This policy statement is approved by Halton, Knowsley, Liverpool, South Sefton, Southport and Formby, St Helens, Warrington, West Lancashire, and Wirral CCGs

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NHS
Pan Mersey
Area Prescribing Committee

BRIMONIDINE TARTRATE Gel (Mirvaso®) for facial erythema of rosacea

The Pan Mersey Area Prescribing Committee recommends the prescribing of BRIMONIDINE TARTRATE Gel (Mirvaso®) for the treatment of moderate to severe, persistent facial erythema associated with rosacea in adults

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Brimonidine gel is the only treatment that specifically targets facial erythema of rosacea. It does not alter the course of the disease or have any effect on other features of rosacea, such as telangiectasia or inflammatory papules, pustules, or phymatous changes of rosacea.[1,2]

NICE Clinical Knowledge Summary (CKS): Rosacea – acne (last revised October 2018)[2] covers the management of rosacea in primary care and recommends that where lifestyle changes prove ineffective and erythema is the predominant symptom in rosacea, with no prominent telangiectasia, prescribing of brimonidine gel may be considered. Lifestyle changes should be continued throughout treatment with brimonidine gel.

The Pan Mersey Area Prescribing Committee (APC) recommends the use of brimonidine gel in accordance with the NICE CKS guidance, in patients with moderate to severe, persistent facial erythema of rosacea because:

- Although the licensed indication is for the symptomatic treatment of facial erythema of rosacea in adults and does not discern between mild, moderate and severe facial erythema of rosacea, the pivotal trials only studied patients with moderate to severe erythema. There is a lack of evidence to support the use of brimonidine gel in people with mild facial erythema of rosacea.
- The Scottish Medicines Consortium and All Wales Medicines Strategy Group both only recommend restricted use in moderate to severe persistent erythema of rosacea, as the manufacturer only submitted evidence to support the use of brimonidine gel in this patient cohort.[3,4]
- Cost-effectiveness for the use of brimonidine gel in less severe erythema of rosacea has not been demonstrated.

The manufacturer has developed a Rosacea Screening Tool that uses the Clinician Erythema Assessment (CEA) and Patient Self-Assessment (PSA) scores, which are based on subjective judgements of erythema severity. Clinicians can use this and/or the Dermatology Life Quality Index (DLQI) to identify patients suitable for treatment with brimonidine gel.

The patient should be reviewed after at least one month's treatment and brimonidine gel only continued if there is evidence of significant reduction in erythema, i.e. mild or no erythema present.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

BRIMONIDINE TARTRATE Gel (Mirvaso®) for facial erythema of rosacea

Effectiveness

Brimonidine is a highly selective alpha-2 adrenergic receptor agonist, with potent vasoconstrictive and vasostabilising activity. Erythema of rosacea is associated with permanent vasodilation of small blood vessels. Facial application of brimonidine gel reduces erythema through direct cutaneous vasoconstriction.[1,5]

In two identical pivotal RCTs (n=553) compared with vehicle gel, a statistically significantly greater 'success rate' (2-Grade reduction in severity of erythema) was seen with brimonidine gel of about 25-30% versus 10% with vehicle gel ($p<0.001$) at day 29; a statistically significantly greater 'responder rate' (1-Grade reduction in severity of erythema) was seen with brimonidine gel of about 70% compared with about 30-40% with vehicle gel at day 29 ($p<0.001$), and a rapid onset of effect was seen with brimonidine gel of within 30 minutes in 28% of people which peaked at about 3 hours and was partially maintained over a 12-hour period.[1,6,7]

Safety

Brimonidine gel is contraindicated in people receiving monoamine oxidase inhibitors (MAOIs) e.g. selegiline or moclobemide, tricyclic or tetracylic antidepressants e.g. mirtazapine, and in children aged less than 2 years.[5]
Safety concerns related to the systemic absorption of brimonidine have also been identified for the age group 2 to 12 years. Brimonidine gel should not be used in children or adolescents aged 2 to 18.[5]
The most common adverse reactions in clinical studies were erythema, pruritus, flushing and skin burning sensation occurring in between 1.2% and 3.3% of people.[5]
The MHRA issued a Drug Safety Update in June 2017. Systemic cardiovascular effects have been reported after application. It is important to avoid application to irritated or damaged skin, including after laser therapy.[8]
There appears to be no clinically meaningful trends in tachyphylaxis or rebound effects (worsening of erythema after stopping treatment) seen with the use of brimonidine gel for 29 days, but a report of 3 people with possible rebound erythema has been published.[6,9]
See SPC for further detailed information.

