LMMG New Medicine Recommendation

Brimonidine (Mirvaso®▼) gel for facial erythema of rosacea in adults 18 years and over

LMMG Recommendation: BLACK

Brimonidine gel is not recommended for use to treat symptomatic persistent facial erythema of rosacea.

Summary of supporting evidence:

- This is the first pharmaceutical agent approved across Europe that directly targets the persistent facial erythema of rosacea. There are several other licensed and off label use of licensed preparations available to treat the symptoms of rosacea, most of these are primarily targeted towards the papulopustular subtype of the disease.
- One brand of topical metronidazole (Rozex®) is licensed for the treatment of inflammatory papules, pustules and erythema of rosacea.
- The two pivotal phase 3 studies and a further supportive long term open label trial consistently demonstrated the efficacy of brimonidine gel against placebo in terms of improvement in Clinician Erythema Assessment (CEA) and Patient Self-Assessment (PSA), (which were considered clinically relevant), but only whilst receiving active treatment. It should be noted that the success rate (defined as a 2 grade reduction in the CEA and PSA) were 25% to 30% with brimonidine gel compared to 10% for the vehicle gel (placebo) at day 29.
- Although the pharmaceutical company developed and validated the CEA and PSA scales for assessing the effectiveness of Mirvaso®, they have been deemed as acceptable for their intended purpose. The scales are based on subjective measures, but are considered of relevance to the type of condition being treated and the intended use (symptomatic reduction of erythema rather than curative). It is unclear whether the tool would be routinely used in everyday clinical practice in the initial assessment and any follow-up to determine clinical effectiveness.
- The two pivotal studies were judged to be relatively short, considering the type of condition being managed, with an active treatment period of 4 weeks.
- 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. There is some concern that due to the effect wearing off throughout the course of the day there may be a tendency for some patients to use further applications. It should be emphasised that the preparation is only licensed for a maximum of once daily application.
- The two pivotal studies were performed under rather standardised experimental conditions which may not reflect “real-life conditions” – patients were allowed to acclimatise to the environment and rest comfortably prior to completion of the assessments. The open-label study design of the supportive long term trial was more closely related to “real life”.
- There are no randomised data available assessing the efficacy of brimonidine gel in patients who are also being treated with other topical products used in the management of rosacea e.g. metronidazole, azelaic acid gel. In clinical practice, a combination of preparations may be

used, for example brimonidine gel may be added in when metronidazole does not sufficiently reduce erythema in patients who also have inflammatory papules and pustules. The open-label long-term study did permit other treatments and almost 30% used additional topical products.

- A comparison against the one brand of metronidazole gel licensed for the treatment of inflammatory papules, pustules and erythema of rosacea may have added further information.
- Evidence demonstrating patient centred outcomes of treatment is limited, although the three studies did include some form of patient assessment of appearance and satisfaction. More people in the brimonidine group reported "satisfied" or "very satisfied" than the vehicle group for both pivotal studies. However, more than a quarter of patients reported that they were "dissatisfied" or "very dissatisfied" in the brimonidine group for both studies. Further evidence is needed to consistently demonstrate increased patient satisfaction and quality of life.
- For the Overall Treatment Effect (OTE), although the pivotal studies were not adequately powered to demonstrate difference in OTE, an interesting observation to note is that about twice as many patients in the brimonidine gel group compared to the vehicle gel group considered their condition had worsened as a result of treatment; about 10% versus 3-5%, however it is unclear whether this is statistically significant. It was noted that this could have been due to several factors, including small number of subjects, recall bias, and suboptimal timing of the administration or assessment.
- Following 4 weeks of non-treatment the CEA returned to close to pre-treatment scores; 0.3 and 0.5 points reduction compared to baseline (day 1/hour 0). In fact some subjects showed worsening on in PSA and CEA scores relative to baseline during the 4 week follow up.
- There have been case reports of rebound erythema in patients treated with brimonidine gel; however it should be noted that these are only case reports and not part of a trial powered to demonstrate statistical significance for this outcome.
- It should be noted that only patients with moderate to severe facial erythema of rosacea, according to the CEA and PSA have been studied. However the licensed indication is for the symptomatic treatment of facial erythema of rosacea in adult patients and does not distinguish between mild, moderate or severe facial erythema of rosacea.
- The most common adverse effects of brimonidine gel are erythema, pruritus, flushing and skin-burning sensation; these were usually transient, mild to moderate in severity and did not usually require discontinuation of treatment. As these symptoms are also included in the clinical symptomatology of rosacea, it is difficult to assess whether they are due to lack of efficacy or true adverse effects.
- The open-label trial of 449 patients indicated there were no specific risks associated with use up to one year. It is currently unclear whether this will be the case with longer term durations of use, which is likely for facial erythema of rosacea.
- There are no authoritative UK-based or European guidelines on the management of rosacea, which makes it difficult to assess the place in therapy of brimonidine gel. Considering the current cost of other topical and oral treatments used in the management of papulopustular rosacea, brimonidine gel is significantly more expensive with a potential financial implication of £110,000 to £220,000 per 100,000 population per annum (£1,650,000 – £3,300,000 for Lancashire).

