New Medicine Recommendation

Ivermectin cream 10mg/g (Soolantra®)

For the topical treatment of inflammatory lesions of rosacea (papulopustular) in adult patients

Recommendation: GREEN

Appropriate for initiation and on-going prescribing in both primary and secondary care.

Generally, little or no routine drug monitoring is required.

Metronidazole cream is generally considered the first-line topical treatment for rosacea. Azelaic acid may be more effective than metronidazole[1], but is often less well tolerated. Results from the phase 3 study[10] would suggest that ivermectin is slightly more effective than metronidazole, and with a comparable incidence of adverse events.[4]

Summary of supporting evidence

- In two identical phase 3 trials (studies 1 and 2) with a total patient cohort of 1371:
  - a significantly greater proportion of patients in the ivermectin group (38% and 40%) achieved Investigator's Global Assessment (IGA) success compared with the vehicle (placebo) group (12% and 19%) (both p<0.001, rounded to nearest percent).
  - The mean difference between treatment groups was -8.13 lesions (95% CI: -10.12 to -6.13, p<0.001) in study 1,9 and -8.22 lesions (95% CI: -10.18 to -6.25, p<0.001) in study 2
  - The secondary endpoint of improvements in quality of life, measured using RosaQoL, were statistically significantly greater for ivermectin compared with vehicle -0.62 vs −0.35, (p<0.001) in study 1 and -0.60 vs. -0.35 (p=0.001) in study 2
  - Percentage change in inflammatory lesion count from baseline to week 12 was assessed as a secondary outcome, and both studies showed a significantly greater reduction with ivermectin compared with vehicle. Mean (standard deviation) percentage change at week 12 was -65% (39.91) in the ivermectin group and -42% (38.83) in the vehicle group (p<0.001) in study 1, and -66% (33.18) in the ivermectin group and -43% (38.42) in the vehicle group (p<0.001) in study 2
- In a 40 week extension study combining the populations of studies 1 and 2
  - At week 12, 38.4% of people treated with ivermectin in study 1 and 40.1% in study 2 had an IGA score of 0 or 1 ('clear' or 'almost clear').
  - This increased to 71.1% and 76.0% respectively by week 52
- Compared with metronidazole 0.75% cream, ivermectin 1% cream, in an 962 patient study conducted for 16 weeks and then extended for a further 36 weeks:
  - Produced an 83% reduction in the inflammatory lesion count compared with 74% for metronidazole (p<0.001).
  - A statistically significant difference was observed between groups from week 3 onwards.
  - In absolute terms, from a baseline of about 32 lesions in both groups, this was a reduction of 28 lesions for ivermectin and 24 lesions for metronidazole

- Network meta-analyses show that ivermectin cream has a statistically greater likelihood of successful treatment of rosacea than azelaic acid 15% gel and metronidazole 0.75% cream at weeks 12 and 15 and has a higher percentage change in inflammatory lesion count than either comparator at 12 weeks.
- For success rate at week 12 compared to vehicle, ivermectin 1% cream OD has an NNT of 3, compared to 9 for azelaic acid gel 15% BD and 6 for metronidazole 0.75% cream BD

Safety

- In the studies comparing ivermectin with placebo adverse events reported on average by 39% of the ivermectin group and 38% of the vehicle group
- The 40-week, long-term extension studies found the overall incidence of adverse events was similar for ivermectin 10 mg/g and azelaic acid 15% gel, reported in approximately 60% of participants.
- In the ivermectin/metronidazole study the incidence of adverse events was similar for ivermectin cream (32.4%) and metronidazole (33.1%)

Economic Considerations

- One 30g tube of 10mg/g ivermectin cream costs £18.29, excluding VAT. A 4 month treatment course will cost £73.16
- A 4 month course of metronidazole gel treatment will cost £38.40
- A 4 month course of azelaic acid 15% gel will cost £29.92
- Based on the SMC assumptions, the net medicines budget impact for Lancashire is estimated at £6,516 in year 1 and £15,297 in year 5.

Details of Review

Name of medicine: Ivermectin (Soolantra®)

Strength and form: 10mg/g cream

Dose and administration: One application a day for up to 4 months. Soolantra® should be applied daily over the treatment course.

Cutaneous application of a pea-size amount of medicinal product to each of the five areas of the face: forehead, chin, nose, and each cheek. The medicinal product should be spread as a thin layer across the entire face, avoiding the eyes, lips and mucosa.

