

ivermectin, 10mg/g, cream (Soolantra®)

SMC No. (1104/15)

Galderma (U.K) Ltd

06 November 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ivermectin (Soolantra®) is accepted for restricted use within NHS Scotland.

Indication under review: topical treatment of inflammatory lesions of rosacea (papulopustular) in adult patients.

SMC restriction: the treatment of moderate to severe inflammatory lesions of rosacea where a topical treatment is considered appropriate.

A phase III, randomised study demonstrated ivermectin 10mg/g cream was significantly superior to an antimicrobial cream at reducing the percentage of inflammatory lesions from baseline to week 16.

The submitting company did not submit evidence for SMC assessment for use in patients with mild papulopustular rosacea, therefore SMC cannot recommend ivermectin 10mg/g cream for use in this sub-population.

Overleaf is the detailed advice on this product.

**Vice-Chairman,
Scottish Medicines Consortium**

Indication

Topical treatment of inflammatory lesions of rosacea (papulopustular) in adult patients.

Dosing Information

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 once daily for up to four months. 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 three months, the treatment should be discontinued.

Product availability date

October 2015

Summary of evidence on comparative efficacy

Rosacea is a chronic facial skin condition characterised by facial flushing, erythema, telangiectasia, papules and pustules.^{1,2} Ivermectin 10mg/g (1%) cream is thought to exert its effect on the inflammatory lesions of rosacea through both anti-parasitic (causing the death of *Demodex folliculorum* mites that have been implicated in the pathogenesis of rosacea) and anti-inflammatory properties.^{3,4} The submitting company has requested that SMC considers ivermectin 1% cream when positioned for the treatment of inflammatory lesions of rosacea where a topical treatment is considered appropriate.

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. The study was conducted for 16 weeks (Period A) and then extended for a further 36 weeks (Period B) to investigate the relapse rate. Adults with an Investigator Global Assessment (IGA) score of three (moderate rosacea) or four (severe rosacea) and with 15 to 70 facial inflammatory lesions (papules and pustules) were recruited to the study.^{4,5}

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 creams were applied as a thin layer to both cheeks, the forehead, chin and nose.⁴

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 a significantly greater reduction in the inflammatory lesion count compared with metronidazole. The mean percentage change at week 16 was -83% in the ivermectin group and -74% in the metronidazole group (p<0.001). Secondary efficacy outcomes included the IGA success rate (percentage of patients achieving an IGA score of zero or one from baseline to week 16), and the absolute change in lesion count. A significantly greater proportion of patients in the ivermectin group (85%) achieved IGA success compared with the metronidazole group (75%), p<0.001. Patients completed a Dermatology Life Quality Index (DLQI) questionnaire (a lower score indicating a greater improvement in quality of life); at week 16 a significant improvement in quality of life was demonstrated in the ivermectin group compared with the metronidazole group with a mean change in score of -5.18 versus -3.92 in the respective groups (p<0.01).^{4,5}

Two identical phase III, multicentre, randomised studies (RD.06.SRE.18170 and RD.06.SRE.18171) were conducted to establish the efficacy and safety of ivermectin 1% cream at treating moderate to severe papulopustular rosacea. The studies recruited adults with an IGA score of three or four, and with 15 to 70 facial inflammatory lesions. Part A of each study comprised a 12-week double-blind efficacy study of ivermectin 1% cream versus vehicle cream, followed by a 40-week investigator-blinded safety study (Part B) of ivermectin 1% cream versus azelaic acid 15% gel. There were no efficacy outcomes in Part B.^{7,8,9}