Details of Review

Name of medicine

Brimonidine (Mirvaso ®▼) **[Galderma]**

Strength(s) and form(s):

3 mg/g (0.5%) gel.

One gram of gel contains 3.3 mg of brimonidine, equivalent to 5 mg of brimonidine tartrate (BT).[1]

Dose and administration:

One application per 24 hours, for as long as facial erythema is present. The maximum daily recommended dose is 1 g of gel, divided into five pea size amounts. One pea size amount should be applied smoothly and evenly as a thin layer to each of the five areas of the face: chin, each cheek, forehead and nose areas; avoiding the eyes, eyelids, lips, mouth and membrane of the inner nose.

It is contraindicated in children < 2 years, patients receiving monoamine oxidase inhibitors, tricyclic or tetracyclic antidepressants (e.g. mirtazapine) which affect noradrenergic transmission.[1]

BNF therapeutic class / mode of action

BNF therapeutic class: 13.6.3 Topical preparations for rosacea.

Highly selective alpha$_2$-adrenergic receptor agonist. By its agonistic action at the alpha$_2$-adrenergic receptor, brimonidine reduces erythema through direct cutaneous vasoconstriction.[1]

Licensed indication(s):

Brimonidine gel is indicated for the symptomatic treatment of facial erythema of rosacea in adults.[1]

Proposed use (if different from, or in addition to, licensed indication above):

Licensed indication.

Course and cost:

30g tube = £33.69

(MIMS on-line Apr 2014)

Current standard of care/comparator therapies:

One brand of metronidazole gel is licensed for inflammatory papules, pustules and erythema of rosacea.[2,3] Brimonidine gel is the first licensed treatment option that directly targets facial erythema of rosacea.[4]

Relevant NICE guidance:

No.

Reason for review:

Expression of interest identified by the annual horizon scanning process.

Background and context

Rosacea is a common long-term skin condition, with remissions and relapses, characterised by redness of the face, flushing, abnormal visible blood vessels and sometimes pimples or pustules. There may be facial burning, stinging and swelling. Less commonly other body parts can be affected.

Rosacea can be classified into four different sub-types and one variant based on specific clinical signs and symptoms:

- *Sub-type 1* – erythematotelangiectatic rosacea – flushing and persistent central facial erythema with or without telangiectasia
- *Sub-type 2* – papulopustular rosacea – persistent central facial erythema with transient, central face papules or pustules, or both
- *Sub-type 3* – phymatous rosacea – thickening of the skin, with irregular surface nodularities, and enlargement (this may occur on the nose, chin, forehead, cheeks or ears).
- *Sub-type 4* – ocular rosacea – inflammation of different parts of the eye and eyelid.
- *Variant* – granulomatous rosacea - non inflammatory, hard, brown, yellow, or red cutaneous papules, or nodules of uniform size.

Rosacea affects between 2% and 10% of people in the European population. 80% of cases appear after the age of 30 years. A study from the UK General Practice Research Database reported an incidence rate of diagnosed rosacea in UK as 1.65 per 1,000 person-years. Ocular symptoms are recorded in 21% of cases. It is more common in women than men, albeit men have a tendency to suffer complicated forms of the disease sometimes associated with disfigurement. It principally occurs in fair skinned people.[5,6,7]

It is not a life threatening condition. However as it mainly affects facial appearance, many people sense the condition affects their social life with an impact on quality of life causing embarrassment, anxiety and low self-esteem. A common public misconception is that the facial redness and rhinophyma associated with rosacea are due to excessive alcohol consumption making rosacea a socially stigmatising condition for many people.[7]

The cause of rosacea is not fully known, it is thought to be due to both genetic and environmental factors. The condition is often worsened by factors like sunlight, strong wind, alcohol, coffee, spicy food, exercise, stress and some cosmetics. Other causative factors include abnormalities of the small blood vessels, damage to the connective tissue and an abnormal inflammatory response. Dilated blood vessels accompanied by flushing allow fluids to leak out into the dermis, which may trigger an inflammatory response. It has also been found that the inflammatory response in papulopustular rosacea could be caused by antigenic proteins related to the bacterium *Bacillus oleroniu.*[6]

