



# Facial erythema of rosacea: brimonidine tartrate gel

Evidence summary

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[www.nice.org.uk/guidance/esnm43](http://www.nice.org.uk/guidance/esnm43)

## Key points from the evidence

The content of this evidence summary was up-to-date in July 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

In 2 short-term randomised controlled trials (RCTs: n=553) brimonidine tartrate gel was statistically significantly more effective than vehicle gel in reducing erythema in people with a clinical diagnosis of rosacea and moderate to severe erythema. However, 'success rates' (defined as a 2-grade reduction in the severity of erythema as assessed by both patients and clinicians) were just 25% to 30% with brimonidine gel compared with about 10% for vehicle gel at day 29.

<p><b>Effectiveness</b></p> <p>In 2 RCTs (n=553), compared with vehicle gel:</p> <ul style="list-style-type: none"><li>• a statistically significantly greater 'success rate' (2-grade reduction in severity of erythema) was seen with brimonidine tartrate gel (about 25% to 30% with brimonidine compared with about 10% for vehicle at day 29; <math>p &lt; 0.001</math>).</li><li>• a statistically significantly greater 'responder rate' (1-grade reduction in severity of erythema) was seen with brimonidine tartrate gel (about 70% with brimonidine compared with about 30% to 40% with vehicle at day 29; <math>p &lt; 0.001</math>).</li><li>• a rapid onset of effect is seen with brimonidine tartrate gel (within 30 minutes in 28% of people), which peaks at about 3 hours and is partially maintained over a 12-hour period.</li></ul>	<p><b>Safety</b></p> <ul style="list-style-type: none"><li>• Brimonidine tartrate gel is contraindicated in people receiving monoamine oxidase inhibitors, tricyclic or tetracyclic antidepressants, and in children aged less than 2 years (<a href="#">Brimonidine tartrate gel [Mirvaso] summary of product characteristics</a>).</li><li>• The <a href="#">summary of product characteristics</a> states that no clinically meaningful trends in tachyphylaxis or rebound effects (worsening of erythema after stopping treatment) were seen with the use of brimonidine tartrate gel for 29 days, but a report of 3 people with possible rebound erythema has been published (<a href="#">Routt and Levitt 2014</a>).</li></ul>
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Patient factors	Resource implications
<ul style="list-style-type: none"> <li>At day 29, about 40% of people using brimonidine tartrate gel were 'satisfied' or 'very satisfied' and about 26% of people were 'dissatisfied' or 'very dissatisfied' with their appearance (2 RCTs, n=553).</li> <li>Brimonidine tartrate gel is generally well tolerated; the <a href="#">summary of product characteristics</a> states that the most common adverse reactions are erythema, pruritus, flushing and skin burning sensation (occurring in between 1.2% and 3.3% of people in clinical studies).</li> <li>Brimonidine tartrate gel is a symptomatic treatment with a transient effect on erythema. It can be used up to once per day, on a daily or as-required basis.</li> </ul>	<ul style="list-style-type: none"> <li>Brimonidine tartrate gel is £33.69 for a 30 g tube (excluding VAT; cost taken from <a href="#">MIMS</a>, May 2014).</li> <li>The maximum daily recommended dose is 1 g of gel (<a href="#">Brimonidine tartrate gel [Mirvaso] summary of product characteristics</a>). In a long-term study the average daily amount used was 0.5 g (<a href="#">Moore et al. 2014</a>).</li> </ul>

## Introduction and current guidance

Rosacea is a chronic relapsing disease of facial skin, characterised by recurrent episodes of facial flushing, persistent erythema, telangiectasia (fine, dilated blood vessels), papules and pustules. For the symptoms of flushing and erythema (without papules and pustules) there is historically no effective treatment in primary care, and management generally consists of lifestyle advice, including applying sunscreen and avoiding trigger factors when practical ([Clinical Knowledge Summaries: rosacea](#)).

Full text of [Introduction and current guidance](#).

## Product overview

Brimonidine tartrate gel (Mirvaso) is the first medicinal product to be approved for the symptomatic treatment of facial erythema of rosacea. Brimonidine tartrate is a highly selective alpha-2 adrenergic receptor agonist, with potent vasoconstrictive and vasostabilising activity. Brimonidine tartrate gel is an aqueous gel that is applied to the face once daily ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#)).

Full text of [Product overview](#).

## Evidence review

- This evidence summary is based on 2 short-term, randomised, vehicle-controlled phase III trials of identical design (trial A [n=260] and trial B [n=293]) of brimonidine tartrate gel in adults with a clinical diagnosis of rosacea and moderate to severe erythema ([Fowler et al. 2013](#)).
- In both RCTs, brimonidine tartrate gel was statistically significantly more effective than vehicle gel in reducing erythema.
  - For the primary end point of 'success rate', defined as a 2-grade improvement on both the 5-point Clinician's Erythema Assessment (CEA) and the 5-point Patient's Self-Assessment (PSA) of erythema over 12 hours, the 'success rate' at day 29 (3 hours after application) was 31.5% with brimonidine gel and 10.9% with vehicle gel in trial A, and 25.4% with brimonidine gel and 9.2% with vehicle gel in trial B (both  $p < 0.001$  over 12 hours).
  - The secondary end point of onset of efficacy (the '30-minute effect'), defined as a 1-grade improvement from baseline on both the CEA and PSA at 30 minutes on day 1, was seen in 27.9% of the brimonidine gel group and 6.9% of the vehicle gel group in trial A and 28.4% of the brimonidine gel group and 4.8% of the vehicle gel group in trial B (both  $p < 0.001$ ).
  - At day 29 (3 hours after application), the 'responder rate' for a 1-grade improvement on both the CEA and PSA was 70.9% with brimonidine gel and 32.8% with vehicle gel in trial A, and 71.1% with brimonidine gel and 40.1% with vehicle gel in trial B (both  $p < 0.001$  over 12 hours).

