

brimonidine, 3.3mg/g (0.33%) gel equivalent to 5mg/g brimonidine tartrate
(Mirvaso[®]) SMC No. (1016/14)

Galderma

05 December 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

brimonidine (Mirvaso[®]) is accepted for restricted use within NHS Scotland.

Indication under review: the symptomatic treatment of facial erythema of rosacea in adult patients.

SMC restriction: for use in patients with moderate to severe persistent facial erythema associated with rosacea.

Two identical phase III studies demonstrated that brimonidine 0.33% gel significantly reduced erythema compared with vehicle gel in patients with rosacea.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

The symptomatic treatment of facial erythema of rosacea in adult patients.

Dosing Information

One application per 24 hours, at a time suitable for the patient for as long as facial erythema is present. Maximum daily recommended dose is 1 g of gel once daily, divided into five pea size amounts to be applied to each five areas of the face: forehead, chin, nose, each cheek.

Product availability date

April 2014

Summary of evidence on comparative efficacy

Brimonidine 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. Brimonidine reduces erythema through direct cutaneous vasoconstriction.^{1,2}

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers this product when positioned for use in patients with moderate to severe facial erythema of rosacea.

The evidence to support the efficacy of brimonidine 0.33% gel comes from two pivotal phase III studies and three supportive studies. Two identically designed, phase III, randomised, double-blind, vehicle controlled studies, 18140 and 18141, provide the main evidence. Both studies recruited patients ≥ 18 years of age with a clinical diagnosis of rosacea, less than three facial inflammatory lesions and moderate to severe erythema according to both the Clinician's Erythema Assessment (CEA) scale and Patient's Self-Assessment (PSA) scale at both screening visit and baseline assessment.³

Patients were randomised to receive once daily brimonidine 0.33% gel (n=277) or vehicle gel (n=276) for four treatment weeks followed by a four week follow-up phase, during which no medication was applied.³

The primary outcome in both studies was defined as a 2-grade improvement from baseline (T0 at day 1) on both scales, (CEA and PSA) on days 1, 15 and 29 at several time points for each day (hours 3, 6, 9 and 12). Primary analysis was performed on the per protocol (PP) population, which is defined as the intention to treat patients who had no major protocol deviations.^{2,3} Multiple imputation procedure was used to handle missing data at any time point.³

Table 1. Results from study 18140

	Brimonidine 0.33% gel (n=129)				Vehicle gel (n=131)			
Time point (composite success)	3 hours	6 hours	9 hours	12 hours	3 hours	6 hours	9 hours	12 hours
Day 29 2- grade	32%	31%	26%	23%	11%	9.4%	10%	8.6%

Day 15 2-grade	25%	27%	20%	16%	3.1%	6.3%	5.5%	2.3%
Day 1 2-grade	16%	23%	19%	13%	3.1%	2.3%	3.8%	3.1%

Table 2. Results from study 18141

	Brimonidine 0.33% gel (n=148)				Vehicle gel (n=145)			
Time point (composite success)	3 hours	6 hours	9 hours	12 hours	3 hours	6 hours	9 hours	12 hours
Day 29 2-grade	25%	25%	18%	21%	9.2%	9.2%	11%	9.9%
Day 15 2-grade	25%	26%	22%	15%	3.5%	4.3%	5.0%	7.1%
Day 1 2-grade	20%	30%	18%	14%	0%	2.1%	0.7%	1.4%

The results for the primary outcome were similar in both studies. In study 18140, success ranged from 13% to 32% for the active treatment group versus 2.3% to 11% for the vehicle gel. In study 18141, the active group success ranged from 14% to 30% and vehicle gel 0% to 11%. These results were across all days and time points.^{2,3} In both studies, brimonidine 0.33% gel was significantly ($p<0.001$) superior to vehicle gel for the primary endpoint on days 1, 15 and 29. The highest response was observed at the 3 hour and 6 hour time points and tended to wear off at later time points.²

In a subgroup analysis with respect to baseline severity of erythema, brimonidine 0.33% showed statistically significant separation from vehicle at each time point in 2-grade composite success on days 1, 15, and 29 in subjects with baseline PSA or CEA severity of 4. Both area a 5-point scale ranging from 0 (no redness) to 4 (severe redness).³

The secondary endpoint evaluated the early effect of treatment (30-minute effect) assessed as a 1-grade improvement on CEA and PSA at 30 minutes post dosing. Approximately 28% of patients in the brimonidine group showed a 1-grade improvement in both CEA and PSA at 30 minutes postdosing on day 1 compared to 5% to 7% of vehicle gel patients.²

Rebound erythema and tachyphylaxis can occur after withdrawal of alpha-2 adrenergic receptor agonists. There was no reported tachyphylaxis or loss of efficacy during the 4-week treatment period. After treatment was stopped, no rebound erythema was observed compared to baseline during the 4-week follow-up period.²

There were three supportive studies, a small crossover study, an open label and a quality of life study.

