NICE National Institute for
Health and Care Excellence

Inflammatory lesions of papulopustular rosacea: ivermectin 10 mg/g cream

Evidence summary

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Key points from the evidence

> The content of this evidence summary was up-to-date in January 2016. See
> summaries of product characteristics (SPCs), British national formulary (BNF) or the
> MHRA or NICE websites for up-to-date information.

Summary

In 2 randomised controlled trials (RCTs) ivermectin cream was statistically significantly
more effective than vehicle cream (placebo) in improving rosacea severity score and
reducing inflammatory lesion count. In another RCT, ivermectin was superior to
metronidazole cream at reducing lesion count and improving rosacea severity score. Local
adverse events, including skin burning sensation, skin irritation, pruritus and dry skin, are
common, although these are mostly transient, mild to moderate in severity and usually
decrease when treatment is continued.

Regulatory status: Ivermectin 10 mg/g cream (Soolantra) received a UK marketing authorisation in April 2015. It was launched in the UK in June 2015.

Effectiveness	Safety
• Statistically significantly more people receiving ivermectin cream were considered treatment successes compared with those using vehicle cream. Success rate, measured using Investigator Global Assessment (IGA), was approximately 39% for ivermectin compared with approximately 15% for vehicle. People treated with ivermectin cream had approximately 8 fewer lesions compared with the vehicle group. Time to onset of efficacy was 4 weeks (2 RCTs, n=1371, 12 weeks). • Ivermectin cream was superior to metronidazole cream at reducing inflammatory lesions, with participants having approximately 10% fewer lesions (1 investigator-blinded RCT, n=962, 16 weeks).	• In 2 RCTs adverse events were reported by between 32 to 40% of people using ivermectin cream. Adverse events considered to be treatment-related were reported by about 4% of people receiving ivermectin. • The most commonly reported adverse events were skin burning, skin irritation, pruritus and dry skin. • Adverse events are typically mild to moderate in severity, and usually decrease when treatment is continued.

Patient factors	Resource implications
• Over two-thirds of people treated with ivermectin cream rated their improvement as 'excellent' or 'good', compared with about one-third of people in the vehicle group. • Ivermectin cream is applied once daily, while other topical treatments for rosacea are applied twice daily. • People with rosacea should be advised to avoid rosacea triggers, for example, sudden exposure to heat, certain foods and excessive sun exposure.	• Ivermectin 10 mg/g cream is £18.29 for a 30 g tube (excluding VAT; cost taken from MIMS, December 2015). • Topical metronidazole 0.75% (cream or gel) costs between £6.60 and £22.63 for a 30 g or 40 g tube (excluding VAT; cost taken from MIMS December 2015 or Drug Tariff, December 2015). • Azelaic acid 15% gel costs £7.48 for a 30 g tube (excluding VAT; cost taken from Drug Tariff, December 2015). • In a clinical trial people receiving ivermectin cream used approximately half the amount of cream each day compared with those treated with metronidazole cream. This is because ivermectin is applied once daily and metronidazole twice daily.

Introduction and current guidance

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. Mild or moderate papulopustular rosacea (with a limited number of papules and pustules, and no plaques) is generally treated with a topical drug (metronidazole or azelaic acid). 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 (Clinical Knowledge Summaries: rosacea).

Full text of introduction and current guidance.

Product overview

Ivermectin is a member of the avermectin class of medicines. The mechanism of action for treating the inflammatory lesions of rosacea is not known, but may be linked to the anti-inflammatory effects of ivermectin, as well as causing the death of *Demodex folliculorum* mites (Soolantra 10 mg/g Cream [ivermectin] summary of product characteristics).

Full text of product overview.

Evidence review

- This evidence summary is based on 2 randomised controlled trials (RCTs) of identical design that compared ivermectin with vehicle (placebo, study 1 [n=683] and study 2 [n=688], Stein Gold et al. 2014a), and a randomised, active-comparator trial that compared ivermectin cream with metronidazole cream (n=962, Taieb et al. 2015). Information on long-term safety, efficacy and recurrence rates is supplied by one 36-week and two 40-week extension studies.

- In 2 RCTs ivermectin was statistically significantly more effective than vehicle at reducing signs and symptoms of papulopustular rosacea:

  — For the co-primary end point of 'treatment success' at 12 weeks, defined as an Investigator Global Assessment (IGA) score of 0 or 1 ('clear' or 'almost clear'), 38.4% and 40.1% of the ivermectin group, and 11.6% and 18.8% of the vehicle group were considered treatment successes (statistically significant difference, both $p<0.001$, number needed to treat [NNT]=5).