- At day 29, more people were 'satisfied' or 'very satisfied' with their appearance in the brimonidine gel groups than in the vehicle gel groups (no statistical analysis reported), and statistically significantly more people in the brimonidine gel groups reported overall improvement in erythema compared with those in the vehicle gel groups ( $p < 0.001$ ). However, a substantial number of people were not satisfied with their appearance. At day 29, 27.6% of people in the brimonidine gel group compared with 43.7% of people in the vehicle gel group were 'dissatisfied' or 'very dissatisfied' in trial A and 24.6% of people in the brimonidine gel group compared with 42.2% in the vehicle gel group were 'dissatisfied' or 'very dissatisfied' in trial B (no statistical analysis reported; [European public assessment report for Mirvaso](#)).
- The brimonidine tartrate gel [summary of product characteristics](#) states that the most commonly reported adverse reactions are erythema, pruritus, flushing and skin burning sensation, all occurring in between 1.2% and 3.3% of patients in clinical studies. They are typically mild to moderate in severity, and usually do not need treatment to be stopped.
- Both RCTs were short-term (4-week treatment phase and 4-week follow-up phase) and compared brimonidine tartrate gel with vehicle gel, not an active comparator. They were conducted in people with moderate to severe erythema (marked or fiery redness), and there is no evidence for the use of brimonidine tartrate gel in people with less severe erythema.
- Long-term efficacy and safety data are limited to those available from an open-label, non-comparative study, which followed people for up to 12 months ([Moore et al. 2014](#)).
- Efficacy end points for erythema of rosacea are not clearly established. The CEA and PSA scales used in the brimonidine tartrate gel trials are novel scales based on subjective judgements, not objective measures, and defining what a clinically important change is on these scales is difficult.

Full text of [Evidence review](#)

## Context

Management of facial erythema of rosacea generally consists of lifestyle advice. Off-label propranolol or clonidine may be used to treat flushing ([Primary Care Dermatology Society guidance on rosacea](#)), but this use is not supported by evidence from RCTs. Mild or

moderate papulopustular rosacea is usually treated with topical metronidazole or azelaic acid.

Full text of [Context](#).

## Estimated impact for the NHS

Brimonidine tartrate gel is the first medicinal product to be approved for the symptomatic treatment of facial erythema of rosacea. It may be an option for adults with a clinical diagnosis of rosacea and moderate to severe erythema (marked or fiery redness) because this was the population assessed in the clinical trials. However, specialists have advised that it is important to ensure that lifestyle recommendations, such as using high-factor sunscreen and avoiding trigger factors, have been optimised before brimonidine is considered, and that these are continued throughout treatment with brimonidine.

Rosacea is a chronic condition and although brimonidine tartrate gel has a transient effect on erythema, it does not alter the course of the disease or have any effect on other features of rosacea, such as telangiectasia or inflammatory papules. It can be used up to once per day, but does not need to be used daily, and specialists have suggested that some people may only use brimonidine tartrate gel on days when they are particularly self-conscious about their appearance. Before continuing longer-term treatment with brimonidine tartrate gel, consideration will need to be given to how treatment efficacy can be assessed given the subjective nature of efficacy outcomes and the low response rates seen in the clinical trials.

Local decision makers will need to take into account the evidence for efficacy and safety, factors relating to individual people with rosacea and cost, when making decisions about using brimonidine tartrate gel.

The cost of brimonidine tartrate gel (Mirvaso) is £33.69 for a 30 g tube (excluding VAT; cost taken from [MIMS](#), May 2014).

Full text of [Estimated impact for the NHS](#).

### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

## Full evidence summary

### Introduction and current guidance

Rosacea is a chronic relapsing disease of the facial skin, characterised by recurrent episodes of facial flushing, persistent erythema, telangiectasia (fine, dilated blood vessels), papules and pustules. Some people have phymatous rosacea with thickening and distortion of the skin (for example, around the nose) and others have ocular rosacea, which is usually bilateral, and often described as a foreign-body sensation. Typically, rosacea first presents at the age of 30 to 50 years in people who are fair-skinned. ([Clinical Knowledge Summaries: rosacea](#)).

The [Clinical Knowledge Summary on rosacea](#) states that there is historically no effective treatment in primary care for the symptoms of flushing and erythema (without papules and pustules), and management generally consists of lifestyle advice. This includes recommendations to frequently apply high-factor sunscreen and to avoid trigger factors, such as extremes of weather (in particular, heat and cold winds), sunlight, strenuous exercise, stressful situations, spicy food, alcohol and hot drinks, when practical. If the skin is dry, hypoallergenic and non-comedogenic emollient creams are recommended. People should avoid using abrasive products or topical corticosteroids on the face, as well as drugs that can aggravate flushing, such as calcium channel blockers.