Several topical and oral medicines are approved in the UK for the treatment of papulopustular rosacea, including metronidazole, azelaic acid, oxytetracycline and doxycycline. Part of the management of rosacea consists of lifestyle advice including avoiding the trigger factors mentioned e.g. extremes of weather and sunlight, strenuous exercise, certain foods and drinks and stressful situations in addition to recommending that high factor suncream is applied frequently. Propanolol and clonidine have been used orally for flushing but this use is off label and is not supported by RCTs.[8] The Rozex® brand of metronidazole gel does have a licence for the treatment of inflammatory papules, pustules and erythema of rosacea.[2,3] Mirvaso® gel is the first product to be approved throughout the European Union that specifically targets persistent facial erythema of rosacea in adult patients.[4]

Grading of the assessment tools used in the trials: (used in the Summary of evidence and Table of Studies).

The tools assess the impact of the erythema of rosacea on the patient which includes:

1) **Clinician Erythema Assessment (CEA)** – A 5 grade assessment specifically focused on the assessment of erythema.
   0 = clear skin with no signs of erythema
   1 = almost clear, slight redness
   2 = mild erythema; definite redness
   3 = moderate erythema; marked redness
   4 = severe erythema; fiery redness
   The CEA has been independently validated and is considered a reliable instrument for the measurement of facial erythema.
2) **Patient Self-Assessment (PSA)** – A simple questionnaire specifically focused on the patient's assessment of erythema.
   0 = no redness
   1 = very mild redness
   2 = mild redness
   3 = moderate redness
   4 = severe redness
   The PSA has been independently validated and is considered a reliable instrument for the measurement of facial erythema.
3) **Patient Assessment of Appearance (PAA)** Scores:
   0=Very satisfied
   1=Satisfied
   2=Neither satisfied or dissatisfied
   3=Dissatisfied
   4=Very dissatisfied
4) **Overall treatment effect (OTE)** – subject self-assessment of the overall impact of therapy on the management of their facial erythema:
   1 = very much worse
   2 = moderately worse
   3 = a little worse
   4 = about the same
   5 = a little better
   6 = moderately better
   7 = very much better[4]

Summary of evidence

Summary of efficacy data in proposed use:

This review focuses on published results from the two pivotal phase 3 studies and one supportive open-label, long-term phase 3 study.[4,9,10] Power calculations were completed for the two pivotal phase 3 studies to ensure 90% power to detect important differences between BT gel 0.5% and Vehicle gel. The primary analyses in the two pivotal phase 3 studies were carried out on the intention-to-treat (ITT) population.[4]

Pivotal studies one and two[4,9] (see also Table of studies)

The two pivotal phase 3 studies of 4-weeks treatment and 4-weeks follow up had identical design and were performed in the USA and Canada. They were multi-centre, randomised, double-blind, vehicle controlled parallel group studies investigating the efficacy and safety of BT gel 0.5% applied topically once daily in adults over 18 years with a clinical diagnosis of facial rosacea with moderate to severe erythema (defined by CEA and PSA scores of ≥ 3). Patients with three or more facial inflammatory lesions of rosacea were excluded from enrolment into the study.

The primary efficacy endpoint was 2-grade Composite Success at 3, 6, 9 and 12 hours after application on day 29. Tests of treatment effects were also analysed on day 15 and day 1. A 2-grade Composite Success was defined as 2-grade improvement on both CEA and PSA at each time-point, was considered a clinically relevant improvement. The secondary efficacy endpoint was 1-grade Composite Success at 30 minutes on day 1. Success was defined as 1-grade improvement in CEA and PSA.

In both studies a significantly greater proportion of patients experienced a 2-grade improvement in CEA and PSA on days 1, 15 and 29 (at the specified time points over 12 hours) with BT gel 0.5% compared to patients treated with Vehicle gel; Study A odds ratio (OR) 3.75 [95% confidence interval {CI} 2.10 to 6.70]) and Study B OR 2.95 (95% CI 1.69 to 5.15). The success rate with BT gel 0.5% at 3, 6, 9 and 12 hours after application were 31.5%, 30.7%, 26.0% and 22.8% respectively versus 10.9%, 9.4%, 10.2% and 8.6% with Vehicle gel in Study A ($p<0.001$); and in Study B over the same time periods 25.4%, 25.4%, 17.6%, 21.1% in the BT gel treated group and 9.2%, 9.2%, 10.6% and 9.9% in the Vehicle gel treated group ($p<0.001$).