Study NCT01659853 was a multicentre, randomised, double-masked, crossover study to compare the efficacy and safety of brimonidine 0.33% gel (n=35) versus azelaic acid 15% gel (n=35) in patients with moderate to severe erythema of rosacea. Patients received 15 days of one therapy, followed by a 3 to 7 day washout period, and were then crossed over to 15 days of the alternative therapy. The primary outcome was a composite defined as a 2-grade success in both the CEA and PSA 6 hours after application on day 15. Only data from the first period were used for the efficacy analysis because of significant carryover of effect from period 1 to period 2. Significantly more patients treated with brimonidine achieved 2-grade success at 6 hours on day 15 in period 1 compared to those treated with azelaic acid; 14% versus 5.7%; $p<0.001$.⁴

Study 18142 was, a one year open-label, non-comparative study of brimonidine 0.33% gel applied once daily in 499 patients with persistent facial erythema of rosacea. There was no restriction on the number of inflammatory lesions of rosacea. Twenty-nine percent of patients received concomitant treatment for the inflammatory lesions of rosacea, most commonly metronidazole, azelaic acid and tetracyclines. Over the course of the study, the mean CEA and PSA scores reduced gradually from day 1 to month 3 and remained stable to month 12 with no tachyphylaxis or loss of efficacy reported.⁵

The PROOF study, (Patient-Reported Outcomes Of Facial Erythema) was a multicentre, randomised, double-blind, vehicle-controlled study to evaluate patient-reported outcomes following treatment of severe facial erythema with brimonidine 0.33% gel (n=48) versus vehicle gel (n=44). Patient-reported outcomes were assessed using the EuroQoL-5 dimensional-3 level (EQ-5D-3L) and dermatology life quality index (DLQI) questionnaires. There was a similar improvement in DLQI score for both treatment groups compared with baseline.⁶

Summary of evidence on comparative safety

Brimonidine 0.33% gel was safe and well tolerated during 4 weeks of continuous application. In both pivotal studies, the majority of adverse events (AEs) were transient, mild cutaneous events.³ In studies 18140 and 18141, the proportion of patients reporting treatment related AEs was 11% versus 7.6% and 9.5% versus 9.7% for brimonidine versus vehicle patients respectively.³ The most commonly reported AEs for the brimonidine 0.33% group were erythema, pruritus, flushing and skin burning sensation, occurring in 1.2% to 3.3% of patients.⁴ These were typically mild to moderate in severity and usually did not require discontinuation of therapy. No serious AEs occurred during the study.^{2,3} There were no reported abnormal changes in blood pressure or heart rate.²

Summary of clinical effectiveness issues

Rosacea is a common chronic skin condition that mainly affects the face. It is estimated to affect up to 1 in 10 people and it most commonly affects fair-skinned people from northern Europe. It affects twice as many women as men and symptoms usually begin between 30 and 50 years of age. A number of treatments are licensed for the inflammation, papules, pustules and nodule components of rosacea. Topical metronidazole gel, azelaic acid gel and oral antibiotics are currently used in practice. These may improve erythema but lack demonstrated efficacy in the symptomatic relief of erythema of rosacea. Standard treatment consists of lifestyle adjustments and use of sunscreens.²

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers this product when positioned for use in patients with moderate to severe facial erythema of rosacea, in line with the study population in the two phase III clinical studies.

Brimonidine 0.33% gel would be a useful addition to the treatment of rosacea, and the only treatment that specifically targets erythema.² Clinical experts consulted by SMC advised that there was a lack of suitable treatment options for erythema.