The [Primary Care Dermatology Society guidance on rosacea](#) states that erythema, flushing and telangiectasia can sometimes be the predominant symptoms. It states that flushing may be helped by using a non-selective cardiovascular beta-blocker such as propranolol 40 mg twice a day, or clonidine 50 micrograms twice a day. However, use of these drugs would be off-label, is not supported by evidence from randomised controlled trials (RCTs), and may cause unacceptable side effects. For persistent erythema or telangiectasia, laser

therapy can be effective although improvement is not permanent, and it may not be available on the NHS. Camouflage cream is also used.

Mild or moderate papulopustular rosacea (with a limited number of papules and pustules, and no plaques) is generally treated with a topical drug. Metronidazole gel or cream is usually preferred because it is well tolerated. Azelaic acid gel is an alternative to metronidazole that may be more effective, especially in people who do not have sensitive skin. However, it may cause transient stinging. For moderate or severe papulopustular rosacea (with extensive papules, pustules, or plaques), oral tetracycline, erythromycin, doxycycline or lymecycline can be prescribed, although not all of these drugs are licensed for treating rosacea ([Clinical Knowledge Summaries: rosacea](#)) and evidence from RCTs to support their use is limited ([van Zuuren et al. 2011](#)).

## Product overview

### Drug action

Brimonidine tartrate is a highly selective alpha-2 adrenergic receptor agonist, with potent vasoconstrictive and vasostabilising activity. Erythema of rosacea is associated with permanent vasodilatation of small vessels. Facial application of brimonidine tartrate reduces erythema through direct cutaneous vasoconstriction ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#)).

### Licensed therapeutic indication

Brimonidine tartrate gel (Mirvaso) is indicated for the symptomatic treatment of facial erythema of rosacea in adults ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#)).

### Course and cost

Brimonidine tartrate gel (Mirvaso) is an aqueous gel that is applied to the face once every 24 hours, at any time that is suitable for the person, for as long as facial erythema is present. The maximum daily recommended dose is 1 g of gel, divided into 5 pea-sized amounts. One gram of gel contains 3.3 mg of brimonidine, equivalent to 5 mg of brimonidine tartrate ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#)). In a long-term study ([Moore et al. 2014](#)) the average daily amount used



was 0.532 g.

A small pea-sized amount of gel is applied to each of the 5 areas of the face: forehead, chin, nose, and each cheek. The gel should be applied smoothly and evenly as a thin layer across the entire face avoiding the eyes, eyelids, lips, mouth and membrane of the inner nose.

Brimonidine tartrate gel should be applied only to the face. Hands should be washed immediately after applying the gel. Brimonidine tartrate gel can be used in conjunction with other topical medicinal products for treating inflammatory lesions of rosacea and with cosmetics. These products should not be applied immediately before the daily application of brimonidine tartrate gel; they may be used only after the applied gel has dried ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#)).

The cost of brimonidine tartrate gel (Mirvaso) is £33.69 for a 30 g tube (excluding VAT; cost taken from [MIMS](#), May 2014).

## Evidence review

This evidence summary is based on 2 randomised, vehicle-controlled phase III trials (trial A and trial B) of brimonidine tartrate gel, which were identical in design. The results of these trials were published in 1 paper ([Fowler et al. 2013](#)). An open-label, non-comparative study to evaluate long-term safety and efficacy ([Moore et al. 2014](#)) is also discussed in the clinical effectiveness and safety and tolerability sections.

Two further studies have been completed but the results are not yet published. These are the Patient-Reported Outcome Of Facial Erythema ([PROOF](#)) study, and an RCT comparing brimonidine tartrate gel with azelaic acid gel ([ClinicalTrials.gov identifier: NCT01659853](#)).

### **Trial A and B** ([Fowler et al. 2013](#))

- Design: both phase III trials were 8-week (4-week treatment phase and 4-week follow-up phase), multicentre, [randomised](#), double-[blind](#), parallel-group, vehicle-controlled trials carried out in the USA and Canada.

- Population: 260 participants were randomised in trial A and 293 in trial B. Both trials enrolled men or women (79% women in trial A and 73% women in trial B) aged 18 years or older (mean age 49 years in trial A and 48 years in trial B), with a clinical diagnosis of rosacea, less than 3 facial inflammatory lesions, and moderate to severe erythema (a score of 3 or 4) according to both the Clinician's Erythema Assessment (CEA) and the Patient's Self-Assessment (PSA) at the screening visit and the baseline visit. The CEA and PSA are specifically developed, novel, 5-point scales of erythema ([Fowler et al. 2012](#)), defined as follows ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#)):
  - CEA: 0=clear skin with no signs of erythema; 1=almost clear, slight redness; 2=mild erythema, definite redness; 3=moderate erythema plus marked redness; and 4=severe erythema plus fiery redness
  - PSA: 0=no redness, 1=very mild redness, 2=mild redness, 3=moderate redness, and 4=severe redness.

At baseline, most participants (over 80%) had moderate erythema, were Caucasian (99%), and had a Fitzpatrick skin phototype of II or III. A washout period was required for medications for inflammatory conditions, rosacea or acne (see the [European public assessment report for Mirvaso](#) for details).

- Intervention and comparison: in both trials, participants were randomised 1:1 to 0.5% brimonidine tartrate gel (5 mg/g) or vehicle gel. The method of allocation described suggests that this was concealed. During the first 4 weeks (treatment phase), participants applied a thin layer of gel (approximately 1 g) over the entire face once daily. No medication was applied during the 4-week follow-up phase, which was included to assess the potential for rebound erythema.