For the secondary efficacy end-point (ITT population, both studies combined) 28% of patients in the BT gel group showed 1-grade improvement on both CEA and PSA at 30 minutes following application on day 1, compared to 5-7% of patients in the Vehicle gel group; $p<0.001$ for both studies.

A tertiary end-point was also pre-specified in the study protocols. This was defined as 1-grade Composite Success on day 29 at 3, 6, 9 and 12 hours, and also on days 15 and 1. Efficacy on the 1-grade improvement is considered to represent an effect that is noticeable to patients and clinicians. The results should be interpreted with caution as the studies were not adequately powered to show difference in this end-point. In study A on day 29 the BT gel and Vehicle gel treated groups were 70.9%, 69.3%, 63.8% and 56.7% vs. 32.8%, 32.0%, 29.7% and 30.5% respectively. In Study B the corresponding results were 71.1%, 64.8%, 66.9% and 53.5% vs. 40.1%, 43.0%, 39.4% and 40.1%; $p<0.001$ for both studies.

There were a number of patient orientated outcome measures reported, including tachyphylaxis and rebound effects, but these were not a component of the primary or secondary efficacy outcomes. The results should be interpreted with caution as the studies were not powered to detect a difference for these outcomes. Refer to Table of studies for further information.

There was a 4 week no treatment follow up period where CEA and PSA scores were measured and compared to baseline at weeks 6 and 8. In both studies the subjects showed some decrease in CEA of 0.3 points and 0.5 points for study A and study B respectively relative to baseline (day 1/Hour 0). For the PSA score relative to baseline the reduction was 0.7 to 0.8 points and 0.7 points for study A and study B respectively. However there was a worsening of PSA and CEA scores in some patients during the follow up period relative to baseline. For study A the CEA increased by 1 point for 6% of patients at week 8 vs. 1% for vehicle group and 3% vs 1% for study B. For the PSA there was a 1 point increase for 2% of patients vs. 1% for vehicle group for study A at week 8 and 3% vs 4% for study B. The statistical significance was not reported for these outcomes.

The results of patient self-assessment of satisfaction using the PAA scale showed that more people in the brimonidine group were satisfied with treatment than in the control group (vehicle gel) for both study A and study B. 7.9% and 9.2% were “very satisfied” in study A and study B

respectively when treated with brimonidine gel at day 29, compared to 0.8% and 2.1% in the vehicle gel group respectively. The results for those "satisfied" with treatment in brimonidine gel group in study A and study B were 35.4% and 26.8% respectively compared to the vehicle gel groups for both studies being 19.5% and 16.9% respectively. No statistical analyses were reported for these results. 27.6% of people in study A and 24.6% in the study B reported they were "dissatisfied" or "very dissatisfied" in the brimonidine group at day 29 (compared to 43.5% and 42.2% in the vehicle gel group respectively). Again no statistical analysis was reported.

Subject self-assessments of the overall impact of therapy on the management of their facial erythema relative to the beginning of the study were based on the OTE. The OTE assessments were completed on Day 29 at 12 hours after application of study drug. The data for the OTE, as assessed by subjects at Hour 12 on Day 29, are summarized in the table of studies.

Study three[4,10]

A supportive study has been completed. This was a multicentre study carried out in 27 centres in the USA of open-label design to evaluate the long-term safety and efficacy of BT gel 0.5% applied topically once daily for up to 52 weeks in 449 people with moderate to severe facial erythema associated with rosacea (CEA and PSA scores of ≥3). There were 2 main differences in eligibility criteria compared to the two phase 3 studies. Subjects with ≥3 inflammatory lesions were eligible to participate and other concomitant topical and oral rosacea treatments were allowed. Almost 30% (n=131) received concomitant rosacea therapies, most commonly topical metronidazole (16%). For people who required new therapy during the study for the presence of inflammatory lesions could be prescribed at the investigator's discretion. The study is therefore more likely to reflect the true rosacea population than the two pivotal studies. The primary outcome of the study was to evaluate and document the long-term safety of BT 0.5% gel and long-term efficacy was evaluated as a secondary outcome. The study included a total of 8 visits: screening baseline/day 1, week 1 and months 1, 3, 6, 9 and 12.

