ≥ 18yo, clinical diagnosis of rosacea, <3 facial inflammatory lesions, mod-sev erythema according to both CEA and PSA</p> <p>Wash-out period mandatory for subjects using prescription medications for rosacea, acne or inflammatory conditions</p> <p>Treatment phase:</p> <ul style="list-style-type: none"> -CEA and PSA assessed on days 1, 15, 29 at baseline, 30min, hrs 3, 6, 9, 12hrs -Telangiectasia, IGA, inflammatory lesion counts assessed at baseline and hr 12 on day 29 <p>Follow-up phase:</p> <ul style="list-style-type: none"> -CEA, PSA, telangiectasia, inflammatory lesions and IGA assessed at weeks 6 and 8 <p>All efficacy variables analyzed based on ITT population. Primary analyses also performed on PP population. Safety population included all subjects who had applied study drug at least once.</p>	<p>260 subjects randomized (mean age 49yo, age range 18-87yo, 79% female, 98.5% Caucasian, 86.2% had moderate CEA, 85% had moderate PSA, 97.7% completed study)</p>	<p>Subjects randomized 1:1 to BT 0.5% or vehicle with instructions to apply a thin film on the entire face x4-weeks. During the 4-week follow-up period, no medication application was performed.</p>	<p>Efficacy</p> <p>Primary: Treatment success defined as 2-grade improvement on both CEA and PSA on days 1, 15, 29 over 12 hrs with BT vs. vehicle</p> <ul style="list-style-type: none"> -Day 29: 31.5%, 30.7%, 26%, 22.8% vs. 10.9%, 9.4%, 10.2%, 8.6% ($p<0.001$ for ITT analyses; $p<0.05$ for PP analyses) at hrs 3, 6, 9, 12, respectively -Day 1 and 15: BT significantly more efficacious ($p<0.001$) – no data <p>Secondary: 1-grade improvement on both CEA and PSA on day 29 over 12 hrs with BT vs. vehicle; 30-min effect defined as 1-grade improvement on both CEA and PSA at 30min on day 1</p> <ul style="list-style-type: none"> -1-grade improvement over 12 hrs: 70.9%, 69.3%, 63.8%, 56.7% vs. 32.8%, 32.0%, 29.7%, 30.5% ($p<0.001$) at hrs 3, 6, 9, 12, respectively on day 29. Days 1 and 15 showed BT significantly more efficacy as well ($p<0.001$) – no data. -30-min effect: 27.9% vs. 6.9% ($p<0.001$) <p>-Rebound: worsening found with 4.0% of BT subjects for CEA and 2.4% for PSA at week 6; 4.7% for CEA and 1.6% for PSA at week 8. Similar effects reported in vehicle group (no data).</p> <p>-No aggravations in inflammatory lesions, telangiectasia, IGA</p>	<p>Sponsor: Galderma R&D</p> <p>GRADE: High</p> <p>Notes:</p> <p>External Validity to VA: Possible (majority of subjects Caucasian, female)</p>

