New Medicine Assessment

Brimonidine Tartrate (Mirvaso) 3mg/g Gel

Indication under review: for the symptomatic treatment of moderate to severe facial erythema of rosacea in adult patients.

Recommendation: GREEN (restricted)

Appropriate for initiation and ongoing prescribing in both primary and secondary care provided:

Additional criteria specific to the medicine or device are met, or

The medicine or device is used following the failure of other therapies as defined by the relevant LSCMMG pathway.

Generally, little or no routine drug monitoring is required.

Restriction:

For use in patients with moderate to severe, persistent facial erythema of rosacea.

The Scottish Medicines Consortium[5] and All Wales Medicines Strategy Group[6] 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.

Pan Mersey APC recommends restricted use in moderate to severe persistent erythema of rosacea,

GMMMG recommends restricted use in severe persistent erythema of rosacea,

Summary of supporting evidence:

The 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).[8] An open-label, non-comparative study to evaluate long-term safety and efficacy (Moore et al. 2014) and an 8 day study of patient reported outcomes (PROOF Study) are also available. [3]

In Trials A and B, 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 $p<0.001$). 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 $p<0.05$).

In the open label, non- comparative study, 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).

The PROOF study concluded that once-daily brimonidine gel 0.33% allowed patients to rapidly control their facial redness and significantly improved patient-reported outcomes in the treatment of persistent facial erythema of rosacea.

Details of Review

Name of medicine (generic & brand name) Brimonidine Tartrate (Mirvaso)[1]

Strength(s) and form(s): 3mg/g Gel

Dose and administration: One application per 24 hours, at any time suitable for the patient, for as long as facial erythema is present.

The maximum daily recommended dose is 1 g of gel in total weight, which corresponds to approximately five pea sized amounts.

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.

BNF therapeutic class / mode of action: Skin / Rosacea

Licensed indication(s): Mirvaso is indicated for the symptomatic treatment of facial erythema of rosacea in adult patients.

Proposed use (if different from, or in addition to, licensed indication above): For the symptomatic treatment of ***moderate to severe*** facial erythema of rosacea in adult patients.

Course and cost: Ongoing. £33.69 for 30g[2]

The **maximum** daily recommended dose is 1 g of gel in total weight, at this maximum dose a tube would last approximately 30 days ie 1 month if used every day.

In a long-term study (Moore et al. 2014)[3] the average daily amount used was 0.532 g. Therefore 1 x 30g tube would last approximately 56 days ie 2 months.

Current standard of care/comparator therapies:

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.

The NICE CKS states: 'If there is persistent erythema, consider prescribing topical brimonidine 0.5% gel (a topical alpha-adrenergic agonist) once daily on an 'as needed' basis, for temporary relief of symptoms, depending on local prescribing guidelines'.[4]

Relevant NICE guidance:

Facial erythema of rosacea: brimonidine tartrate gel. Evidence summary [ESNM43] Published: 08 July 2014[4]

NICE CKS - Scenario: Rosacea. Last revised in February 2023
https://cks.nice.org.uk/topics/rosacea/management/rosacea/

SMC 1016/14 - Brimonidine (Mirvaso®) is accepted for restricted use within NHS Scotland[5]

AWMSG 2168 - Brimonidine (Mirvaso®) is recommended for restricted use within NHS Wales[6]

Background and context

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 vessels. Brimonidine reduces erythema through direct cutaneous vasoconstriction.[7]

Brimonidine tartrate gel should be applied only to the face.

Maximal drug effects are typically observed 3 hours after application and continue 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. [7]

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.

Brimonidine tartrate gel is licensed for the symptomatic treatment of facial erythema of rosacea in adults. 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.

Telangiectasia may be accentuated as general erythema is reduced.

Summary of evidence

Summary of efficacy data in proposed use:

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).[8] An open-label, non-comparative study to evaluate long-term safety and efficacy (Moore et al. 2014) is also available.[3]

Fowler et al 2013 (Trials A and B) [8]

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.

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. 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.

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.

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.

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 $p<0.001$). 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 $p<0.05$).

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 $p<0.001$).

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.

There was no evidence of tachyphylaxis or loss of efficacy during the 4-week treatment period in either trial. 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).[7] However, case reports of possible rebound erythema have since been published.