- Outcomes: the primary efficacy end point was the 'success rate', defined as a 2-grade improvement on both the CEA and PSA over 12 hours (at hours 3, 6, 9 and 12) on days 1, 15 and 29. The secondary efficacy end point, which aimed to assess the onset of efficacy, was the '30-minute effect', defined as a 1-grade improvement from baseline on both the CEA and PSA at 30 minutes on day 1. Other end points included a 1-grade improvement on both the CEA and PSA on days 1, 15 and 29; Telangiectasia Grading Assessment; Investigators Global Assessment of lesions and facial inflammatory lesion counts; Patient Assessment of Appearance; Patient Assessment of Whitening; Overall Treatment Effect, quality of life; tachyphylaxis or loss of efficacy; and rebound effects. Efficacy analyses were based on the intention-to-treat (ITT) population using a multiple imputation procedure (which replaces missing data with a set of plausible values that represents the uncertainty about the value to impute) to handle missing data at any time point. Safety was evaluated by physical examinations and monitoring of adverse events and vital signs. There were 6 visits in each trial: screening visit, days 1, 15 and 29 during the treatment phase, and weeks 6 and 8 during the follow-up phase.

**Table 1 Summary of trial A:** Fowler et al. (2013)

	<b>Brimonidine tartrate gel 0.5%</b>	<b>Vehicle gel</b>	<b>Analysis</b>
<b>Efficacy</b> (ITT population <sup>a</sup> )	n=129	n=131	
Primary outcome: 'success rate' (percentage of participants with a 2-grade improvement on both the CEA and PSA over 12 hours on day 29 <sup>b</sup> )	Hour 3: 31.5% (40/127)  Hour 6: 30.7% (39/127)  Hour 9: 26.0% (33/127)  Hour 12: 22.8% (29/127)	Hour 3: 10.9% (14/128)  Hour 6: 9.4% (12/128)  Hour 9: 10.2% (13/128)  Hour 12: 8.6% (11/128)	p<0.001 over 12 hours

Secondary outcome: '30-minute effect' (percentage of participants with a 1-grade improvement from baseline on both the CEA and PSA at 30 minutes on day 1 <sup>b</sup> )	27.9% (36/129)	6.9% (9/131)	p<0.001
Other selected outcomes:			
Percentage of participants with a 1-grade improvement on both the CEA and PSA over 12 hours on day 29 <sup>b</sup>	Hour 3: 70.9% (90/127) Hour 6: 69.3% (88/127) Hour 9: 63.8% (81/127) Hour 12: 56.7% (72/127)	Hour 3: 32.8% (42/128) Hour 6: 32.0% (41/128) Hour 9: 29.7% (38/128) Hour 12: 30.5% (39/128)	p<0.001 over 12 hours
<b>Safety</b> (safety population <sup>c</sup> )	n=129	n=131	
Participants reporting adverse events	29.5% (38/129)	25.2% (33/131)	No statistical analysis reported
Participants reporting treatment-related adverse events	11.6% (15/129)	5.3% (7/131)	No statistical analysis reported
Participants discontinuing treatment because of adverse events	1.6% (2/129)	0.8% (1/131)	No statistical analysis reported

Abbreviations: CEA, Clinician's Erythema Assessment; ITT, intention to treat; p, p value; PSA, Patient's Self-assessment.

<sup>a</sup> The ITT population is all participants who were randomised and given the study drug.

<sup>b</sup> The CEA and PSA are specifically developed novel scores of erythema (Fowler et al. 2012), defined as follows: CEA: 0=clear skin with no signs of erythema; 1=almost clear, slight redness; 2=mild erythema, definite redness; 3=moderate erythema plus marked redness; and 4=severe erythema plus fiery redness. PSA: 0=no redness, 1=very mild redness, 2=mild redness, 3=moderate redness, and 4=severe redness (Brimonidine tartrate gel [Mirvaso] summary of product characteristics).

<sup>c</sup> The safety population is all participants who had applied the study drug at least once.

**Table 2 Summary of trial B:** Fowler et al. (2013)

	<b>Brimonidine tartrate gel 0.5%</b>	<b>Vehicle gel</b>	<b>Analysis</b>
<b>Efficacy (ITT population<sup>a</sup>)</b>	n=148	n=145	
Primary outcome: 'success rate' (percentage of participants with a 2-grade improvement on both the CEA and PSA over 12 hours on day 29 <sup>b</sup> )	Hour 3: 25.4% (36/142)  Hour 6: 25.4% (36/142)  Hour 9: 17.6% (25/142)  Hour 12: 21.1% (30/142)	Hour 3: 9.2% (13/142)  Hour 6: 9.2% (13/142)  Hour 9: 10.6% (15/142)  Hour 12: 9.9% (14/142)	p<0.001 over 12 hours
Secondary outcome: '30-minute effect' (percentage of participants with a 1-grade improvement from baseline on both the CEA and PSA at 30 minutes on day 1 <sup>b</sup> )	28.4% (42/148)	4.8% (7/145)	p<0.001

Other selected outcomes:			
Percentage of participants with a 1-grade improvement on both the CEA and PSA over 12 hours on day 29 <sup>a</sup>	Hour 3: 71.1% (101/142) Hour 6: 64.8% (92/142) Hour 9: 66.9% (95/142) Hour 12: 53.5% (76/142)	Hour 3: 40.1% (57/142) Hour 6: 43.0% (61/142) Hour 9: 39.4% (56/142) Hour 12: 40.1% (57/142)	p<0.001 over 12 hours
<b>Safety</b> (safety population <sup>c</sup> )	n=148	n=145	
Participants reporting adverse events	33.8% (50/148)	24.1% (35/145)	No statistical analysis reported
Participants reporting treatment-related adverse events	9.5% (14/148)	9.7% (14/145)	No statistical analysis reported
Participants discontinuing because of adverse events	0.7% (1/148)	0.7% (1/145)	No statistical analysis reported

Abbreviations: CEA, Clinician's Erythema Assessment; ITT, intention to treat; p, p value; PSA, Patient's Self-assessment.