Cost

Product	Cost per year (£) ex VAT[10]
Brimonidine gel 0.5*-1g daily	**202-404**
Azelaic acid 15% gel 0.5g twice daily	90
Metronidazole 0.75% gel 1g daily	79

**In a long-term study of brimonidine gel, the average daily amount used was 0.5g.*[1]
In the Scottish Medicines Consortium's assessment of brimonidine gel, the company submitted a cost-utility analysis comparing brimonidine gel with no pharmacological treatment. A number of uncertainties surrounding the analysis were raised which led the company to revise their base case analysis. This resulted in a revised cost per QALY of £10,455 versus no treatment, £5,528 versus metronidazole and £5,372 versus azelaic acid.[3]
Costs for brimonidine are likely to be in addition to alternative topical treatments, rather than instead of.[4]
Patient numbers are low. Total spend for Pan Mersey APC CCGs Aug 2018 – Jul 2019 = £11,608.45; this equates to an average of less than £600 per 100,000 population.

Patient factors

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.[1]
Brimonidine gel is a symptomatic treatment with a transient effect on erythema, not a cure. In the clinical trials highest response rates were observed 3 and 6 hours after once daily application of brimonidine gel and tended to wear off at later time points.[6]
There is some concern that due to the effects of brimonidine gel wearing off throughout the course of the day there may be a tendency for some people to use further applications.

Prescribing and implementation information[1,2,5]

- The recommended dose of brimonidine gel is 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 1g of gel once daily, divided into five pea size amounts to be applied to each area of the face: forehead, chin, nose and each cheek. One 30g tube is sufficient for one month's treatment. Patients should be advised not to exceed the maximum daily dose.
- Treatment should be initiated with a smaller amount of gel (less than the maximum) for at least one week. The amount of gel can then be increased gradually based on tolerability and patient response.
- Ongoing prescribing should only be continued if significant reduction in erythema is demonstrated, defined as a reduction to mild or no erythema present.
- Reiterate the lifestyle recommendations to patients, e.g. using high factor sunscreen, camouflage creams and avoidance of trigger factors. These should be continued throughout treatment with brimonidine gel.
- Brimonidine gel will not treat papules or pustules of rosacea, which should be treated with topical metronidazole or azelaic acid.
- Brimonidine gel can be used in conjunction with other cutaneous medicinal products for the treatment of inflammatory lesions of rosacea, and with cosmetics. These products should not be applied immediately before the daily application of brimonidine gel; they may be used only after the applied brimonidine gel has dried.

References

1. National Institute for Health and Care Excellence. Evidence Summary (ESNM43): Facial erythema of rosacea: brimonidine tartrate gel. July 2014. Accessed 27 September 2019.
2. National Institute for Health and Care Excellence. Clinical Knowledge Summaries: Rosacea – acne; Last revised October 2018. Accessed 27 September 2019:
3. Scottish Medicines Consortium. SMC No. (1016/14): Brimonidine (Mirvaso). 05 December 2014. Accessed 27 September 2019.
4. All Wales Medicines Strategy Group. Appraisal No. 2168: Brimonidine (Mirvaso®) 3mg/g gel; 15 July 2015. Accessed 27 September 2019.
5. Galderma. Summary of Product Characteristics: Mirvaso 3mg/g Gel; May 2017. Accessed 27 September 2019.
6. European Medicines Agency: Mirvaso. European Public Assessment Report; 19 December 2013. Accessed 27 September 2019.
7. Fowler J, Jackson J.M, Moore A, 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 Randomised, Double-Blind, Vehicle-Controlled Pivotal Studies. Journal of Drugs in Dermatology 2013;12: 650-56.
8. Medicines and Healthcare products Regulatory Agency. Drug Safety Update – Brimonidine gel (Mirvaso): risk of systemic cardiovascular effects; not to be applied to damaged skin. 21 June 2017. Accessed 27 September 2019.
9. Routt E, Jevitt J. Rebound erythema and burning sensation from a new topical brimonidine tartrate gel 0.33%. Letter. Journal of Am Acad Dermatol 2014; 70(2): e37-e38. Accessed 27 September 2019.
10. NHS Business Services Authority. dm+d browser. Accessed 27 September 2019.