A total of 449 patients were enrolled in the study. 279 (62.1%) completed the study and 355 (74.6%) completed at least 6 months of treatment. The majority of discontinuations were due to adverse events (16.7%) and patient request (11.6%). At baseline the majority of patients had a skin phototype of II or III (80%), were female (74.8%), white/Caucasian (97.6%) and had moderate erythema of rosacea according to CEA (87.8%) or PSA (84.4%) with a mean of 5.4 inflammatory lesions.

In terms of efficacy over the course of the study, the mean CEA score at hour 0 (prior to daily application of BT gel) reduced from 3.1 to 2.4 at month 3 and remained stable until month 12 (CEA=2.3). On day 1, after first application of BT gel the mean CEA score decreased from 3.1 at hour 0 to 1.7 at hour 3. This improvement was maintained until month 12. The results of PSA were similar to those of CEA. No tachyphylaxis was observed over the 52 week period.

Other efficacy data:

One study has been completed to consider patient reported outcomes in severe facial erythema (PROOF study). This is currently only available in abstract form[11] and has not been discussed further as part of this review.

There have been case reports published in the Journal of the American Academy of Dermatology stating that some patients have experienced rebound erythema following application of brimonidine gel. The cases discuss an initial improvement in erythema for the first 6 hours, followed by an increase in symptoms to a level of erythema worse than that prior to application.[12] It should be noted that these are only observational case reports and not outcomes of a RCT and so cannot be relied on as definite exacerbation or rebound erythema caused by application of the brimonidine gel or any more frequently than the rebound erythema

reported in the trials discussed above.

An efficacy and safety head to head study of brimonidine gel compared to azelaic gel has been carried out in subjects with erythema of rosacea but the results have yet to be published.[13]

Summary of safety data:

Overall the most common adverse effects (AEs) observed following treatment with topical BT gel are erythema, flushing, pruritus and skin burning sensation. They were typically mild to moderate in severity and in most cases did not require discontinuation of treatment.[1,4]

Erythema and flushing are common symptoms of facial rosacea and it is difficult to assess if these symptoms are due to lack of efficacy or true adverse events. Pruritus and skin burning are common adverse events of topically applied medicinal products such as metronidazole. The CHMP (Committee for Medicinal Products for Human Use) concluded there was no cause for concern.

Brimonidine tartrate has an established safety profile and clinical experience of use in ophthalmic solutions. The systemic exposure to brimonidine tartrate following treatment with BT gel at the licensed dosage is similar to that obtained with ophthalmic solutions of brimonidine tartrate. No systemic AEs were reported across all clinical studies except those caused by accidental oral ingestion and are not anticipated at the proposed clinical use.[4]

In the long-term safety and efficacy study[4,10] the overall incidence of AEs was highest in the first quarter of the study (21.4% subjects with at least one related AE) and decreased during subsequent quarters to 4.2% at quarter 4. AEs observed most frequently 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 one death (advanced squamous cell carcinoma of the lung) and 12 patients reported 16 serious AEs. All were deemed to be unrelated to BT gel. For the two, 4 week placebo controlled trials, the incidence of related AEs in the treatment group was 11.6% compared to 5.3% in the vehicle group for study A and 9.5% compared to 9.7% in study B.[9] No meaningful differences in the safety profile were observed between older people 65 years and over compared to people 16-64 years.[4]

Strengths and limitations of the evidence:

Overall study design

- The two pivotal phase 3 studies were relatively short in treatment duration (4 weeks) considering rosacea is a chronic skin disease characterised by flushing and persistent erythema. Treatment duration in excess of one year is likely.
- The CEA and PSA that were used for the primary outcomes of all studies were developed by the manufacturer of BT Gel. The EMA deemed the scales to be sufficiently described and validated for their intended purpose. It should be acknowledged that both the PSA and CEA are scales that are based on subjective judgements and not objective measures.
- The pivotal studies were adequately powered for the primary outcome.
- There were a large number of exclusions in the two pivotal studies. Of particular note is the exclusion of other topical and systemic rosacea treatments.
- In comparison, the open-label supportive study included almost 30% of patients taking concomitant treatments for inflammatory lesions associated with their rosacea, resulting in a study population more reflective of the true rosacea population.

Population

- The baseline demographics were similar in both pivotal phase 3 studies and open-label supportive study.
- Male representation was low relative to females but this is consistent with the incidence of rosacea.
- Only patients with moderate to severe facial erythema of rosacea according to CEA and PSA have been studied. However the licensed indication is for the symptomatic treatment of facial erythema of rosacea in adult patients and does not discern between mild, moderate and severe facial erythema of rosacea.
- The open label study's design and participant attrition over time hampers the interpretation of its efficacy results.