<sup>a</sup> The ITT population is all participants who were randomised and given study drug.

<sup>b</sup> The CEA and PSA are specifically developed novel scores of erythema (Fowler et al, 2012), defined as follows: CEA: 0=clear skin with no signs of erythema; 1=almost clear, slight redness; 2=mild erythema, definite redness; 3=moderate erythema plus marked redness; and 4=severe erythema plus fiery redness. PSA: 0=no redness, 1=very mild redness, 2=mild redness, 3=moderate redness, and 4=severe redness (Brimonidine tartrate gel [Mirvaso] summary of product characteristics).

<sup>c</sup> The safety population is all participants who had applied the study drug at least once.

## Clinical effectiveness

In both RCTs, 0.5% brimonidine tartrate gel (5 mg/g) was statistically significantly more effective than vehicle gel in reducing erythema. At day 29, the primary end point of 'success rate', defined as a 2-grade improvement on both the clinician's (CEA) and patient's (PSA) assessment of erythema over 12 hours, was statistically significantly higher in the active compared with the vehicle gel groups in both studies based on the ITT population (both  $p < 0.001$ ; see tables 1 and 2 for details). Three hours after application the 'success rate' was 31.5% with brimonidine gel and 10.9% with vehicle gel in trial A, and 25.4% with brimonidine gel and 9.2% with vehicle gel in trial B. In both trials, the 'success rate' was also statistically significantly higher with active compared with vehicle gel on day 1 and day 15 (all  $p < 0.001$ ); and per-protocol analyses and sensitivity analyses also gave similarly statistically significant differences (all  $p < 0.05$ ; Fowler et al. 2013).

The secondary end point of onset of efficacy (the '30-minute effect'), defined as a 1-grade improvement from baseline on both the CEA and PSA at 30 minutes on day 1, was also statistically significantly improved with 0.5% brimonidine tartrate gel compared with vehicle gel. The '30-minute effect' was seen in 27.9% of the brimonidine gel group and 6.9% of the vehicle gel group in trial A, and 28.4% of the brimonidine gel group and 4.8% of the vehicle gel group in trial B (both  $p < 0.001$ ; Fowler et al. 2013).

Efficacy was also assessed using the less stringent measure of a 1-grade improvement on both the clinician's (CEA) and patient's (PSA) assessment of erythema over 12 hours. Statistically significantly more participants in the brimonidine gel groups than in the vehicle gel groups had this response at day 1, 15 and 29 (all  $p < 0.001$ ; see table 1 and 2 for day 29

results). At day 29, 3 hours after application the 'responder rate' was 70.9% with brimonidine gel and 32.8% with vehicle gel in trial A, and 71.1% with brimonidine gel and 40.1% with vehicle gel in trial B ([Fowler et al. 2013](#)).

Maximal drug effects were typically observed 3 hours after application and continued for about 6 hours after application. The [European public assessment report for Mirvaso](#) states that there is some tapering off of the effect on rosacea by 12 hours after application, but at hour 12 there is still an approximate 1-grade improvement on CEA or PSA relative to hour 0 with brimonidine tartrate gel.

Other end points included facial inflammatory lesions and telangiectasias. These symptoms of rosacea are not considered specific indications for brimonidine tartrate gel, but they were assessed to evaluate whether any worsening would occur. In both trials, baseline lesion scores were similar between the brimonidine gel and vehicle gel groups and no significant worsening was observed at hour 12 on day 29 or during the follow-up period (weeks 6 and 8). The same was true for telangiectasias. In both trials, the Telangiectasia Grading Assessment (TGA) was similar between the groups at baseline, and there was no significant worsening in mean TGA scores at hour 12 on day 29 or during the follow-up period (weeks 6 and 8) ([European public assessment report for Mirvaso](#)).

Because rebound effects and tachyphylaxis can occur after withdrawal of alpha-2 adrenergic receptor agonists, both trials investigated the potential of brimonidine tartrate gel to show reduced efficacy over time or to cause more severe erythema after stopping treatment. There was no evidence of tachyphylaxis or loss of efficacy during the 4-week treatment period in either trial ([Fowler et al. 2013](#), [European public assessment report for Mirvaso](#)).

After treatment was stopped, no rebound erythema was seen compared with baseline during the 4-week follow-up period for either treatment group in both trials. Some individuals showed worsening in CEA and PSA scores relative to baseline during the follow-up period; and more people in the brimonidine tartrate gel groups compared with the vehicle groups tended to experience worsening during the follow-up period. The numbers were small, with less than 5% of people showing 1-grade increases in CEA or PSA ([European public assessment report for Mirvaso](#)). However, case reports of possible rebound erythema have since been published ([Routt and Levitt 2014](#)) (see [safety and tolerability](#) section).

As well as rating their erythema with PSA, participants in the study rated their appearance



with the Patient Assessment of Appearance (PAA) scale, assessed the overall impact of treatment with the Overall Treatment Effect (OTE) scale, and assessed the potential of brimonidine to over-whiten the skin using the Patient Assessment of Whitening (PAW) scale.