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
Fowler J, Jackson JM, Moore A, Jarratt M, Jones, T, Meadows K, et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized double-blind, vehicle-controlled pivotal studies. <i>J Drugs Dermatol.</i> 2013;12(6):650-6. (STUDY B)				
<p>Design: 8-week randomized, double-blind, parallel-group, vehicle-controlled, phase III study</p> <p>Inclusion: ≥ 18yo, clinical diagnosis of rosacea, <3 facial inflammatory lesions, mod-sev erythema according to both CEA and PSA</p> <p>Wash-out period mandatory for subjects using prescription medications for rosacea, acne or inflammatory conditions</p> <p>Treatment phase:</p> <ul style="list-style-type: none"> -CEA and PSA assessed on days 1, 15, 29 at baseline, 30min, hrs 3, 6, 9, 12hrs -Telangiectasia, IGA, inflammatory lesion counts assessed at baseline and hr 12 on day 29 <p>Follow-up phase:</p> <ul style="list-style-type: none"> -CEA, PSA, telangiectasia, inflammatory lesions and IGA assessed at weeks 6 and 8 	<p>293 subjects randomized (mean age 48yo, age range 19-78yo, 73% female, 98.6% Caucasian, 76.2% had moderate CEA, 85.7% had moderate PSA, 96.6% completed study)</p>	<p>Subjects randomized 1:1 to BT 0.5% or vehicle with instructions to apply a thin film on the entire face x4-weeks. During the 4-week follow-up period, no medication application was performed.</p>	<p><u>Efficacy</u></p> <p>Primary: Treatment success defined as 2-grade improvement on both CEA and PSA on days 1, 15, 29 over 12 hrs with BT vs. vehicle</p> <ul style="list-style-type: none"> -Day 29: 25.4%, 25.4%, 17.6%, 21.1% vs. 9.2%, 9.2%, 10.6%, 9.9% ($p<0.001$ for ITT analyses; $p<0.05$ for PP analyses) at hrs 3, 6, 9, 12, respectively -Day 1 and 15: BT significantly more efficacious ($p<0.001$) – no data <p>Secondary: 1-grade improvement on both CEA and PSA on days 1, 15, 29 over 12 hrs with BT vs. vehicle; 30-min effect defined as 1-grade improvement on both CEA and PSA at 30min on day 1; rebound defined as worsened erythema compared to baseline during follow-up phase</p> <ul style="list-style-type: none"> -1-grade improvement over 12 hrs: 71.1%, 64.8%, 66.9%, 53.5% vs. 40.1%, 43.0%, 39.4%, 40.1% ($p<0.001$) at hrs 3, 6, 9, 12, respectively at day 29. Days 1 and 15 showed BT significantly more efficacy as well ($p<0.001$) – no data. -30-min effect: 28.4% vs. 4.8% ($p<0.001$) -Rebound: worsening found with 3.6% of 	<p>Sponsor: Galderma R&D</p> <p>GRADE: High</p> <p>Notes:</p> <p>External Validity to VA: Possible</p>

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
			<p>BT subjects for CEA and 4.3% for PSA at week 6; 2.1% for CEA and PSA at week 8. Similar effects reported in vehicle group (no data).</p> <p>-No aggravations in inflammatory lesions, telangiectasia, IGA observed</p> <p><u>Safety:</u> Incidence of related AE was 9.5% for BT group vs 9.7% for vehicle group. 7 subjects with worsening erythema/flushing, 1 pruritus, 2 worsening of rosacea. No serious AEs. Majority of AEs dermatological, transient and mild.</p> <p>-No changes in BP or HR</p>	

Jackson JM, Fowler J, Moore A, et al. Improvement in facial erythema within 30 minutes of initial application of brimonidine tartrate in patients with rosacea. *J Drugs Dermatol.* 2014;13(6):699-704.