Moore et al 2014[3]

This was 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. 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.

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).

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.

Layton et al 2015 (PROOF study) [9]

The objective of this study was to evaluate patient-reported outcomes, as well as efficacy and safety, in subjects with self-perceived severe erythema treated with brimonidine gel 0.33% compared to vehicle.

This was an 8-day multicentre, randomised study comparing once-daily brimonidine gel 0.33% with vehicle gel using a facial redness questionnaire, subject satisfaction questionnaire and a patient diary of facial redness control to assess patient-reported outcomes.

Of the 92 included subjects with self-perceived severe erythema, very few were satisfied with their appearance at baseline (4.2% brimonidine group, 0 vehicle group). On Day 8, significantly more brimonidine group subjects were satisfied with their facial appearance compared to vehicle group (36.9% vs. 21.5%; $P < 0.05$), with the overall treatment effect (69.6% vs. 40.4%; $P < 0.01$), and with the improvement in their facial redness (67.4% vs. 33.3%; $P < 0.001$). More brimonidine group subjects were able to control their facial redness daily (e.g. 83.0% vs. 38.9% on Day 1). On Day 8, significantly more brimonidine group subjects than vehicle group had at least a one-grade improvement from baseline in the Clinician Erythema Assessment score (71.7% vs. 35.7%; $P = 0.0011$) and Patient Self-Assessment score (76.1% vs. 47.6%; $P = 0.004$). More subjects in the brimonidine group (29.2%) reported treatment-related adverse events than in the vehicle group (15.9%) but most were mild and transient.

The study concluded that once-daily brimonidine gel 0.33% allowed patients to rapidly control their facial redness and significantly improved patient-reported outcomes in the treatment of persistent facial erythema of rosacea.

There is another RCT comparing brimonidine tartrate gel with azelaic acid gel (ClinicalTrials.gov identifier: NCT01659853) underway, but this has not yet been published.

Summary of safety data :

Summary of safety profile

In both phase 3 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.[8]

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.[8]

In the open-label, non-comparative study (Moore et al) (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.[3]

Adverse reactions

Brimonidine tartrate gel is contraindicated in people receiving monoamine oxidase inhibitors) or tricyclic or tetracyclic 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.[1]

Mirvaso should not be applied on irritated skin (including following laser therapy) or open wounds. In case of severe irritation or contact allergy, the treatment with the medicinal product should be discontinued.

Exacerbation of rosacea symptoms is very common in patients treated with Mirvaso. Across all clinical studies, 16% of patients receiving Mirvaso experienced an event of symptom exacerbation. Treatment should be initiated with a small amount of gel and the dose increased gradually, based on tolerability and response to treatment.

The concomitant use of other systemic alpha adrenergic receptor agonists may potentiate the undesirable effects of this class of medicinal products in patients:
- with severe or unstable or uncontrolled cardiovascular disease;
- with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, thrombangiitis obliterans, scleroderma, or Sjögren's syndrome.

Any increase in the daily amount applied above 5 pea sized amounts and/or increase in frequency of daily application of the medicinal product should be avoided, since the safety of higher daily doses or repeated daily application has not been assessed.

The following adverse reactions are classified by System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to <1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data)

System Organ Class	Frequency	Adverse reactions
Cardiac disorders	Rare	Bradycardia*
Nervous system disorders	Uncommon	Headache, paraesthesia
Eye disorders	Uncommon	Eyelid oedema
Vascular disorders	Common	Flushing, pallor at the application site*
	Uncommon	Dizziness*
	Rare	Hypotension*
Respiratory, thoracic and mediastinal disorders	Uncommon	Nasal congestion
Gastrointestinal disorders	Uncommon	Dry mouth
Skin and subcutaneous tissue disorders	Common	Erythema, pruritus, rosacea, skin burning sensation
	Uncommon	Acne, allergic contact dermatitis, contact dermatitis, dermatitis, dry skin, pain of skin, skin discomfort, rash papular, skin irritation, skin warm, swelling face*, urticaria*
	Rare	Angioedema*
General disorders and administration site conditions	Uncommon	Feeling hot, peripheral coldness

* Adverse reactions reported from post-marketing data.