Intervention

- The decision to study BT 0.5% gel applied once daily was based on phase 2b dose/response and pharmacokinetic studies.

Comparator

- A vehicle gel as the control was a reasonable comparator since there are no other licensed pharmaceutical treatments that specifically target facial erythema of rosacea. However as one brand of topical metronidazole (Rozex®) is licensed for the treatment of inflammatory papules, pustules and erythema of rosacea a comparison may have added further information.

Outcomes

- The primary outcome was based on subjective judgement changes in CEA and PSA.
- Using only one time-point for the baseline assessments of CEA and PSA and four time-points at follow-up assessments (3, 6, 9 and 12 hours after treatment) makes it difficult to assess the time course of effect during the day. Baseline assessments covering the same time points of the day without treatment would have been of interest to evaluate whether the degree of erythema shows a diurnal variation.
- None of the studies were adequately powered to assess effect on patients' quality of life.

Summary of evidence on cost effectiveness:

No published evidence on the cost effectiveness of BT gel in the UK has been identified for a condition that could require long term treatment (in excess of one year).

Prescribing and risk management issues:

In the main and supporting studies, all patients were of American and Canadian, mainly white origin, with moderate to severe rosacea. No evidence was found to suggest that the results would have been any different in white European patients. It is currently unknown how effective the treatment would be in patients with mild rosacea or more complicated forms of rosacea e.g. rhinophyma. Although not studied, beneficial effects would be expected in patients with mild disease, although the benefits may not be so pronounced. The product licence of Mirvaso® does not preclude the use in mild facial erythema of rosacea.[1]

Two important risks have been identified: accidental oral ingestion and sensitivity skin reactions to either the brimonidine or excipients. To minimise potential accidental oral ingestion the manufacturers have incorporated the child proof lock. Sensitivity reactions tend to be unpredictable and not preventable. The product should not be used by patients known to be sensitive to any of the product excipients (carbomer, E218, phenoxyethanol, glycerol, titanium dioxide, propylene glycol and sodium hydroxide).[14]

Commissioning Considerations

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Brimonidine gel 3 mg/g	1g of gel applied once daily to the whole face divided into five pea size amounts to chin, forehead, nose and both cheeks	1x30g £33.69	£202 - £404 per year (365 days, based on average use of 6-12 tubes per year).[15]
Metronidazole cream & gel 0.75% (Rozex®)*	Topically twice daily to the inflammatory papules and pustules of the face	1 x 30 g = £6.60 1 x 40 g = £9.98	£27-£41 (per 4 months course)
Doxyxycline 40 mg M/R capsules	40 mg daily in the morning for 16 weeks; consider discontinuing treatment if no response after 6 weeks	14 x 40 mg = £7.99	£63.92 (per 16 week course)
Costs based on MIMS list prices April 2014. **This table does not imply therapeutic equivalence of drugs or doses.**			

*Rozex (gel and cream) is the only topical metronidazole brand where the licence indication includes erythema of rosacea and where concomitant facial inflammatory papules and pustules is present.[2,3]

Associated additional costs or available discounts:

None.

Productivity, service delivery, implementation:

None.

Anticipated patient numbers and net budget impact:

The following are assumptions:

- Prevalence of rosacea is 6% (range 2-10%).[7]
- Prevalence of symptomatic, persistent, facial erythema is 30% of the rosacea population.
- Uptake of BT gel is 30% of the eligible population.
- Usage of 6-12 x 30g tubes of BT gel per patient per year.

Extrapolating the above figures to a population of 100,000, this would equate to a potential eligible population of 540 patients at a cost of £202-£404 per patient per year, total cost £109,080 to £218,160 per annum.

Innovation, need, equity:

BT gel is the first pharmaceutical agent approved across Europe that directly targets the persistent facial erythema of rosacea. There are several pharmaceutical treatments available but these are primarily targeted towards the papulopustular rosacea subtype of the disease. One brand of topical metronidazole (Rozex®) is licensed for the treatment of inflammatory papules, pustules and erythema of rosacea.

No specific equity considerations are anticipated.

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15. New Drugs Online. Accessed 09 Apr 2014 at http://www.ukmi.nhs.uk/applications/NDO/record_view.asp?newDrugID=5932

Table of studies: Summary of pivotal Mirvaso gel 3mg/g (0.5%) RCTs relevant for use in facial erythema of rosacea.