  — From a baseline of approximately 32 lesions, people treated with ivermectin had a reduction of about 21 lesions and people treated with vehicle had a reduction of 13 lesions. At 12 weeks this equates to an absolute mean reduction in inflammatory lesion count (second co-primary end point) of approximately 8.2 fewer inflammatory lesions for ivermectin compared with vehicle ($p<0.001$ both studies).

  — Statistically significantly more people receiving ivermectin reported 'excellent' or 'good' improvements at week 12 compared with vehicle (secondary end point).

  — Statistically significant improvements in participant satisfaction and quality of life

were reported. Although the minimal clinically important difference in reduction of Dermatology Life Quality Index (DLQI) score was not reached, baseline DLQI scores were not poor, meaning large improvements would not be expected.

- A 16-week randomised, investigator-blinded study compared the efficacy of ivermectin with metronidazole 0.75% cream (n=962, Taieb et al. 2015).

  - The primary end point of this study was mean absolute change in inflammatory lesion count. Participants receiving ivermectin cream experienced an 83.0% reduction in inflammatory lesion count, compared with a reduction of 73.7% in the metronidazole group (p<0.001). This equated to a treatment difference of approximately 4 lesions between ivermectin and metronidazole.

  - The secondary efficacy end point was treatment success (defined using IGA score) at week 16, which was achieved by 84.9% in the ivermectin group, compared with 75.4% for metronidazole (p<0.001, NNT=11).

  - The incidence of adverse events was similar for ivermectin cream (reported by 32.4% of people) and metronidazole cream (33.1%), as was the incidence of treatment-related adverse events (2.3% for ivermectin and 3.7% for metronidazole, Taieb et al. 2015).

- The most common adverse events reported by people receiving ivermectin cream were skin burning sensation (1.3%), skin irritation (1.0%), pruritus (0.8%) and dry skin (0.7%). No systemic adverse events were reported in the clinical studies (Soolantra PAR).

Full text of evidence review.

Context

Mild or moderate papulopustular rosacea is usually treated with topical metronidazole or azelaic acid, with moderate or severe papulopustular rosacea often managed with oral tetracycline, erythromycin, doxycycline or lymecycline (Clinical Knowledge Summaries: rosacea).

Full text of context.

Estimated impact for the NHS

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using ivermectin 10 mg/g cream or other topical treatments for papulopustular rosacea. A Cochrane review states that topical ivermectin appeared to be slightly more effective than topical metronidazole for papulopustular rosacea (van Zuuren et al. 2015). There are no published studies that directly compare the efficacy of ivermectin and azelaic acid.

Full text of estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

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. (Clinical Knowledge Summaries: rosacea.)

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 (Clinical Knowledge Summaries: rosacea) and evidence from RCTs to support their use is limited (van Zuuren et al. 2015). 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. 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).

Product overview

Drug action

Ivermectin 10 mg/g cream (Soolantra) is a member of the avermectin class, which have anthelmintic and insecticidal properties. The mechanism of action for treating the inflammatory lesions of rosacea is not known, but may be linked to the anti-inflammatory effects of ivermectin and by causing the death of *Demodex folliculorum* mites, that have been reported to be a factor in inflammation of the skin (Soolantra 10 mg/g Cream [ivermectin] summary of product characteristics [SPC]).

Licensed therapeutic indication

Ivermectin 10 mg/g cream (Soolantra) is indicated for the topical treatment of inflammatory lesions of rosacea (papulopustular) in adults (Soolantra 10 mg/g Cream summary of product characteristics). It was approved through the European Decentralised Procedure; Sweden acted as the Reference Member State. It was launched in the UK in June 2015.

Course and cost

Ivermectin cream should be applied once daily for up to 4 months. If there is no improvement after 3 months, the treatment should be discontinued. The treatment course may be repeated. A pea-size amount of ivermectin cream can be applied to each of the 5 areas of the face: forehead, chin, nose, and each cheek. The cream should be spread as

a thin layer across the entire face, avoiding the eyes, lips and mucosa. Ivermectin cream should only be applied to the face and hands should be washed after application (Soolantra 10 mg/g Cream summary of product characteristics).