In Part A, patients were randomly allocated in a 2:1 ratio to 12-weeks treatment with ivermectin 1% cream applied once-daily at bedtime (RD.06.SRE.18170 n=451; RD.06.SRE.18171 n=459), or vehicle cream applied once-daily at bedtime (RD.06.SRE.18170 n=232; RD.06.SRE.18171 n=229). The creams were applied as a thin layer to both cheeks, the forehead, chin and nose. The co-primary endpoint was the percentage of patients achieving IGA success and the absolute change in inflammatory lesion count from baseline to week 12. 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 studies p<0.001). Both studies also demonstrated a significantly greater reduction in the absolute change in inflammatory lesion count with ivermectin compared with vehicle. The mean difference between treatment groups was -8.13 lesions (95% CI: -10.12 to -6.13, p<0.001) in study RD.06.SRE.18170, and -8.22 lesions (95% CI: -10.18 to -6.25, p<0.001) in study RD.06.SRE.18170.^{7,8,9}

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 RD.06.SRE.18170, and -66% (33.18) in the ivermectin group and -43% (38.42) in the vehicle group (p<0.001) in study RD.06.SRE.18170. Significant improvements in quality of life for ivermectin compared with vehicle were demonstrated in both studies for the rosacea quality of life index (RosaQoL) total score, and a significantly higher proportion of patients rated their rosacea improvement as 'excellent' or 'good' in the ivermectin group compared with the vehicle group.^{7,8,9}

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In Period A of the ATTRACT study, in the ivermectin and metronidazole groups, respectively, adverse events were reported in 32% and 33% of patients, with serious adverse events reported in 1.4% (13/962) of patients overall. Treatment discontinuation as a result of adverse events occurred in 1.3% (6/478) of patients in the ivermectin group and in 2.7% (13/484) in the metronidazole group, while treatment-related dermatological adverse events were reported in 1.9% (9/478) and 2.5% (12/484) of patients, most commonly skin irritation (0.6% [3/478] and 0.8% [4/484]).

Comparative safety data from Part B of studies RD.06.SRE.18170 and RD.06.SRE.18171 reported serious adverse events in 1.7% (7/412) and 3.0% (13/428) in the ivermectin groups and 3.8% (8/210) and 1.9% (4/208) in the azelaic acid groups.^{8,9}

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Rosacea predominantly affects the forehead, cheeks, nose and chin, and the symptoms can lead to feelings of embarrassment, anxiety and depression. Current guidelines recommend topical metronidazole or azelaic acid for the treatment of mild to moderate rosacea, and oral antibiotics for moderate to severe disease, or when topical preparations have failed. Topical clindamycin or erythromycin have also been used 'off-label' for the treatment of rosacea.^{1,2,12,13}

The submitting company had requested that SMC consider ivermectin 1% cream when positioned for use in the treatment of inflammatory lesions of rosacea where a topical treatment is considered appropriate. SMC further refined the restriction to take account of the clinical evidence submitted which only assessed efficacy and safety in patients with moderate to severe papulopustular rosacea. In addition, the economic analysis also only used data from patients with moderate to severe papulopustular rosacea.

Clinical experts consulted by SMC considered that there is unmet need in those patients who do not respond to existing treatments and the place in therapy of ivermectin 1% cream is likely to be in those patients who have failed treatment with topical metronidazole and azelaic acid (although this sub-population was not assessed in the clinical studies).

All phase III studies demonstrated that ivermectin 1% cream, compared with vehicle alone or with metronidazole 0.75% cream, significantly reduced both the percentage change and absolute change in inflammatory lesion counts, and significantly improved the IGA success rate in patients with moderate to severe papulopustular rosacea.

The ATTRACT study was limited by its single-blind design. Studies RD.06.SRE.18170 and RD.06.SRE.18171 were limited by their vehicle-controlled design in Part A and although Part B included azelaic acid 15% gel as a comparator, it was single-blind and no efficacy outcomes were assessed. Only patients with moderate to severe papulopustular rosacea were included in the study populations (which is narrower than the licensed indication for ivermectin 1% cream), and evidence to support its use in patients with mild papulopustular rosacea is lacking. Although the actual difference in treatment outcomes between ivermectin and metronidazole in ATTRACT were not large, they were statistically significant and may have a beneficial impact on the lives of patients who feel self-conscious and anxious about their rosacea.