Post-marketing cases of bradycardia, hypotension (including orthostatic hypotension) and dizziness have been reported, some of which required hospitalisation. Some cases involved application of Mirvaso following laser procedures

Strengths and limitations of the evidence:

Strengths

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.

Moore et al was a 12 month study with 449 participants, with over half the participants completing the study.

The PROOF study was a multicentre, randomised study

Limitations

Both RCTs (Fowler et al) 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, was an open label, non comparative study – reason being as above.

The PROOF Study reported only patient reported outcomes over a short period of time.

Other

Brimonidine tartrate gel is licensed for the symptomatic treatment of facial erythema of rosacea in adults. 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 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.[7]

Prescribing and risk management issues:

N/A

Commissioning considerations:

Innovation, need and equity implications of the intervention:

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.

Financial implications of the intervention:

In the SMC 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.[5] Costs for brimonidine are likely to be in addition to alternative topical treatments, rather than instead of.[6]

Over the last 12 months (April 2022-March 2023) there have been 201 units of brimonidine gel prescribed at a cost of approximately £6434 across NHS Lancashire and South Cumbria ICS.

However, it is uncertain as to whether this has been prescribed only for those patients with moderate to severe, persistent facial erythema of rosacea as per the RCTs, or whether it has been prescribed as per its licensed indication which does not discern between mild, moderate and severe facial erythema of rosacea.

If its use is restricted to those patients with moderate to severe persistent facial erythema of rosacea the annual spend may be less.

Service Impact Issues Identified:

N/A

Equality and Inclusion Issues Identified:

None anticipated.

Cross Border Issues Identified:

Pan Mersey APC Formulary have given Brimonidine gel (Mirvaso) a GREEN RAG rating for the treatment of moderate to severe, persistent facial erythema associated with rosacea in adults. [10]

GMMMG have given Brimonidine gel (Mirvaso) a GREEN RAG rating for treatment of acne rosacea erythema. Only for use in patients with severe erythema, where all other formulary options have failed, and immediately prior to referring for laser treatment. [11]

Legal Issues Identified:

None identified.

Media/ Public Interest:

N/A

References

[1] Brimonidine tartrate (Mirvaso) SPC https://www.medicines.org.uk/emc/product/5303/smpc

[2] Drug Tariff May 2023 https://www.drugtariff.nhsbsa.nhs.uk/#/00837338-DC/DD00836938/Part%20VIIIA%20products%20B

[3] Moore 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. JDD January 2014 | Volume 13 | Issue 1. https://jddonline.com/articles/long-term-safety-and-efficacy-of-once-daily-topical-brimonidine-tartrate-gel-05-for-the-treatment-of-S1545961614P0056X/

[4] Facial erythema of rosacea: brimonidine tartrate gel Evidence summary [ESNM43]Published: 08 July 2014 https://www.nice.org.uk/advice/esnm43/chapter/Full-evidence-summary#relevance-to-nice-guidance-programmes

[5] SMC 1016/14 https://www.scottishmedicines.org.uk/medicines-advice/brimonidine-mirvaso-fullsubmission-101614/

[6] AWMSG 2168 https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/brimonidine-mirvaso/

[7] European Medicines Agency (EMA) European Public Assessment Report – brimonidine (Mirvaso). Procedure No. EMEA/H/C/002642 https://www.ema.europa.eu/en/medicines/human/EPAR/mirvaso

[8] Fowler 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, and Vehicle-Controlled Pivotal Studies. JDD June 2013 | Volume 12 | Issue 6. https://jddonline.com/articles/efficacy-and-safety-of-once-daily-topical-brimonidine-tartrate-gel-05-for-the-treatment-of-moderate-S1545961613P0650X/#close

[9] Layton et al; Brimonidine gel 0.33% rapidly improves patient-reported outcomes by controlling facial erythema of rosacea: a randomized, double-blind, vehicle-controlled study. J Eur Acad Dermatol Venereol. 2015 Dec; 29(12): 2405–2410 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5054962/

[10] Pan Mersey APC Formulary Decision- updated January 2020 https://www.panmerseyapc.nhs.uk/media/1837/brimonidine_rosacea.pdf?UNLID=6012009082023517153148

[11] GMMMG RAG rating / fomulary - updated Nov 2019 https://gmmmg.nhs.uk/rag-category/adult/#brimonidine-gel-mirvaso