The cost of ivermectin 10 mg/g cream is £18.29 for a 30 g tube (excluding VAT, price from MIMS, December 2015).

Evidence review

This evidence review is based on 2 randomised controlled trials (RCTs) of identical design that compared ivermectin cream with vehicle (placebo, Stein Gold et al. 2014a), and an investigator-blinded, randomised trial comparing ivermectin cream with metronidazole 0.75% cream (Taieb et al. 2015). Long-term safety and efficacy data comes from two 40-week, investigator-blinded, active-controlled extension studies (Stein Gold et al. 2014b). Information from the studies has been supplemented and clarified using the Soolantra (ivermectin) public assessment report (PAR). The results of an unpublished 23-week extension study looking at recurrence rates which are reported in the PAR are also discussed briefly.

All trials included in this evidence summary reported treatment 'success' based on the Investigator Global Assessment (IGA) scale, a grading system for rosacea which addresses the presence and size of papules/pustules and severity of erythema (Table 1).

Table 1: Investigator Global Assessment (IGA) scale (Soolantra 10 mg/g Cream summary of product characteristics)

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

Ivermectin compared with vehicle (Stein Gold et al. 2014a and

Stein Gold et al. 2014b)

- Design: 2 multicentre, randomised, double-blind, parallel-group, vehicle-controlled trials with identical designs (designated as study 1 and study 2) which compared the efficacy and safety of ivermectin and vehicle over 12 weeks (Part A). A 40-week single-blind, active-controlled, extension period (Part B) provided long-term safety and efficacy data.

- Population: study 1 randomised 683 participants and study 2 randomised 688 participants; both were conducted in the US and Canada. The trials recruited people (68.2% women in study 1 and 66.7% women in study 2) aged 18 years or older (mean age 50.4 years in study 1 and 50.2 years in study 2) with moderate or severe papulopustular rosacea (defined as an IGA score of 3 or 4 respectively) and 15 to 70 facial inflammatory lesions (papules and pustules). Nearly all participants were white (96.2% in study 1 and 95.3% in study 2) with an average of 31 to 33 inflammatory lesions. The majority of people had moderate rosacea (IGA score=3), approximately 79% across the 2 studies. The PAR states that people with more than 2 nodules on their face, with particular forms of rosacea (for example, isolated rhinophyma) or other facial dermatoses (for example, acne) were excluded from the studies.

- Intervention and comparator: participants in both trials were randomised in a 2:1 ratio to ivermectin 10 mg/g cream (n=451 study 1, n=459 study 2) or vehicle cream (n=232 study 1, n=229 study 2), to be applied to the entire face, once daily at bedtime for 12 weeks. According to the PAR, other rosacea treatments were not permitted. Participants were instructed to avoid rosacea triggers, for example, sudden exposure to heat, certain foods and excessive sun exposure. Allocation was concealed.

- Outcomes: the first of 2 co-primary end points was 'success' rate, defined as the proportion of participants with an IGA score of 1 ('almost clear') or 0 ('clear'). The second co-primary end point was absolute change in inflammatory lesion count from baseline to week 12. Secondary end points included participant's evaluation of improvements and 2 quality of life questionnaires: the Dermatology Life Quality Index (DLQI) and the rosacea-specific RosaQoL questionnaire. The DLQI is a 10 question validated questionnaire that asks people to measure how much their condition affects their life. It is scored from 0 to 30, with higher scores meaning the condition is having a larger effect on the person's life. Although the minimal clinically important difference for the DLQI is yet to be established for the different skin diseases there is general acceptance that this ranges between 2.5 and 5.0 (van Zuuren et al. 2015). The 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 (Nicholson et al. 2007).

- Analysis: primary analyses were performed on data for the intention-to-treat (ITT) population, defined as all subjects who were randomised and to whom the study drug was administered. Results were confirmed using the per-protocol (PP) population, defined as the ITT population who had no major protocol deviations. Missing data for all end points was imputed by Last Observation Carried Forward (LOCF).

- Long-term extension phase: a 40-week, investigator-blinded, active-controlled, extension study assessed the long-term 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. Safety assessments included adverse events, local tolerability signs and symptoms (evaluated on a scale from 0 [none] to 3 [severe]) and laboratory safety tests. Efficacy was assessed using IGA score at each 4-week study visit. Although not discussed in the original study publication (Stein Gold et al. 2014b), the PAR for Soolantra states that treatment was stopped if a participant was considered to be 'clear' (IGA score=0). The participant had their treatment restarted if their IGA score became 1 or more (where a score of 1 means 'almost clear').