The treatment course may be repeated.

In case of no improvement after 3 months, the treatment should be discontinued.

Soolantra® should be applied only to the face.[2]

BNF therapeutic class / mode of action: 13 Skin > 13.10 Anti-infective skin preparations > 13.10.4 Parasiticidal preparations[3]

Ivermectin is a member of the avermectin class. Avermectin has anti-inflammatory effects by inhibiting lipopolysaccharide-induced production of inflammatory cytokines. Anti-inflammatory properties of cutaneous ivermectin have been observed in animal models of skin inflammation. Ivermectin also causes death of parasites, primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells. The mechanism of action of ivermectin in treating the inflammatory lesions of rosacea is not known but may be linked to anti-inflammatory effects of ivermectin as well as causing the death of Demodex mites that have been reported to be a factor in inflammation of the skin.[2]

Licensed indications:

Ivermectin cream (Soolantra®) is indicated for the topical treatment of inflammatory lesions of rosacea (papulopustular) in adult patients.[2]

Proposed use: As above

Background

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

Mild or moderate papulopustular rosacea (with a limited number of papules and pustules, and no plaques) is generally treated with a topical drug. Metronidazole gel or cream is usually preferred because it is well tolerated. Azelaic acid gel is an alternative to metronidazole that may be more effective, especially in people who do not have sensitive skin, however, it may cause transient stinging. For moderate or severe papulopustular rosacea (with extensive papules, pustules, or plaques), oral tetracycline, erythromycin, doxycycline or lymecycline can be prescribed, although not all of these drugs are licensed for treating rosacea and evidence from RCTs to support their use is limited.[4] The Primary Care Dermatology Society (PCDS) guidance on rosacea advises that initial systemic treatment should be for at least 3 months, although if the person responds well to treatment the dose may be reduced after 1 month.[5] The guidance advises that if symptoms recur frequently, once symptoms have settled on a standard dose of treatment the

person can then be kept on a lower dose of the antibiotic to reduce flare-ups. For more severe symptoms that respond poorly to treatment, the PCDS guidance suggests referral to a dermatologist for consideration of other treatments such as low dose isotretinoin (unlicensed indication).

Relevant Guidance

NICE have published an 'Evidence summaries: new medicines' document for 'Inflammatory lesions of papulopustular rosacea: ivermectin 10 mg/g cream'.[6] The strengths and weaknesses of the relevant evidence are critically reviewed within the summary to provide useful information for those working on the managed entry of new medicines for the NHS, but the summary is not NICE guidance.

Ivermectin cream was approved by the All Wales Medicines Strategy Group for treatment of inflammatory lesions of rosacea (papulopustular) in adult patients in February 2016.[7]

In December 2015, the Scottish Medicine Consortium accepted ivermectin (Soolantra®) for topical treatment of inflammatory lesions of rosacea (papulopustular) in adult patients, restricting its use to the treatment of moderate to severe inflammatory lesions of rosacea where a topical treatment is considered appropriate.[8]

Clinical Evidence

The regulatory dossier for ivermectin 1% cream includes five clinical studies; two phase 2 studies (40027 and 40106), two pivotal, double-blind, vehicle-controlled phase 3 studies (18170 and 18171)[9] and one investigator-blinded, active-controlled phase 3 study (40173).[10] All were randomized, parallel-group studies.

This evidence review is guided mainly by the NICE evidence summary[6] with some data from the AWMSG,[7] SMC[8] and the product's Assessment Report.[11] Phase 2 studies are not included in the review. Long-term safety and efficacy data comes from two 40-week, investigator-blinded, active-controlled extension studies are included.[12]

Ivermectin compared with vehicle[9]

The two pivotal studies had an identical design and were conducted in parallel. Study 1 had 683 participants and study 2 had 688 participants aged 18 years or older with moderate or severe papulopustular rosacea (defined as an Investigator's Global Assessment (IGA) score of 3 or 4 respectively) and 15 to 70 facial inflammatory lesions (papules and pustules). Nearly all participants were white, the majority with moderate rosacea with an average of 31 to 33 inflammatory lesions. People with more than 2 nodules on their face, with certain forms of rosacea or other facial dermatoses (e.g. acne) were excluded from the studies. Participants were randomised in a 2:1 ratio to ivermectin 10 mg/g cream or vehicle cream to be applied to the entire face, once daily at bedtime for 12 weeks.[6]

The two co-primary end points were:

- 'success' rate, defined as the proportion of participants with an IGA score of 1 ('almost clear') or 0 ('clear') and
- absolute change in inflammatory lesion count from baseline to week 12.