Two well conducted, identically designed, phase III, randomised controlled studies demonstrated that brimonidine 0.33% gel was significantly better than vehicle gel in reducing erythema of rosacea at days 1, 15 and 29. The treatment effect was rapid with onset of action seen within 30 minutes of application.²

The primary outcomes of CEA and PSA were developed by the submitting company and are based on subjective judgements; however, the EMA considered the scales were adequately described and

validated.² Although there was a statistically significant improvement in the primary outcome for brimonidine 0.33% gel compared with vehicle gel, the success rate in the active treatment group was relatively low in both studies.

A study comparing brimonidine 0.33% gel with azelaic acid gel showed superior efficacy of brimonidine for a composite outcome of a 2-grade success in both the CEA and PSA.⁴

Brimonidine 0.33% gel is a symptomatic treatment for erythema of rosacea with a transient effect; it can be used once daily on a regular or as-required basis.¹ It may be used in conjunction with other topical treatments for the inflammatory lesions of rosacea and with cosmetics¹ but clinical data to support such use are lacking.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing brimonidine with no pharmacological therapy for the symptomatic treatment of facial erythema of rosacea in adults. SMC clinical experts indicated that no treatment is a relevant comparator but there is some usage of other treatments. The company therefore provided additional analyses to compare against metronidazole and azelaic acid.

A Markov model was used with three health states (HS) to reflect severity of erythema: HS1 - clear and almost clear, HS2 – mild erythema and HS3 – moderate or severe erythema. All patients initiate treatment in HS3. A one year time horizon and weekly cycle length were used. The model structure was appropriate.

The sources of clinical data were the two phase III, randomised, multicentre, double blinded brimonidine clinical studies described above. Transition probabilities for the health states in the Markov model were derived using data on the proportion of patients presenting with different severity of erythema, assessed using a composite of the CEA and PSA scales, measured over time in the brimonidine clinical studies. The progression of patients in the no treatment arm was derived using data from the placebo arms of the brimonidine clinical studies.

The utility values for each health state were estimated by converting quality of life values obtained from the brimonidine studies using the 12-item Short Form Survey to EQ-5D values. The utility values were 0.911 for HS1, 0.905 for HS2 and 0.898 for HS3.

Drug acquisition and medical visit costs were included. The base case assumed the following number of medical visits (GP and dermatologist) per health state: HS1 – 1 visit, HS2 – 1.5 visits, HS3 – 2 visits. Adverse events were not included in the model and the base case assumed a dose per day of 0.5g.

The base case results showed that, compared with no pharmacological treatment, brimonidine was associated with an incremental cost-effectiveness ratio (ICER) of £20,148 per quality-adjusted life-year (QALY), based on incremental QALYs of 0.0025 and an incremental cost of £50.

The results of the scenario analyses show that, compared with metronidazole, brimonidine was cost effective with a cost per QALY of £524. Compared with azelaic acid, brimonidine was dominant (i.e. less costly and more effective). These results were based on the assumption that the efficacy of both comparators is the same as no pharmacological treatment.

Sensitivity analyses indicated that the base case results were very sensitive to small variations in a number of parameters within the model. For example, small changes to the following parameters

each caused the ICER to increase beyond £50k: variation of the transition probabilities, changes in utility values, frequency of medical visits.

The key uncertainties surrounding the analysis were as follows:

- There were some concerns relating to the assumptions made about the number of GP visits per month, and therefore that company may have overestimated the impact of brimonidine on GP visit reductions. SMC expert responses indicate that these may be overestimated, and that patients are more likely to visit a GP once a month at most, even those with severe erythema. In sensitivity analyses, the ICER was sensitive to variation in the number of visits assumed, with the ICER increasing to above £60k in three analyses.
- There were also some concerns surrounding the utility values used within the model. The base case analysis assumes a very small QALY gain from brimonidine and also there to be very little difference in quality of life between the least severe and most severe health states. As such, the utility changes appeared to be particularly conservative.

Taking account of the uncertainties associated with GP visits and the utility values, the company provided a revised base case analysis. In this analysis, the company assumed that the number of GP visits per month would be 0.25, 0.5 and 0.75 for HS1, HS2 and HS3 respectively. Revised utility estimates of 0.89, 0.87 and 0.84 were used for HS1, HS2 and HS3 respectively. This resulted in a cost per QALY of £10,455 versus no treatment, £5,528 versus metronidazole and £5,372 versus azelaic acid.