<table>
<tr><th>Ref</th><th>Trial design and treatment</th><th>Trial population</th><th>Outcomes</th><th>Grading of evidence* / risk of bias</th></tr>
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<td>4, 5</td>
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Two 8-week, randomised, multicentre, double-blind, parallel-group studies.
The studies consisted of a 4-week treatment phase and a 4-week follow-up phase.
Patients were randomised in a 1:1 ratio to receive either brimonidine tartrate (BT) 0.5% gel or vehicle gel, once daily application stratified by centre.

Inclusion criteria:

Male or female at least 18 years of age.
A clinical diagnosis of facial rosacea.
A CEA score of ≥ 3 at screening and on baseline/ day 1 (prior to the study drug application).
A PSA score of ≥ 3 at screening and at baseline
Females of childbearing potential with a negative urine pregnancy test at screening and at baseline, or females of non-child-bearing potential (post-menopausal, documented hysterectomy, or bilateral oophorectomy).

Exclusion criteria

Rosacea conglobata, fulminans, isolated

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260 patients randomised in Study A and 293 patients randomised in Study B. 97.7% and 96.6% completed the studies respectively. ITT populations, n=260 and n=293 respectively.

79.2% and 72.7% female.
Mean age 48.8 years and 47.5 years.
98.5% and 98.6% Caucasian/White. (Fitzpatrick skin phototype II-III 82%).
Overall 100% had moderate to severe erythema based on CEA and <1.5% had mild rosacea based on PSA.
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Primary outcome

2-grade Composite success at 3, 6, 9 and 12 hours following application of study drug on day 29, then on day 15 and day 1, with 2-grade Composite Success being defined as a 2-grade improvement from baseline on both CEA and PSA at each time point.

Table 1. 2-grade Composite Success : ITT Population
<table>
<tr><th rowspan="2">% Compo-site Success</th><th colspan="4">Study A (18140)</th><th colspan="4">Study B (18141)</th></tr>
<tr><th>BT gel 0.5% N=129</th><th>Vehicle gel N=131</th><th>p-value</th><th>Odds ratio (95% CI)</th><th>BT gel 0.5% N=148</th><th>Vehicle gel N=145</th><th>p-value</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Day 29</td><td colspan="8"></td></tr>
<tr><td>Hour 3</td><td>31.5</td><td>10.9</td><td rowspan="4"><0.001</td><td rowspan="4">3.75 (2.10, 6.70)</td><td>25.4</td><td>9.2</td><td rowspan="4"><0.001</td><td rowspan="4">2.95 (1.69, 5.15</td></tr>
<tr><td>Hour 6</td><td>30.7</td><td>9.4</td><td>25.4</td><td>9.2</td></tr>
<tr><td>Hour 9</td><td>26.0</td><td>10.2</td><td>17.6</td><td>10.6</td></tr>
<tr><td>Hour 12</td><td>22.8</td><td>8.6</td><td>21.1</td><td>9.9</td></tr>
<tr><td>Day 15</td><td colspan="8"></td></tr>
<tr><td>Hour 3</td><td>25.0</td><td>3.1</td><td rowspan="4"><0.001</td><td rowspan="4">NC*</td><td>25.2</td><td>3.5</td><td rowspan="4"><0.001</td><td rowspan="4">NC</td></tr>
<tr><td>Hour 6</td><td>27.3</td><td>6.3</td><td>25.9</td><td>4.3</td></tr>
<tr><td>Hour 9</td><td>19.5</td><td>5.5</td><td>21.7</td><td>5.0</td></tr>
<tr><td>Hour 12</td><td>16.4</td><td>2.3</td><td>15.4</td><td>7.1</td></tr>
<tr><td>Day 1</td><td colspan="8"></td></tr>
<tr><td>Hour 3</td><td>16.3</td><td>3.1</td><td rowspan="4"><0.001</td><td rowspan="4">NC</td><td>19.6</td><td>0</td><td rowspan="4"><0.001</td><td rowspan="4">NC</td></tr>
<tr><td>Hour 6</td><td>23.3</td><td>2.3</td><td>29.7</td><td>2.1</td></tr>
<tr><td>Hour 9</td><td>19.4</td><td>3.8</td><td>18.2</td><td>0.7</td></tr>
<tr><td>Hour 12</td><td>13.2</td><td>3.1</td><td>13.5</td><td>1.4</td></tr>
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*NC = not calculated

Secondary outcome (not powered)
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rhinophyma, isolated pustulosis of the chin, or other concomitant skin conditions similar to rosacea (e.g. peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrhoeic dermatitis, acute lupus erythematosus or actinic telangiectasia.
- Presence of 3 or more facial inflammatory lesions of rosacea.
- Treatment at the time of screening/day 1 with monoamine oxidase inhibitors, barbiturates, opiates, sedatives, systemic anaesthetics, or alpha-agonists.
- Less than 3 months stable dose treatment with tricyclic antidepressants, cardiac glycosides, beta blockers or other antihypertensive agents.
- Diagnosis at the time of screening/day 1 of Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome or depression.
- Exposed to excessive UV radiation within 1 week prior to baseline.
- Presence of beard or excessive facial hair at screening.
- Treatment at the time of screening/day 1 with

1-grade Composite Success (1-grade improvement on both CEA and PSA) at 30 minutes on day 1.