Three Bayesian network meta-analyses (NMA) were presented 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. The efficacy outcomes assessed were IGA success at week 12 (10 studies) and week 15 (three studies), and percentage change in inflammatory lesion count at week 12 (13 studies). The results at week 12 demonstrated that ivermectin 1% cream had a higher IGA success rate compared with metronidazole 0.75% cream, azelaic acid 15% gel and vehicle, with an 89% probability of being the best treatment. A greater change in the percentage of inflammatory lesion counts found in favour of ivermectin 1% cream compared with metronidazole 0.75% cream/gel, azelaic acid 15% gel, and vehicle at week 12; no 'probability of being best treatment' result was presented. At week 15, ivermectin 1% cream had a higher IGA success rate compared with metronidazole 0.75% cream/gel, and only comparable results with azelaic acid 15% gel. The probability of being the best treatment was 41% for ivermectin and 33% for azelaic acid. Only patients with moderate to severe papulopustular rosacea were included in the study populations and evidence for use in mild disease was not presented. Heterogeneity was observed in baseline characteristics and study durations, and no formal analyses of heterogeneity or consistency were

performed. Outcomes in the common control vehicle arms of the studies were variable. No formal conclusion of the NMA was presented by the submitting company.

Ivermectin 1% cream is applied once daily which may be more convenient for the patient than the twice-daily application required for topical metronidazole and azelaic acid.

Other data were also assessed but remain commercially confidential.*

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing ivermectin 10mg/g (1%) cream to metronidazole 0.75% cream and azelaic acid 15% gel for the topical treatment of inflammatory lesions of rosacea (papulopustular) in adult patients with moderate to severe rosacea. SMC expert responses have indicated that the comparators were appropriate, specifically noting metronidazole 0.75% cream as the comparator most likely to be displaced in Scotland.

The economic model consisted of two health states 'rosacea' and 'no rosacea' defined according to the patients IGA score, where a score of 0 (clear) or 1 (almost clear) represented no rosacea while a score of ≥ 2 (mild to severe) represented rosacea. In the rosacea health state, patients received initial treatment and could then enter the post initial treatment phase (systemic antibiotic therapy) or relapsed phase, while in the no rosacea health state, patients who successfully responded stopped treatment and entered the maintenance phase and treated relapse phase. The analysis was based on a 3 year time horizon.

The clinical data used in the economic analysis were taken from a number of sources. Treatment success rates at 12 weeks were derived from a NMA, which included patients with moderate to severe papulopustular rosacea. The values were 63%, versus 49% and 45.4% for metronidazole 0.75% cream and azelaic acid 15% gel respectively. The economic analysis also incorporated monthly probabilities associated with time to relapse and treatment success of failed response or relapsed patients based on data from period B of the ATTRACT study.

Drug costs were included in the analysis and were based on the cost per day of treatment. It should be noted that the cost of metronidazole 0.75% cream was based on a weighted average of different preparations of metronidazole. The analysis also included the cost of GP visits (for both patients with and without rosacea) and specialist visit costs. The costs of adverse events were not included in the analysis.

Utility values were estimated using EQ-5D data collected in the pivotal study. The study collected EQ-5D data at various time points, including baseline, week 16, week 32 and week 52. Patients with and without rosacea were assigned utility values of 0.86 and 0.93 respectively.

Based on the results of the analysis, ivermectin 1% cream was estimated to be dominant versus both metronidazole 0.75% cream and azelaic acid 15% gel, resulting in incremental savings of £73 and £37 and an incremental QALY gain of 0.0091 and 0.0113 respectively.