The Investigator's Global Assessment (IGA) scale relied on the judgement of the treating clinicians:

Investigator's Global Assessment (IGA) scale

Grade	Score	Clinical Description
Clear	0	No inflammatory lesions present, no erythema
Almost Clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, mild erythema
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

In both studies, a significantly greater proportion of patients in the ivermectin group (38% and 40%) achieved IGA success compared with the vehicle group (12% and 19%) (both p<0.001, rounded to nearest percent). Both studies also demonstrated a significantly greater reduction in the absolute change in inflammatory lesion count with ivermectin compared with vehicle.[8] The mean difference between treatment groups was -8.13 lesions (95% CI: -10.12 to -6.13, p<0.001) in study 1,[9] and -8.22 lesions (95% CI: -10.18 to -6.25, p<0.001) in study 2.[12,8]

The secondary endpoint of improvements in quality of life, measured using RosaQoL,[a] were statistically significantly greater for ivermectin compared with vehicle -0.62 vs −0.35, (p<0.001) in study 1 and -0.60 vs. -0.35 (p=0.001) in study 2. Percentage change in inflammatory lesion count from baseline to week 12 was assessed as a secondary outcome, and both studies showed a significantly greater reduction with ivermectin compared with vehicle. Mean (standard deviation) percentage change at week 12 was -65% (39.91) in the ivermectin group and -42% (38.83) in the vehicle group (p<0.001) in study 1, and -66% (33.18) in the ivermectin group and -43% (38.42) in the vehicle group (p<0.001) in study 2.

Other end-points addressed Percent Change in Inflammatory Lesion Count, Subject's assessment of rosacea improvement at Week 12 (5-point scale ranging from Excellent Improvement to Worse), erythema and nodule counts and quality of life (Dermatology Life Quality Index).[b]

Extension study

A 40-week, investigator-blinded, active-controlled, extension study assessed the long-term efficacy and safety of ivermectin 10 mg/g cream. A total of 622 participants from study 1 and 636 participants from study 2 entered the extension phase.

People originally randomised to ivermectin 10 mg/g cream continued on this treatment for 40 weeks, and people from the vehicle group were switched to azelaic acid 15% gel twice daily for 40 weeks.[12] At week 12, 38.4% of people treated with ivermectin in study 1 and 40.1% in study 2 had an IGA score of 0 or 1 ('clear' or 'almost clear'). This increased to 71.1% and 76.0% respectively by week 52.

Ivermectin compared with metronidazole

The ATTRACT study was a phase III, randomised, investigator-blinded study to compare the efficacy and safety of ivermectin 1% cream versus metronidazole 0.75% cream at reducing inflammatory lesions in patients with moderate to severe papulopustular rosacea.[10,13] The study was conducted for 16 weeks (Period A) and then extended for a further 36 weeks (Period B) to investigate the relapse rate. 962 Adults with an IGA score of three (moderate rosacea) or four (severe rosacea) and with 15 to 70 facial inflammatory lesions (papules and pustules) were

[a] RosaQoL is a 21-item validated questionnaire that requires people to score the emotional, symptomatic and functional impact rosacea is having on their quality of life. Each item is scored from 1 ('never') to 5 ('all the time'), with higher scores indicating a greater impact on quality of life.

[b] DLQI: a 10 item questionnaire measuring how much a dermatological condition affects a person's life. Scored from 0 to 30, with higher scores indicating a larger effect on the person's life.

recruited to the study. In Period A, patients were randomly allocated to treatment with topical ivermectin 1% cream applied once-daily at bedtime (n=478), or metronidazole 0.75% cream applied twice-daily in the morning and at bedtime (n=484).

The primary outcome in Period A was the percentage change in inflammatory lesion count on the cheeks, forehead, nose and chin from baseline to week 16. Ivermectin produced an 83% reduction in the inflammatory lesion count compared with 74% for metronidazole ($p<0.001$, rounded to nearest percent). A statistically significant difference was observed between groups from week 3 onwards. In absolute terms, from a baseline of about 32 lesions in both groups, this was a reduction of 28 lesions for ivermectin and 24 lesions for metronidazole. The median time to first relapse, defined as an IGA score of 2 or more, was 115 days in the ivermectin group and 85 days in the metronidazole group ($p=0.0365$).[11]

A secondary efficacy end point was treatment success at week 16, defined as an IGA score of 0 or 1, which was achieved by 84.9% in the ivermectin group, compared with 75.4% for metronidazole ($p<0.001$, NNT=11). Statistically significant improvements in quality of life, measured using DLQI score, were observed for ivermectin (improvement of 5.18 points) compared with metronidazole (improvement of 3.92 points, $p<0.01$).