Given this revised analysis, the economic case was demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specific patient group.

- A submission was made by Skin Conditions Campaign Scotland (SCCS), which is a registered charity.
- SCCS has received funding from several pharmaceutical companies in the past two years, including from the submitting company.
- Rosacea is a skin condition which causes a burning sensation in the face which is worse in a warm environment or when under stress. The unpredictably variable redness, often extreme, and pus spots can cause embarrassment, shame, reduced self-esteem and work effectiveness, and can lead to mental health problems. Patients can feel shunned, which can affect all aspects of interaction in daily life.
- There is currently no treatment that is effective, tolerable, and easy to use. Current treatments can control but not cure the pus spots, but have little effect on the redness. Covering creams are a partial and temporary answer, whilst systemic treatments are often only partially effective at tolerable doses.
- Brimonidine is effective and easy to use and is unlikely to have problem side-effects. It reduces redness and may help improve the psychosocial effects of rosacea, leading to increased confidence and a sense of “looking normal”, allowing a more positive outlook.

Additional information: guidelines and protocols

NICE clinical knowledge summaries (September 2012)

Flushing, erythema (without inflammation), telangiectasia and rhinophyma – there is no effective treatment for these symptoms in primary care, so management should consist of lifestyle advice or referral.⁷

NICE advice (evidence summary: new medicine [ESNM43]) Facial erythema of rosacea: brimonidine tartrate gel (July 2014)

In two short-term, randomised controlled trials 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.⁸

Primacy Care Dermatology Society guidelines updated 22 August 2014 states that erythema, flushing and telangiectasia can sometimes be predominant symptoms. Flushing may be helped by using a non-selective cardiovascular beta-blocker such as propranolol 40mg twice daily or clonidine 50 micrograms twice daily. However, use of these drugs would be off-label, and is not supported by evidence from randomised controlled trials. For persistent erythema/telangiectasia: brimonidine 0.33% gel is indicated for the treatment of persistent facial erythema of rosacea. Laser therapy can also be very effective although improvement is not permanent.⁹

Additional information: comparators

Metronidazole gel and azelaic acid gel are licensed for pustular forms of rosacea.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Brimonidine 0.33% gel	0.5 - 1g daily	204 - 409*
Azelaic acid 15% gel	0.5g twice daily	91
Metronidazole 0.75% gel	Apply twice daily (assume 1g daily)	80

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online, accessed 08/10/14.

* In the clinical studies with brimonidine 0.33% gel, the average daily dose was 0.5g.

Additional information: budget impact

The submitting company estimated there to be 6,675 patients eligible for treatment with brimonidine in year 1, rising to 6,792 in year 5, with an estimated uptake rate of 13% and 60% in years 1 and 5 respectively.

The submitting company estimated the gross medicines budget impact to be £138k in year 1 and £736k in year 5. As no other medicines were assumed to be displaced, the net medicines budget was equivalent to the gross budget impact estimates.

SMC clinical experts have suggested that brimonidine is likely to be used in addition to existing therapies, so the company may have under-estimated the net budget impact.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Summary of Product Characteristics for Brimonidine 0.33% gel (Mirvaso®)
2. European Medicines Agency (EMA) European Public Assessment Report brimonidine (Mirvaso®) Procedure No. EMEA/H/C/002642
3. 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 blinded, vehicle-controlled pivotal studies. Fowler J et al. J drugs Dermatol. 2013; 12(6):650-656
4. NCT01659853. Efficacy and safety study comparing CD07805/47 gel 0.5% to azelaic acid gel 15% in subjects with erythema of rosacea. Clinicaltrials.gov accessed 16/09/2014 NCT01659853
5. 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. Moore A et al. J Drugs Dermatol. 2014; 13(1): 56-61
6. NCT01885000. Patient reported outcome of facial erythema. Clinicaltrials.gov accessed 16/09/2014 NCT01885000
7. National Institute for Clinical Excellence (NICE). Clinical knowledge summaries: rosacea. Last revised September 2012
8. NICE advice [ESNM43] Facial erythema of rosacea: brimonidine tartrate gel (July 2014) www.nice.org.uk accessed 22/09/2014
9. Primary Care Dermatology Society. Clinical guideline for rosacea. Last revised 22 August 2014

This assessment is based on data submitted by the applicant company up to and including 14 November 2014.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.