Ivermectin compared with metronidazole (Taieb et al. 2015)

- Design: multicentre, randomised, investigator-blinded, parallel-group study compared the efficacy and safety of ivermectin 1% and metronidazole 0.75% cream over 16 weeks.

- Population: 962 participants were randomised across 64 centres in Europe. The inclusion criteria were the same as those used in Stein Gold et al. (2014a); adults (mean age 51.5 years; 65.2% women) with moderate or severe papulopustular rosacea (defined as an IGA score of 3 or 4; 83.3% had an IGA score of 3) and with 15 to 70 facial inflammatory lesions (mean 32.5 lesions). Allocation was concealed.

- Intervention and comparator: participants were randomised in a 1:1 ratio to ivermectin 10 mg/g cream once daily (n=478) or metronidazole 0.75% cream twice daily (n=484), to be applied to the entire face for 16 weeks. Participants were advised to maintain a

consistent lifestyle throughout the study regarding rosacea triggers (for example, avoiding trigger foods and excessive sun exposure).

- Outcomes: the primary end point was percentage change in inflammatory lesion count from baseline to week 16. Secondary end points were success rate based on IGA score and change in lesion count (both measured from baseline to week 16). Quality of life was measured using the DLQI at baseline and week 16. LOCF was the primary method for imputation of missing data, and multiple imputations method was used for sensitivity.

- Long-term extension phase: a 23-week extension phase studying recurrence rates has been completed but the results have not yet been published in a peer-reviewed journal, although the PAR for Soolantra discusses some methods and results. People considered 'clear' (IGA score=0) or 'almost clear' (IGA score=1) at the end of the 16 week treatment period were eligible for the extension phase. At week 16 the study drugs were discontinued and time to relapse was recorded. Relapse was defined as an IGA score of 2 or more (where a score of 2 means 'mild'). A total of 757 people entered the extension phase, of which 64% had an IGA score of 1 ('almost clear').

Table 2 Summary of Stein Gold et al. 2014a

		Ivermectin 1% cream	Vehicle	Analysis
Randomised	Study 1	n=451	n=232	
	Study 2	n=459	n=229	
Efficacy[a]	Study 1	n=451	n=232	
	Study 2	n=459	n=229	
Co-primary outcome: treatment success, based on IGA score at week 12[b]	Study 1	38.4% (173/ 451)	11.6% (27/ 232)	p<0.001
	Study 2	40.1% (184/ 459)	18.8% (43/ 229)	p<0.001

Co-primary outcome: change in mean inflammatory lesion count from baseline to week 12 (95% CI)	Study 1	Change from baseline −20.5 lesions[c]	Change from baseline −12.0 lesions[c]	Mean treatment difference 8.13 lesions (95% CI 10.12 to 6.13, p<0.001 compared with vehicle).
	Study 2	Change from baseline −22.2 lesions[c]	Change from baseline −13.4 lesions[c]	Mean treatment difference 8.22 lesions (95% CI 10.18 to 6.25, p<0.001 compared with vehicle).
Selected secondary outcomes:				
Percentage of participants rating their improvement as 'excellent' or 'good' after treatment	Study 1	69.0%	38.6%	p<0.001
	Study 2	66.2%	34.4%	p<0.001
Change in DLQI score[d]	Studies 1 and 2	About 53% improvement	About 35% improvement	p<0.001 (both studies)
Improvement from baseline in RosaQoL score[e] (SD)	Study 1	−0.64 (0.7)	−0.35 (0.5)	p<0.001
	Study 2	−0.60 (0.6)	−0.35 (0.5)	p=0.001
Safety[a]	Study 1	n=451	n=232	No statistical analysis reported for safety outcomes.
	Study 2	n=459	n=229	
Participants reporting serious adverse events	Study 1	0.7% (3/451)	0.4% (1/232)	
	Study 2	1.5% (7/459)	1.7% (4/229)	
Participants reporting adverse events	Study 1	40.5% (183/451)	39.4% (91/232)	
	Study 2	36.5% (168/459)	36.5% (84/229)	

Participants reporting treatment related adverse events	Study 1	4.2% (19/451)	7.8% (18/232)	
	Study 2	2.6% (12/459)	6.5% (15/229)	
Participants reporting treatment related adverse events leading to discontinuation	Study 1	1.3% (6/451)	1.7% (4/232)	
	Study 2	0.2% (1/459)	1.7% (4/229)	

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; p, p value; QoL, quality of life; SD, standard deviation.