<p>Sub-analysis of the 2013 Fowler J, Jackson JM, Moore A, Jarratt M, Jones, T, Meadows K, et al study above.</p> <p>Design: Two 8-week randomized, double-blind, parallel-group, vehicle-controlled, phase III studies</p> <p>Inclusion: ≥ 18 yo, clinical diagnosis of rosacea and moderate to severe erythema according to both CEA and PSA at both screening visit and baseline visit. Mandatory washout period required for subjects receiving prescription medications for inflammatory conditions, rosacea, or acne</p> <p>Exclusion: ≥ 3 facial inflammatory</p>	<p>Study A:</p> <p>260 subjects randomized (mean age 49yo, age range 18-87yo, 79% female, 98.5% Caucasian, 86.2% had moderate CEA, 85% had moderate PSA, 97.7% completed study)</p> <p>Study B:</p> <p>293 subjects randomized (mean age 48yo, age range 19-78yo, 73% female, 98.6% Caucasian, 76.2% had moderate CEA, 85.7% had moderate PSA, 96.6% completed study)</p>	<p>Study A and B:</p> <p>Subjects randomized 1:1 to BT 0.5% or vehicle with instructions to apply a thin film on the entire face for 4-weeks.</p>	<p>Efficacy: secondary efficacy outcome in both Study A and B was the 30-minute effect</p> <p>Study A:</p> <ul style="list-style-type: none"> -Secondary efficacy outcome: 1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 1: BT gel 0.5% vs vehicle 27.9% vs. 6.9% ($P <0.001$); difference. NNT= 5 -1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 15: BT gel 0.5% vs vehicle 55.9% vs. 21.1% ($P <0.001$); difference. NNT= 3 -1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 29: BT gel 0.5% vs vehicle 58.3% vs. 32.0% ($P <0.001$); difference. NNT= 4 	<p>Sponsor: Galderma R&D</p> <p>GRADE: High</p> <p>External Validity to VA: Possible</p>
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Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
lesions Treatment phase: -CEA and PSA assessed for 1 grade improvement at baseline and at 30 minutes on days 1, 15, 29			Study B: -Secondary efficacy outcome: 1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 1: BT gel 0.5% vs vehicle 28.4% vs. 4.8% ($P <0.001$); difference. NNT= 5 -1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 15: BT gel 0.5% vs vehicle 45.5% vs. 28.4% ($P=0.003$); difference. NNT= 6 -1 grade improvement on both CEA and PSA at 30 minutes post-dosing on day 29: BT gel 0.5% vs vehicle 53.5% vs. 34.5% ($P =0.001$); difference. NNT= 5 Safety: outcomes and adverse events are not reported in this subanalysis, see Fowler et al 2013 above.	
Moore A, Kempers S, Murakawa G, et al. Long-term safety and efficacy of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of a 1 -year open-label study. J Drugs Dermatol. 2014;13(1):56-61				
-Open label study, safety and efficacy, 27 centers in US -Inclusion: 18 years of age or older, clinical diagnosis of rosacea and moderate or severe erythema according to CEA and PSA -Exclusion: diagnosis of Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjogren's syndrome, or depression	-586 subjects screened, 449 were enrolled in the study and included in the safety population. -355 subjects (74.6%) completed at least 6 months of treatment, and 279 subjects (62.1%) completed 12 months of treatment -74.8% of subjects were female, 97.6% Caucasian/white, average age 50.9, majority of subjects had moderate erythema or rosacea according to either CEA (87.8%) or PSA (84.4%) with a	-All subjects instructed to apply thin film of topical brimonidine tartrate gel 0.5% once daily in the morning over the entire face for up to 12 months	Efficacy: mean CEA score at hour 0 decreased from 3.1 on day 1 to 2.4 at month 3 and remained stable until month 12. On day 1 mean CEA decreased from 3.1 at hour 0 to 1.7 at hour 3. Improvement was observed at each study visit -Mean PSA score at hour 0 reduced gradually from 3.1 on day 1 to 2.3 at month 3 and remained stable until month 12. On day 1, mean PSA decreased from 3.1 at hour 0 to 2.1 at hour 3. Improvement was maintained until end of study. Safety: 139 subjects (31.0%) reported 238 related AEs during the course of the	Sponsor: Galderma R&D GRADE: Low Notes: 131 subjects (29.2%) received concomitant therapies indicated for their facial papules and pustules (metronidazole, azelaic acid, and tetracycline, minocycline, and doxycycline) External Validity to VA: Probably

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
-8 visits: screening, baseline/day 1, week 1, month 1, month 3, month 6, month 9, and month 12. At each post screening visit, efficacy assessments included CEA, PSA, telangiectasia, and inflammatory lesion count prior to study drug application (hour 0) and CEA and PSA 3 at hour 3	mean number of inflammatory lesions of 5.4		<p>study</p> <p>-related AEs observed most frequently in the study: flushing (9.1%), worsening of erythema (6.5%), worsening of rosacea (3.6%), skin burning sensation (3.3%), skin irritation (3.1%), dermatitis contact (2.2%), and pruritus (2.0%),</p> <p>-One death (advanced squamous cell carcinoma of the lung)</p> <p>-12 subjects reported serious AEs during the study, all of which deemed to be unrelated to the study drug</p>	

Abbreviations: BT=brimonidine tartrate; mod=moderate; sev=severe; yo=years old; CEA=clinician erythema assessment; PSA=patient's self-assessment