Higher percentages of people in the brimonidine gel group were 'bothered by too much whitening' compared with the vehicle gel groups. However, the number of reports of unwanted over-whitening decreased over the course of the trials, and there were no discontinuations because of over-whitening ([European public assessment report for Mirvaso](#)).

The patient self-assessment using the PAA scale showed that more people were satisfied with their appearance in the brimonidine gel groups compared with the vehicle gel groups. At day 29, more people were 'satisfied' or 'very satisfied' in the brimonidine gel groups ('very satisfied': 7.9%, 'satisfied': 35.4% in trial A; 'very satisfied': 9.2%, 'satisfied': 26.8% in trial B) than in the vehicle gel groups ('very satisfied': 0.8%, 'satisfied': 19.5% in trial A; 'very satisfied': 2.1%, 'satisfied': 16.9% in trial B); no statistical analyses were reported. The overall results from the assessment using the OTE scale also favoured brimonidine, with statistically significantly more people in the brimonidine gel groups reporting improvement in the management of their facial erythema compared with those in vehicle gel groups ( $p < 0.001$ ) ([European public assessment report for Mirvaso](#)).

However, PAA and OTE results also showed that a substantial number of people were not satisfied with their appearance or experienced worsening of the condition at the end of treatment. Based on PAA at day 29, 27.6% of people in the brimonidine gel group compared with 43.7% of people in the vehicle gel group were 'dissatisfied' or 'very dissatisfied' in trial A and 24.6% of people in the brimonidine gel group compared with 42.2% in the vehicle gel group were 'dissatisfied' or 'very dissatisfied' in trial B (no statistical analysis reported). For OTE, on day 29, twice as many participants in the active treatment group (10.1% in trial A and 10.1% in trial B) compared with the vehicle group (5.3% in trial A and 3.4% in trial B) considered that their condition had worsened as a result of the treatment (no statistical analysis reported). However, as the European public assessment report states, it is plausible that some people will relate the wearing off of the effect at the end of the day to a worsening, and that this is more pronounced in the active than the vehicle group. The overall OTE results showed that the majority of participants in the study experienced an improvement with brimonidine tartrate gel. The trials also included quality of life assessments, but no notable differences were seen between brimonidine tartrate and vehicle gel ([European public assessment report for Mirvaso](#)).

An open-label, non-comparative study carried out in the USA included 449 people with a clinical diagnosis of rosacea and moderate or severe erythema according to both the CEA and PSA ([Moore et al. 2014](#)). Participants applied a thin film of 0.5% brimonidine tartrate gel over the entire face once daily in the morning for up to 12 months. In contrast to the RCTs, inclusion of people with 3 or more inflammatory lesions and with concomitant standard treatments for inflammatory lesions of rosacea was allowed, which resulted in a study population that probably better reflects the true rosacea population ([European public assessment report for Mirvaso](#)).

As in the RCTs, most people were female (75%), Caucasian (98%), and with moderate erythema (88% based on CEA and 84% based on PSA). The mean age of the participants was 51 years and 29% were receiving concomitant treatments for inflammatory lesions of rosacea, such as metronidazole, azelaic acid, tetracycline, minocycline or doxycycline. Of the 449 people enrolled, 335 (74.6%) completed at least 6 months of treatment and 279 (62.1%) completed the study (up to the 12-month visit) ([Moore et al. 2014](#)).

On day 1, after the first application of brimonidine tartrate gel, the mean CEA score decreased from 3.1 at hour 0 to 1.7 at hour 3. This improvement was maintained at each visit until month 12, when the mean CEA score reduced from 2.3 at hour 0 to 1.3 at hour 3. Similar results were seen with PSA, which decreased from 3.1 at hour 0 to 2.1 at hour 3 on day 1, and from 2.2 at hour 0 to 1.5 at hour 3 on the study visit at month 12 (no statistical analyses were reported). No tachyphylaxis or loss of efficacy was seen ([Moore et al. 2014](#)).

## Safety and tolerability

In both RCTs, 0.5% brimonidine tartrate gel was generally well tolerated. Adverse events occurred in 29.5% of people in the brimonidine gel group and 25.2% of people in the vehicle gel group in trial A, and in 33.8% of the brimonidine gel group and 24.1% of the vehicle gel group in trial B (no statistical analysis reported). Treatment-related adverse events were less frequent, occurring in 11.6% and 9.5% of the brimonidine gel groups in trial A and B respectively, and in 5.3% and 9.7% of the vehicle gel groups (no statistical analyses reported). In trial A, 2 people (1.6%) discontinued because of an adverse event in the active group compared with 1 person (0.8%) in the vehicle group; in trial B, 1 person (0.7%) discontinued because of an adverse event in each group ([Fowler et al. 2013](#)).

The most frequent treatment-related adverse events with brimonidine in the 2 RCTs were worsening of erythema or flushing (7 people in each trial), pruritus (4 people in trial A and 1

person in trial B), skin irritation (3 people in trial A) and worsening of rosacea (1 person in trial A and 2 people in trial B). No serious treatment-related adverse events occurred in either RCT, and no changes in blood pressure or heart rate were seen ([Fowler et al. 2013](#)).