Network meta-analyses

The manufacturer of ivermectin cream provided network meta analyses (NMA) to the SMC and AWMSG to compare ivermectin 1% cream once daily, metronidazole 0.75% cream/gel twice daily, azelaic acid 15% gel twice daily and vehicle in adults with moderate to severe papulopustular rosacea.[7,8] Both analyses appear similar but are not available for direct comparison. One noticeable difference in the analyses is the number of studies used for IGA success at week 12 – the SMC based this on 10 studies, the AWMSG on 12. The results appear comparable, with the AWMSG providing more details therefore this will be used for the LMMG review.

The literature search results were used to create NMAs for the following endpoints: success rate at 12 weeks; success rate at 15 weeks; percentage change in inflammatory lesion count at 12 weeks. Success was associated with IGA scores of 0 or 1 on a five-point scale or 1 or 2 on a seven-point scale. In the NMA for success at 12 weeks, obtained using 12 studies, ivermectin was associated with a statistically significantly higher success rate compared to azelaic acid and compared to metronidazole. Analysis at 15 weeks, based on three studies, indicated statistically significantly higher success rate for ivermectin compared to metronidazole and comparable efficacy for ivermectin and azelaic acid. The NMA for percentage change in inflammatory lesion count at 12 weeks, based on 13 studies indicated a higher change for ivermectin compared to the comparators. Data are presented in the table, below.

Data from the meta analyses presented to the AWMSG

Success rate at 12 weeks (risk ratio for ivermectin 1% cream once daily versus comparator)		
Comparator	**Risk ratio**	**95% credible interval**
Azelaic acid 15% gel twice daily	1.230	1.111 to 1.371
Metronidazole 0.75% cream twice daily	1.169	1.085 to1.286
Success rate at 15 weeks (risk ratio for ivermectin 1% cream once daily versus comparator)		
Comparator	**Risk ratio**	**95% credible interval**
Azelaic acid 15% gel twice daily	0.998	0.699 to 1.299
Metronidazole 0.75% cream twice daily	1.415	1.187 to 1.708
% change inflammatory lesion count at 12 weeks (ivermectin 1% cream once daily versus comparator)		
Comparator	**Absolute difference**	**95% credible interval**
Azelaic acid 15% gel twice daily	−5.96	−11.31 to −0.58
Metronidazole 0.75% cream twice daily	−9.43	−13.06 to −5.78
Risk ratios > 1 favour ivermectin; absolute difference < 0 favours ivermectin		

A meta-analysis was published in 2016, comparing ivermectin with currently available topical treatments for the inflammatory lesions of rosacea, using data from January 2011 to June 2015.[14] The analysis evaluated the efficacy, safety, and tolerability of ivermectin 1 % cream once daily against currently available topical treatment options for papulopustular rosacea. The studies of interest were randomized controlled trials published in English reporting any intervention that might be considered to treat moderate-to-severe papulopustular rosacea, as assessed by individual study investigators. The review is of interest as it provides a publically available reference for comparison against the meta-analysis used by the SMC and AWMSG – the data have similarities but are not identical in both reviews. The table, below, presents data from the publically available meta-analysis.

Success rate for ivermectin 1 % cream once daily versus comparators at week 12

Comparator treatment	**12 weeks 12 studies**
RR (95 % CrI) (vs. ivermectin 1 % cream QD)	
Azelaic acid 15 % gel QD	1.33 (0.99 to 2.20)
Azelaic acid 15 % gel BID	*1.25 (1.14 to 1.37)*
Metronidazole 0.75 % cream BID	*1.17 (1.08 to 1.29)*
Metronidazole 1 % gel QD	1.18 (0.98 to 1.56)
Silica encapsulated benzoyl peroxide 1 % gel QD	1.09 (0.86 to 1.78)
Silica encapsulated benzoyl peroxide 5 % gel QD	0.94 (0.81 to 1.29)
Vehicle	*1.56 (1.46 to 1.65)*
NNT (95 % CrI) (vs. vehicle)	
Azelaic acid 15 % gel QD	7 (−120 to 120)
Azelaic acid 15 % gel BID	*9 (6 to 14)*
Metronidazole 0.75 % cream BID	*6 (4 to 13)*
Metronidazole 1 % gel QD	*6 (3 to 41)*
Silica encapsulated benzoyl peroxide 1 % gel QD	4 (−31 to 44)
Silica encapsulated benzoyl peroxide 5 % gel QD	*3 (2 to 9)*
Ivermectin 1 % cream QD	*3 (3 to 4)*