[a]The ITT population is all participants who were randomised and given the study drug.

[b]Treatment success is defined as an IGA score of 0 ('clear') or 1 ('almost clear', see Table 1 for more details).

[c]Additional results taken from the Public Assessment Report for Soolantra. Data from the two sources do not agree (to 1 decimal place) due to rounding at different points in study.

[d]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.

[e]RosaQoL: a 21-item questionnaire that scores the emotional, symptomatic and functional impact rosacea is having on quality of life. Higher scores indicating a greater impact on quality of life.

Table 3 Summary of Taieb et al. (2015)

	Ivermectin 1% cream	Metronidazole 0.75% cream	Analysis
Randomised	n=478	n=484	
Efficacy[a]	n=478	n=484	
Primary outcome: percentage change in inflammatory lesion count from baseline to week 16	83.0%	73.7%	p<0.001
Selected secondary outcomes:			

Success rate based on IGA score at week 16	84.9%	75.4%	p<0.001
Percentage of participants rating their improvement as 'excellent' or 'good' after treatment	85.5%	74.8%	No statistical analysis reported
Mean change in DLQI score[c]	−5.18	−3.92	p<0.01
Absolute change from baseline in inflammatory lesion counts (SD)[d]	−28 (15) lesions	−24 (16) lesions	Statistically significant difference, p<0.001
Safety[a]	n=478	n=484	
Participants reporting adverse events	32.4%	33.1%	
Participants reporting treatment related adverse events	2.3% (11/478)	3.7% (18/484)	
Participants reporting treatment related adverse events leading to discontinuation	0.6% (3/478)	2.1% (10/484)	

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; p, p value; QoL, quality of life.

[a] The ITT population is all participants who were randomised and given the study drug.

[b] Treatment success is defined as an IGA score of 0 ('clear') or 1 ('almost clear', see Table 1 for more details).

[c] 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.

[d] Results taken from the Public Assessment Report for Soolantra.

Clinical effectiveness

Ivermectin compared with vehicle

In 2 RCTs, ivermectin 10 mg/g cream was statistically significantly more effective than

vehicle at reducing symptoms of rosacea (Stein Gold et al. 2014a). The co-primary end point of 'treatment success', defined as an IGA score of 0 or 1 ('clear' or 'almost clear'), was statistically significantly higher in the active group compared to vehicle (see table 2 above). At week 12 the proportion of people graded as 'clear' or 'almost' clear was 38.4% (study 1) and 40.1% (study 2) for ivermectin, compared with 11.6% (study 1) and 18.8% (study 2) for vehicle (p<0.001 in both studies, number needed to treat [NNT]=5). A statistically significant difference between groups was first observed after 4 weeks of treatment.

For the other co-primary end point, mean reduction in inflammatory lesion count, a statistically significant reduction was observed in the ivermectin group compared with vehicle in both studies. At the end of treatment, participants treated with ivermectin had on average 8.2 fewer inflammatory lesions compared with vehicle (both studies p<0.001). This relates to a reduction of about 21 lesions in the ivermectin group and about 13 lesions in the vehicle group, both from a baseline of approximately 32 lesions.

Response to treatment was rated as 'excellent' or 'good' on average, by 68% of people receiving ivermectin, compared with about 37% on average for vehicle (p<0.001 in both studies). Quality of life was reported using the DLQI and RosaQoL tools, with statistically significant improvements in quality of life score observed for both questionnaires. For the DLQI, at the end of the study about 53% in the ivermectin group and about 35% in the vehicle group considered that their rosacea was having no effect on their overall quality of life (p<0.001). Although not reported in Stein Gold et al. (2014a), a Cochrane review on rosacea (van Zuuren et al. 2015) reports that in study 1 the mean change from baseline in DLQI score was −3.50 (SD 2.77) for the ivermectin group compared to −2.30 (SD 2.71) in the vehicle group (mean difference of −1.20 (95% CI −1.64 to −0.76; p<0.00001; PP population). In study 2 the reductions in DLQI were similar: −3.20 (SD 2.54) in the ivermectin group compared with −2.10 (SD 2.48) in the vehicle group with a mean difference of −1.10 (95% CI −1.51 to −0.69; p<0.00001; PP population; van Zuuren et al. 2015). Across the 2 studies, improvements in quality of life, measured using RosaQoL, were statistically significantly greater for ivermectin (approximately −0.62) compared with vehicle (−0.35, p<0.001 in study 1 and p=0.001 in study 2).