In the open-label, non-comparative study (n=449), the incidence of adverse events was highest during the first quarter of the study (90 days) and declined after that. Overall, adverse events were reported by 61.2% of people, and treatment-related adverse events by 31.0% of people. The most frequent treatment-related adverse events were flushing (9.1%), worsening of erythema (6.5%), worsening of rosacea (3.6%), skin burning sensation (3.3%), skin irritation (3.1%), contact dermatitis (2.2%) and pruritus (2.0%). There was 1 death from lung cancer and 16 serious adverse events during the study, all of which were deemed unrelated to the study drug. There were no abnormal trends in blood pressure, heart rate or intraocular pressure during the study ([Moore et al. 2014](#)).

The brimonidine tartrate gel [summary of product characteristics](#) states that the most commonly reported adverse reactions are erythema, pruritus, flushing and skin burning sensation, all occurring in between 1.2% and 3.3% of people in clinical studies. They are typically mild to moderate in severity, and usually do not require discontinuation of treatment.

Brimonidine tartrate gel is contraindicated in people receiving monoamine oxidase inhibitors (for example selegiline or moclobemide) or tricyclic (such as imipramine) or tetracyclic (such as maprotiline, mianserin or mirtazapine) antidepressants. It is also contraindicated in children aged less than 2 years and should not be used in children or young people aged 2 to 18 years. Safety concerns related to the systemic absorption of brimonidine have been identified for the age group 2 to 12 years. Brimonidine tartrate gel should not be applied on irritated skin or open wounds, or close to the eyes. In the case of severe irritation or contact allergy, treatment should be discontinued. Any increase in the daily amount applied and/or frequency of application should be avoided, because the safety of higher daily doses or repeated daily application has not been assessed ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#)).

The [summary of product characteristics](#) states that no clinically meaningful trends with respect to tachyphylaxis or rebound effects (worsening of erythema after stopping treatment) were seen with the use of brimonidine tartrate gel for 29 days. However, a report of severe erythema and burning sensation in 3 people using brimonidine tartrate gel has recently been published ([Routt et al. 2014](#)). The authors state that these could be rebound vasodilation reactions to brimonidine, similar to rebound nasal congestion seen

with overuse of alpha-adrenergic agonist nasal sprays. They suggest that counselling people about the potential for worsening erythema, use of a test area, and limiting use to special occasions may be warranted.

## Evidence strengths and limitations

The 2 randomised, vehicle-controlled phase III trials ([Fowler et al. 2013](#)) were well-designed and well-conducted, with no major differences between the active treatment and the vehicle groups in baseline characteristics. In both trials, patients and clinicians were blinded to which treatment they were given, but some degree of unblinding was possible because of the clinical effects of brimonidine on the skin.

Both trials were short-term (4-week treatment phase and 4-week follow-up phase) and compared brimonidine tartrate gel with vehicle gel, not an active comparator; although, because there are no approved medicinal products in Europe that directly target facial erythema of rosacea, this is probably reasonable. Long-term efficacy and safety data are limited to that available from the open-label, non-comparative study, which followed people for up to 12 months ([Moore et al. 2014](#)).

Brimonidine tartrate gel is licensed for the symptomatic treatment of facial erythema of rosacea in adults ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#)). However, the 2 RCTs and the open-label study were conducted in people with moderate to severe erythema (marked or fiery redness) according to both the CEA and PSA. There is no evidence for the use of brimonidine tartrate gel in people with less severe erythema, which could represent a substantial proportion of the primary care population.

The [European public assessment report for Mirvaso](#) (EPAR) states that there is no European guideline available for products indicated for the treatment of rosacea, and efficacy end points are not clearly established. Therefore, the manufacturer developed the clinician assessment (CEA) and patient assessment (PSA) scales used in these RCTs. Both of these scales are based on subjective judgements and not objective measures. However, considering the type of condition and the intended use of the product (symptomatic reduction of erythema rather than curative treatment), the EPAR states that these scales are sufficiently described and validated for their intended purpose. The primary efficacy end point was a 2-grade improvement on both the CEA and PSA over 12 hours. The authors of the phase II studies ([Fowler et al. 2012](#)) stated that this was a stringent criterion for success required for regulatory approval. They suggest a 1-grade improvement on both CEA and PSA represents an effect that is noticeable by both investigators and patients,

and is therefore clinically relevant. However, specialists have suggested that without further validation, defining what a clinically important change is on these scales is difficult.

The [European public assessment report for Mirvaso](#) states that the efficacy and safety of brimonidine tartrate gel in people whose condition is being treated with other topical products for rosacea, such as metronidazole or azelaic acid gel, has not been systematically investigated. However, in the open-label, long-term study, other rosacea treatments were allowed and, although not large numbers, 70 people used metronidazole gel and 27 used azelaic acid gel.

## Context

### Alternative treatments

There are no other approved medicinal products in Europe that directly target facial erythema of rosacea, and management generally consists of lifestyle advice. Off-label propranolol or clonidine may be used to treat flushing ([Primary Care Dermatology Society guidance on rosacea](#)), but this use is not supported by evidence from RCTs. For persistent erythema or telangiectasia, laser therapy can be effective although improvement is not permanent, and this may not be available on the NHS. Camouflage cream is also used.

Mild or moderate papulopustular rosacea is usually treated with topical metronidazole or azelaic acid. The activity of these drugs on underlying erythema and flushing is based on reduction of inflammatory redness and long term action on small vessels, but they provide no immediate and evident improvement of baseline erythema that can be evident in the short term ([European public assessment report for Mirvaso](#)).

For moderate or severe papulopustular rosacea, oral tetracycline, erythromycin, doxycycline or lymecycline can be prescribed, although not all of these drugs are licensed for treating rosacea ([Clinical Knowledge Summaries: rosacea](#)) and RCT data to support their use are limited ([van Zuuren et al. 2011](#)).