Cochrane

A Cochrane review of treatments for rosacea considered the two vehicle comparison studies high quality studies[9,12] that demonstrated a statistically significant and clinically important improvement in favour of topical ivermectin when compared to placebo. [15] Participants' assessments in these studies showed a RR of 1.78 (95% CI 1.50 to 2.11) and RR of 1.92 (95% CI 1.59 to 2.32), which were supported by physicians' assessments. The Cochrane review also states that topical ivermectin appeared to be slightly more effective than topical metronidazole for papulopustular rosacea, based on the metronidazole comparison study,[10] for improving quality of life and participant and physician assessed outcomes (high quality evidence for these outcomes).

Safety Summary

In the studies comparing ivermectin with placebo[9,12] adverse events reported on average by 39% of the ivermectin group and 38% of the vehicle group (no stats reported). Skin burning, pruritus and dry skin occurred in 4.2% and 2.6% of the ivermectin groups in study 1 and study 2 respectively, and in 7.8% and 6.5% of the vehicle groups. Serious adverse events were reported in 0.7% and 1.5% of the ivermectin groups in studies 1 and 2 respectively, compared with 0.4% and 1.7% for vehicle.[9] Across both trials treatment-related adverse events led to discontinuation in 1.3% and 0.2% in the ivermectin groups, compared with 1.7% in the vehicle group.

The 40-week, long-term extension studies[12] found the overall incidence of adverse events was similar for ivermectin 10 mg/g and azelaic acid 15% gel, reported in approximately 60% of participants. Incidence of treatment-related adverse events was 1.9% and 2.1% for ivermectin in study 1 and 2 respectively, compared with 6.7% and 5.8% for azelaic acid (no statistical analysis reported). Across both studies, the most common treatment-related adverse events reported were skin burning and irritation in the ivermectin groups (each affecting 0.4% [3/840] participants); and skin irritation (1.7% [7/418] participants), and dryness (1.4% [6/418] participants) in the azelaic acid groups. Across both extension studies, 1% (8/840) of participants receiving ivermectin cream discontinued treatment due to an adverse event, compared with 2% of people (9/418) treated with azelaic acid gel. None of the adverse events leading to discontinuation were considered to be related to the study drug in the ivermectin groups, with 7 out of 9 in the azelaic groups thought to be due to the study drug.

In the ivermectin/metronidazole study[10] the incidence of adverse events was similar for ivermectin cream (32.4%) and metronidazole (33.1%), as was the incidence of treatment-related adverse events (2.3% for ivermectin and 3.7% for metronidazole). The most common treatment-related adverse event was skin irritation, reported by 0.6% (3/478) in the ivermectin group and 0.8% (4/484) in the metronidazole group. 3 participants (0.6%) in the ivermectin group discontinued due to treatment-related adverse events, compared with 10 people (2.1%) in the metronidazole group.

The SPC for Soolantra®[2] lists the following adverse events:

Incidence of Event	**Adverse Event**
Common (≥1/100 to <1/10)	Skin burning sensation
Uncommon (≥1/1,000 to <1/100)	Skin irritation, pruritus, dry skin

Commissioning Considerations

One 30g tube of 10mg/g ivermectin cream costs £18.29,[16] excluding VAT. The dose is a 'pea sized amount' to five areas of skin each day.

It is difficult to estimate the amount of cream that will be used each day by an average patient:

- In one study, a pea sized amount was shown to weigh around 0.25g,[17] which would imply that 1.25g would be used each day.
- In one of the pivotal studies, participants using ivermectin used a mean of 0.72 g daily.[10]
- The Australian consumer medicine information leaflet for Soolantra, developed by the pharmaceutical company responsible for the medicine, estimates that about 1g of cream will be used per day.[18]

Using the estimates from the three sources, it is reasonable to concur with the patient information sheet and ***assume that 1g of cream will be used each day by each patient***.