Although not a specific end point of the studies, more people in the ivermectin groups showed an improvement in erythema compared with vehicle (Soolantra PAR).

Ivermectin compared with metronidazole cream

In a 16-week, investigator-blinded, randomised trial ivermectin 10 mg/g cream was statistically significantly more effective than metronidazole 0.75% cream at improving symptoms of rosacea (Taieb et al. 2015, see table 3 above). The primary end point of this study was percentage change in inflammatory lesion count, with participants receiving ivermectin cream experienced an 83.0% reduction in inflammatory lesion count, compared with a reduction of 73.7% in the metronidazole group (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 is a reduction of 28 lesions for ivermectin and 24 lesions for metronidazole, a treatment difference of 4 lesions.

The secondary efficacy end point was treatment success at week 16, defined as an IGA score of 0 ('clear') or 1 ('almost clear'), which was achieved by 84.9% in the ivermectin group, compared with 75.4% for metronidazole (p<0.001, NNT=11).

For the patient-reported end points, 85.5% of the ivermectin group rated their improvement as 'excellent' or 'good', compared to 74.8% in the metronidazole group (no statistical analysis reported). According to the results of the patient's appreciation questionnaire, more people in the ivermectin group were satisfied with their study medication compared with metronidazole (76.0% compared with 61.3%, no statistical analysis reported). 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). After 16 weeks treatment 71% of people treated with ivermectin felt their rosacea had no detrimental effect on their quality of life, compared with 64% in the metronidazole group (no statistical analysis reported).

Long-term efficacy data

Long-term efficacy data for ivermectin were reported in a 40-week extension study (Stein Gold et al. 2014b), that found ivermectin 1% cream showed increased efficacy during the study. At week 12 (the start of the extension phase), 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 (end of extension study).

The Soolantra PAR includes some results from a 36-week extension study for Taieb et al. (2015) that looked at recurrence rates. A total of 757 participants with an IGA score of 1 ('almost clear', n=487) or 0 ('clear', n=270) entered the 23-week extension phase. 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). Relapse rates were 63% of people who were treated with ivermectin and 68% of people receiving metronidazole (no statistical analysis reported). The mean number of treatment-free days was approximately 180 days in the ivermectin group and 170 days in the metronidazole group (Soolantra PAR).

Safety and tolerability

In both RCTs comparing ivermectin 10 mg/g cream with vehicle (Stein Gold et al. 2014a), ivermectin was generally well tolerated, with adverse events reported on average by 39% of the ivermectin group and 38% of the vehicle group (no statistical analysis reported, see table 2). Treatment-related adverse events, including skin burning, pruritus and dry skin, were less frequent, occurring 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 (no statistical analysis reported). Serious adverse events were relatively uncommon, 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 (Stein Gold et al. 2014a). 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 (Stein Gold et al. 2014b) 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. It should be noted that participants in ivermectin group had already received that treatment for 12 weeks before agreeing to take part in the extension phase, and those in the azelaic acid group had been treated with vehicle cream for the same period.

In the randomised, active-controlled, investigator-blinded trial (Taieb et al. 2015) 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, see table 3). The most common treatment-related adverse event was skin irritation, reported by 0.6% (3/478) in the ivermectin group and 0.6% (4/484) in the metronidazole group. A total of 3 participants (0.6%) in the ivermectin group discontinued due to treatment-related adverse events (skin irritation and hypersensitivity), compared with 10 people (2.1%) in the metronidazole group (skin irritation, allergic dermatitis, aggravation of rosacea, erythema, pruritus and general disorders [feeling hot]). Regarding local tolerance, the incidence of worsening from baseline was numerically higher for metronidazole compared with ivermectin for stinging or burning (15.5% compared with 11.1%), dryness (12.8% compared with 10.0%) and itching (11.4% compared with 8.8%), although no statistical analysis was reported.

The PAR for Soolantra reported that 1555 participants in the clinical development program were exposed to the licensed formulation of ivermectin 10 mg/g for at least 3 months, with 519 participants exposed for 1 year or more. The most common adverse events associated with ivermectin 10 mg/g were skin burning sensation (1.3%), skin irritation (1.0%), pruritus (0.8%) and dry skin (0.7%). Local adverse reactions were usually transient, mild to moderate in severity, usually decrease when treatment is continued and do not result in discontinuation of treatment. No systemic adverse events have been reported in clinical studies (Soolantra PAR).