### Costs of topical treatments for rosacea

	Usual use <sup>a</sup>	Cost excluding VAT
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Metronidazole 0.75% gel <sup>b</sup>	Thin layer applied to affected skin areas twice daily	1×30 g: £6.60 to £12.00 <sup>c</sup> 1×40 g: £9.88 to £22.63 <sup>c</sup>
Metronidazole 0.75% cream <sup>b</sup>	Thin layer applied to affected skin areas twice daily	1×30 g: £6.60 <sup>d</sup> 1×40 g: £9.88 <sup>d</sup>
Azelaic acid 15% gel <sup>b</sup>	Applied to affected skin areas twice daily	1×30 g: £7.48 <sup>d</sup>
Brimonidine tartrate 0.5% gel	Thin layer applied to entire face once daily <sup>e</sup>	1×30 g: £33.69 <sup>c</sup>

<sup>a</sup> Taken from the [summaries of product characteristics](#). These directions do not represent the full range that can be used and they do not imply therapeutic equivalence.

<sup>b</sup> The activity of these drugs on underlying erythema and flushing is based on reduction of inflammatory redness and long term action on small vessels, but they provide no immediate and evident improvement of baseline erythema that can be evident in the short term ([European public assessment report for Mirvaso](#)).

<sup>c</sup> Costs taken from [MIMS](#), May 2014.

<sup>d</sup> Costs taken from [Drug Tariff](#), May 2014.

<sup>e</sup> The maximum daily recommended dose is 1 g of gel in total weight, divided into 5 pea-sized amounts (applied to each of the 5 areas of the face: forehead, chin, nose, and each cheek ([Brimonidine tartrate gel \[Mirvaso\] summary of product characteristics](#))). In the long-term study ([Moore et al. 2014](#)) the average daily amount used was 0.532 g.

## Estimated impact for the NHS

### Likely place in therapy

The 2 short-term RCTs showed that in people with moderate to severe erythema (marked or fiery redness), brimonidine tartrate gel had a statistically significant effect on erythema compared with vehicle gel. It had a rapid onset of effect (within 30 minutes in 28% of people) that was partially maintained over a 12-hour period, although efficacy peaked at about 3 hours. However, response rates for a 2-grade reduction in the severity of

erythema as assessed by both patients and clinicians were just 25% to 30% with brimonidine gel (compared with about 10% for vehicle gel) at day 29.

The majority of people experienced an overall improvement with brimonidine tartrate gel, and more people were satisfied with their appearance in the brimonidine gel groups compared with the vehicle gel groups. However, about 26% of people using brimonidine gel (compared with about 40% in the vehicle gel groups) were not satisfied with their appearance after 4 weeks of treatment.

Brimonidine tartrate gel is not indicated for papulopustular rosacea and there is only limited data on its use in people treated with other topical products for this, such as metronidazole or azelaic acid gel. The [summary of product characteristics](#) states that brimonidine tartrate gel can be used in conjunction with these other topical treatments: they should not be applied immediately before the daily application of brimonidine gel, but after the brimonidine gel has dried.

The [European public assessment report for Mirvaso](#) states that limited long-term efficacy data are available, but a comparison of results across studies has shown a similar level of activity after 4 weeks and after 1 year of use, suggesting that efficacy is maintained over time.

Brimonidine tartrate gel is generally well-tolerated with mainly local adverse events such as erythema, pruritus, flushing and skin burning sensation. The [European public assessment report for Mirvaso](#) states that these are common adverse events for other topically applied medicinal products, for instance metronidazole gel, and do not raise cause for concern. However, a case report of possible rebound erythema in 3 people has recently been published ([Routt et al. 2014](#)).

The cost of brimonidine tartrate gel (Mirvaso) is £33.69 for a 30 g tube (excluding VAT; cost taken from [MIMS](#), May 2014).

Brimonidine tartrate gel is the first medicinal product to be approved for the symptomatic treatment of facial erythema of rosacea. It may be an option for adults with a clinical diagnosis of rosacea and moderate to severe erythema (marked or fiery redness) because this was the population assessed in the clinical trials. However, specialists have advised that it is important to ensure that lifestyle recommendations, such as using high-factor sunscreen and avoiding trigger factors, have been optimised before brimonidine is considered, and that these are continued throughout treatment with brimonidine.

Rosacea is a chronic condition, and although brimonidine tartrate gel has a transient effect on erythema, it does not alter the course of the disease or have any effect on other features of rosacea, such as telangiectasia or inflammatory papules. It can be used up to once per day, but does not need to be used daily, and specialists have suggested that some people may only use brimonidine tartrate gel on days when they feel their appearance is particularly important. Before continuing longer-term treatment with brimonidine, consideration will need to be given to how treatment efficacy can be assessed given the subjective nature of efficacy outcomes and the low response rates seen in clinical trials. Not everyone will respond to treatment and some assessment of the continuing need for treatment would seem appropriate.

Local decision makers will need to take into account the evidence for the efficacy and safety of brimonidine tartrate gel, factors relating to individual people with rosacea and cost.

## Estimated usage

It is not possible to provide estimated usage based on the available data.

## Relevance to NICE guidance programmes

Brimonidine tartrate was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

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## Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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## Declarations of interest

No relevant interests declared.

### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

## Changes after publication

**October 2015:** Minor maintenance.

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