One application should be used each a day for up to 4 months. If there is no improvement after 3 months, treatment should be discontinued.

- For a **successful patient**, 120g of cream will be needed for the 4 month course. This will cost **£73.16** for a treatment course
- For an **unsuccessful patient**, stopping after 3 month's treatment, 90g of cream will be needed. This will cost **£54.87** for a treatment course

The treatment course may be repeated.

All prices taken from MIMS, August 2016, excluding VAT

Comparative Unit Costs

Drug	Example regimen	Pack cost	Cost per patient per month	Cost per patient per course
Ivermectin 10 mg/gram cream	Apply to the whole face once daily. Assume 1g daily. Course up to 4 months	1x30g: **£18.29**	**£18.29**	**£73.16**
Azelaic acid 15% gel	Applied to affected skin areas twice daily. Assume 1g daily and course is 4 months	1×30g: £7.48	£7.48	£29.92
Metronidazole 0.75% gel	Thin layer applied to affected skin areas twice daily. Assume 1g daily. Course 3 to 4 months.	1×30g: between £6.60 and £22.63 the average price in Lancashire is £9.60*	£9.60*	£38.40*
Costs based on MIMS prices August 2016, excluding administration costs and VAT. Table does not imply therapeutic equivalence of drugs or doses. *epact.net April – June 2016, average price for 30g for Lancashire CCGs				

In the SMC application, the submitting company estimated the population eligible for treatment to be 6,708 in year 1 rising to 6,761 in year 5 with an estimated uptake rate of 5% in year 1 and 13% in year 5. As other drugs were assumed to be displaced the net medicines budget impact

decreased to £23k in year 1 and £54k in year 5.

With an estimated population in Lancashire of approximately1.5million this equates to a patient population of 1,900 rising to 1,915 in year 5 and an uptake in 95 patients in year 1 and 249 in year 5

Based on the SMC assumptions, the net medicines budget impact for Lancashire is estimated at £6,516 in year 1 and £15,297 in year 5.

Strengths and Limitations of the Evidence

Strengths

- In 2 randomised, vehicle-controlled phase III trials[9] there were no major differences between treatment groups in baseline characteristics, participants and investigators were blinded to which treatments were received, and allocation appears to have been concealed
- Statistically significantly more people receiving ivermectin reported 'excellent' or 'good' improvements at week 12 compared with vehicle (i.e. placebo).[9] Similar results were observed in the trial comparing ivermectin and metronidazole.[10]
- Adverse events in the pivotal studies for ivermectin were similar to placebo vehicle cream.[9,12]
- The 40-week, long-term extension studies[12] found the overall incidence of adverse events was similar for ivermectin 10 mg/g and azelaic acid 15% gel.
- In the ivermectin/metronidazole study[10] the incidence of adverse events was similar for ivermectin cream (32.4%) and metronidazole (33.1%)

Limitations

- There are no clearly established efficacy end points to be used in studies of products indicated for the treatment of rosacea.[11]
- The study comparing ivermectin and metronidazole[10]
    - did not include a vehicle group, although superiority to vehicle has been demonstrated in other studies
    - was investigator-blinded, meaning participants were aware of which treatment they were receiving; this may have introduced bias and led to a possible overestimation of treatment benefits.
- Different definitions for recurrence or relapse of rosacea were used in the 2 extension studies; an IGA score 1 or more in study 2[12] and an IGA score of 2 or more in the extension to the metronidazole study[10]
- At the start of the 23-week extension phase of the metronidazole study there was an imbalance in rosacea severity between treatment groups, with more people in the ivermectin group having an IGA score of 0 ('clear'; 42%) than in the metronidazole group (29%). This may have had an effect on the time to relapse.
- No studies have looked at the efficacy and safety of ivermectin beyond 12 months
- There are no studies comparing ivermectin cream with oral treatments licensed for papulopustular rosacea; however, oral treatments are usually considered once topical treatments have failed to improvement symptoms, so the lack of such comparisons is acceptable

Prescribing and risk management issues:

N/A

Associated additional costs or available discounts:

N/A

Productivity, service delivery, implementation:

N/A

Innovation, need, equity:

Ivermectin will be a third topical option for the treatment of rosacea. Brimonidine gel (Mirvaso®) is licensed for the symptomatic treatment of facial erythema of rosacea in adult patients – a relatively limited license that does not cover inflammatory lesions of rosacea. Brimonidine gel was categorised as **Black** following review by the LMMG.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
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	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
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	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR

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