Evidence strengths and limitations

In 2 randomised, vehicle-controlled phase III trials (Stein Gold et al. 2014a) 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.

There are no clearly established efficacy end points to be used in studies of products indicated for the treatment of rosacea. (Soolantra PAR). The PAR states that the end points used in Stein Gold et al. (2014a) are considered relevant.

The study comparing ivermectin and metronidazole (Taieb et al. 2015) did not include a vehicle group, although the PAR states that this is acceptable as superiority to vehicle has been demonstrated in other studies. Also, the study was designed to demonstrate superiority and not non-inferiority to metronidazole, meaning assay sensitivity is less of an

issue (Soolantra PAR).

Statistically significantly more people receiving ivermectin reported 'excellent' or 'good' improvements at week 12 compared with vehicle (Stein Gold et al. 2014a). Similar results were observed in the trial comparing ivermectin and metronidazole (Taieb et al. 2015), although participants were aware of which treatment they were receiving, making the participant-ratings less convincing in this trial (Soolantra PAR).

The study comparing ivermectin with metronidazole (Taieb et al. 2015) 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. A single-blind design was used because of differences in the frequency of application of the treatment (once- versus twice-daily), although this could have been overcome used a double-dummy design. Participant awareness of treatment may be important because metronidazole is generally considered the first-line topical treatment option, although less than 10% of participants in the trial reported previous use of topical metronidazole (Soolantra PAR).

According to the PAR, different definitions for recurrence or relapse of rosacea were used in the 2 extension studies; an IGA score 1 or more in Stein Gold (2014b) and an IGA score of 2 or more in the extension to Taieb et al. (2015).

The PAR for Soolantra states that at the start of the 23-week extension phase of Taieb et al. (2015) 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.

The majority of people randomised to participate in the clinical trials discussed in this evidence summary had moderate rosacea, defined as an IGA score of 3 (80.7%, 1883 out of 2333 participants), with the remaining participants having severe rosacea (IGA score of 4). There are no published data reporting on the effectiveness of initiating ivermectin cream in people with mild rosacea (IGA score of 2 or below). 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 (for example, doxycycline modified release). However, oral treatments are often considered once topical treatments have failed to improvement symptoms, so the lack of such comparisons is acceptable.

There were no specific assessments for telangiectasia (fine, dilated blood vessels) in the phase III trials for ivermectin cream, although the PAR for Soolantra states that in phase II studies the majority of participants showed no change from baseline in their telangiectasia score and only a few participants reported worsening of telangiectasia.

All trials discussed in this evidence summary reported some improvement in quality of life measures, with statistically significant improvements observed for ivermectin compared with vehicle. However, quality of life scores at baseline were not poor, meaning large improvements are not to be expected (Soolantra PAR). In addition the clinical importance is unclear as minimal clinically important difference in reduction of DLQI score was not reached (van Zuuren et al. 2015) and the minimal clinically important difference is not yet established for RosaQoL (van Zuuren et al. 2015).

There are no published trials assessing the efficacy of ivermectin 10 mg/g cream in people whose condition is being treated with other topical products for rosacea (for example, metronidazole and azelaic acid), although the PAR for Soolantra suggests that a combination of ivermectin cream and another topical anti-inflammatory agent would not generally be used in clinical practice.

Context

Alternative treatments

Mild or moderate papulopustular rosacea is usually treated with topical metronidazole or azelaic acid. For moderate or severe papulopustular rosacea, oral tetracycline, erythromycin, doxycycline or lymecycline can be prescribed, although not all of these drugs are licensed for treating rosacea (Clinical Knowledge Summaries: rosacea) and RCT data to support their use are limited (van Zuuren et al. 2015).

Costs of alternative treatments

	Usual dose[a]	Cost per tube, excluding VAT
Ivermectin 10 mg/ gram cream	Apply to the whole face once daily.	1x30 g: £18.29[b, c]

Azelaic acid 15% gel	Applied to affected skin areas twice daily.	1×30 g: £7.48[d]
Metronidazole 0.75% cream	Thin layer applied to affected skin areas twice daily.	1×30 g: £6.60[d] to £7.50[b] 1×40 g: £9.88[d]
Metronidazole 0.75% gel	Thin layer applied to affected skin areas twice daily.	1×30 g: £6.60 to £12.00[b] 1×40 g: £9.88 to £22.63[b]

[a]Taken from the summaries of product characteristics. These directions do not represent the full range that can be used and they do not imply therapeutic equivalence.