Table 2. 30-minute CEA and PSA effect. Two main phase 3 studies; ITT Population.

Success %	**Study A (18140)**				**Study B (18141)**			
	BT gel 0.5% N=129	**Vehicle gel N=131**	**p-value**	**Odds ratio (95% CI)**	**BT gel 0.5% N=148**	**Vehicle gel N=145**	**p-value**	**Odds ratio (95% CI)**
30-minute effect	27.9	6.9	<0.001	4.75 (2.22-10.17)	28.4	4.8	<0.001	7.45 (3.26-17.04)

Selected additional outcomes (not powered)

Overall Treatment Effect (OTE) – Patient self-assessment of the overall impact of treatment on the management of their facial erythema on day 29 at 12 hours after the first daily application of treatment.

Table 3. Patient self-assessment of OTE. Two main phase 3 studies; ITT Population.

OTE n/n (%)	**Study A**		**Study B**	
	BT gel 0.5% N=129	**Vehicle gel N=131**	**BT gel 0.5% N=148**	**Vehicle gel N=145**
1 = very much worse	1 (0.8%)	1 (0.8%)	1 (0.7%)	1 (0.7%)
2 = moderately worse	6 (4.8%)	3 (2.3%)	4 (2.8%)	1 (0.7%)
3 = a little worse	6 (4.8%)	3 (2.3%)	10 (7.0%)	3 (2.1%)
4 = about the same	30 (23.8%)	72 (56.3%)	37 (26.1%)	80 (56.3%)
5 = a little better	33 (26.2%)	32 (25.0%)	25 (17.6%)	29 (20.4%)
6 = moderately better	33 (26.2%)	11 (8.6%)	39 (27.5%)	19 (13.4%)
7 = very much better	17 (13.5%)	6 (4.7%)	26 (18.3%)	9 (6.3%)
Total	126 (100%)	128 (100%)	142 (100%)	142 (100%)

Tachyphylaxis and rebound effects

Tachyphylaxis was assessed over a 12-hour observation period on 3 separate clinic days: 1, 15 and 29. Evidence of tachyphylaxis was not observed.

	brimonidine tartrate ophthalmic solution. ▪ Patients who had received, applied, or taken the following treatments within the specified time prior to the baseline/day 1 clinic visit: – **Topical facial treatments*:*** Laser, Photodynamic Therapy or intense pulsed light (IPL) treatment, electrocoagulation, dermabrasion, facial peels, any other dermatologic/ surgical procedure on the face within 4 weeks; topical azelaic acid or metronidazole, immunomodulator or corticosteroids within 4 weeks; antibiotics within 2 weeks; OTC medicines for treatment of acne within 1 week or astringents or abrasives within 2 days. – **Systemic treatments:** Isotretinoin within 6 months; immunomodulators within 12 weeks; doxycycline, tetracycline, macrolides for the treatment of rosacea or acne, oral or injectable corticosteroids within 4 weeks; phototherapy within 4 weeks; antibiotics within 4 weeks; anti-inflammatory medicines within 2 weeks; chronic, daily use of OTC anti-inflammatory medicines for more than 1 week (excluding low-dose aspirin for cardiac prophylaxis) or nicotinic acid ≥ 500 mg per day within 1 week.		Rebound erythema was assessed based on mean changes in CEA and PSA scores during post-treatment follow-up period at weeks 6 and 8 in both studies. In both studies mean changes in CEA scores at week 6 and 8 showed reductions in the BT gel group of 0.3 points and 0.5 points in study A and B respectively; and 0.7 to 0.8 points and 0.7 points in study A and B for the PSA relative to day 1/hour 0 up to 4 weeks following cessation of treatment. Some patients (<5%) showed worsening in CEA and PSA scores relative to baseline during the follow-up period.	

Grading of evidence (based on SORT criteria):

Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies
Level 3	Disease-oriented evidence or evidence from: • consensus guidelines • expert opinion • case series

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