[b]Costs taken from MIMS, December 2015.

[c]People treated with once daily ivermectin are likely to use less cream compared with those treated with twice daily metronidazole. In Taieb et al. (2015) participants using ivermectin used a mean of 0.72 g daily, compared with 1.31 g for metronidazole.

[d]Costs taken from Drug Tariff, December 2015.

Estimated impact for the NHS

Likely place in therapy

In 2 randomised, double-blind, vehicle-controlled trials in people with moderate to severe papulopustular rosacea, ivermectin cream had a statistically significant improvement in treatment success rate and inflammatory lesion count reduction compared with vehicle cream (Stein Gold et al. 2014a). Results of an investigator-blinded, randomised, active-comparator trial that used the same inclusion criteria as the 2 RCTs found that ivermectin was superior to metronidazole cream for reducing inflammatory lesions and treatment success (Taieb et al. 2015). Success rate (IGA 'clear or 'almost clear') for ivermectin ranged from approximately 40% to 80% in the 3 studies. By the end of the treatment periods, people treated with ivermectin had about 8 fewer inflammatory lesions compared with vehicle (Stein Gold et al. 2014a), and 4 fewer lesions compared with metronidazole cream (Taieb et al. 2015).

Metronidazole cream is generally considered the first-line topical treatment for rosacea. Azelaic acid may be more effective than metronidazole (Clinical Knowledge Summaries: rosacea), but is often less well tolerated. Results from Taieb et al. (2015) would suggest that ivermectin is slightly more effective than metronidazole, and with a comparable incidence of adverse events (van Zuuren et al. 2015). The results of a long-term extension study involving ivermectin and azelaic acid found that treatment-related adverse events were reported in approximately 2.0% of people receiving ivermectin and in approximately 6.3% of the azelaic group (no statistical analysis reported). Discontinuation rates due to adverse events were comparable for ivermectin and azelaic acid. No conclusions can be made regarding the comparative efficacy of ivermectin and azelaic acid because of differences in treatment duration in the trial (Stein Gold et al. 2014b).

Ivermectin cream is not indicated for erythema of rosacea, although the PAR for Soolantra reports that there were some improvements in erythema observed in the clinical trials for ivermectin. In addition, brimonidine tartrate gel is indicated for the treatment of facial erythema of rosacea and can be used in conjunction with other cutaneous medicinal products for the treatment of inflammatory lesions of rosacea (Mirvaso [brimonidine tartrate] summary of product characteristics). A NICE evidence summary: new medicine facial erythema of rosacea: brimonidine tartrate gel was published in July 2014.

Although the summary of product characteristics for Soolantra states that the mechanism of action of ivermectin may be linked its anti-parasitic effect on *Demodex* mites, the link between *Demodex* and rosacea thus far has not been established as causal (Stein Gold et al. 2014b). It has been hypothesised that these *Demodex* mites or bacteria associated with them (*Bacillus oleronius*) could trigger the inflammatory or specific immune reactions in rosacea patients (Stein Gold et al. 2014a). Additional studies examining the levels of *Demodex* in rosacea patients before and after treatment would need to be conducted to explore this possible mechanism of action (Stein Gold et al. 2014b).

The cost of ivermectin 10 mg/g cream is £18.29 for a 30 gram tube (excluding VAT; cost taken from MIMS, December 2015).

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using ivermectin cream or another topical treatment for papulopustular rosacea.

Estimated usage

It is not possible to provide estimated usage based on the available data.

Relevance to NICE guidance programmes

Ivermectin cream was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

Expert advisers

Dr Julian Peace, GP with a Special Interest (GPwSI) in Dermatology Barnsley NHS Foundation Trust; GP Principal, Stocksbridge

Professor Hywel C Williams, Professor of Dermato-Epidemiology and Co-Director of the Centre of Evidence-Based Dermatology, University of Nottingham

Declarations of interest

Dr Peace has received payment from Galderma UK and Leo Pharma UK in the past 12 months for speaking at educational meetings. The meetings were not specifically about ivermectin (Soolantra).

Professor Williams had no conflicts to declare.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

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