The company provided a range of sensitivity analyses including one-way, scenario and probabilistic sensitivity analysis. Results were most sensitive to a change in the dose for ivermectin 1% cream. When the dose for ivermectin 1% cream was increased to 1.31g (in line with comparator doses), ivermectin 1% cream resulted in an ICER of £1,389 versus metronidazole 0.75% cream, based on an incremental cost of £13 and incremental QALY gain of 0.0091 and an ICER of £4,299 versus azelaic acid 15% gel, based on an incremental cost of £48 and an incremental QALY gain of 0.0113. As a conservative analysis the company was asked to provide a cost-minimisation analysis versus both

comparators. Based on topical drug costs alone (i.e. excluding antibiotic costs and costs associated with GP visits), over three years ivermectin 1% cream resulted in incremental savings (undiscounted) of £24 versus metronidazole 0.75% cream and an incremental cost of £29 versus azelaic acid 15% gel. Over one year ivermectin 1% cream resulted in incremental savings of £12 versus metronidazole 0.75% cream and an incremental cost of £32 versus azelaic acid 15% gel.

There were weaknesses with the analysis as follows:

- There were some concerns around the weighted average approach used to estimate the cost of metronidazole 0.75% cream. However, as the costs per course for the various commonly prescribed metronidazole 0.75% creams did not vary significantly a revised analysis using only the most widely prescribed cream was unlikely to have a major impact on results.
- It should be noted that ivermectin 1% cream is indicated for the topical treatment of inflammatory lesions of rosacea (papulopustular) in adult patients. However, as noted above, the patients included in the economic analysis were those with moderate to severe rosacea. Therefore due to lack of clinical data supporting the use of ivermectin in patients with mild rosacea, there is no evidence to support the cost- effectiveness of treatment within this patient group.

Despite the uncertainties outlined above, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from the Skin Conditions Campaign Scotland (SCCS), which is a registered charity.
- SCCS has received pharmaceutical company funding in the past two years, including from the submitting company.
- People affected by papulopustular rosacea feel embarrassed and ashamed about the papules (round red bumps), pustules (pus filled swellings) and redness which occur. The pus-spots are shaming and reduce people's self esteem and ability to work effectively which can lead to low mood and poor self-esteem. Rosacea is very difficult to camouflage. In addition, other people frequently mistake rosacea for infection, or an indication of heavy alcohol intake, creating difficulty with work that involves interaction with other people, recruitment for work and social relationships.
- Ivermectin may act differently from existing treatments and offer the possibility of a good response to those who have failed to respond to or are intolerant of existing topical or oral treatments. This treatment is applied once a day rather than twice a day (compared with the other current treatments).
- More treatments are needed for PPR and this new treatment gives more choice available to people living with rosacea.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summary for rosacea (September 2012) advises that mild or moderate papulopustular rosacea should be treated with topical metronidazole 0.75% gel or 1% cream, or alternatively with azelaic acid. Moderate or severe papulopustular rosacea should be treated with an oral tetracycline or erythromycin.²

Patient information on rosacea published by the British Association of Dermatologists (August 2004; updated December 2014) recommends a topical preparation such as metronidazole or azelaic acid (used for at least eight weeks) to control the inflammation of mild to moderate rosacea. Inflammation of moderate or severe rosacea is treated with oral antibiotics (e.g. a tetracycline or erythromycin). Topical and oral treatments may be used together. Other treatment options include laser therapy or brimonidine gel for erythema, beta-blockers or clonidine for blushing, and isotretinoin for severe rosacea.¹

The Primary Care Dermatology Society guidelines on the treatment of rosacea papules, pustules and nodules (13th July 2012; updated 27th November 2014) advise on the use of topical metronidazole or azelaic acid for mild symptoms and systemic treatments (e.g. a tetracycline or erythromycin) for more severe symptoms or when topical preparations have failed.¹²

The Scottish Dermatological Society referral and management pathway for rosacea (November 2010) recommends six-weeks treatment with topical therapy (e.g. metronidazole gel/cream, azelaic acid 15% gel, clindamycin gel/lotion, or erythromycin lotion/gel) or two to three months therapy with oral antibiotics (e.g. a tetracycline or erythromycin).¹³

All treatment guidelines predate the availability of ivermectin 1% cream.

Additional information: comparators

Topical preparations licensed for the treatment of inflammatory exacerbations/papulo-pustules of rosacea include metronidazole 0.75% cream/gel (e.g. Acea[®] gel, Metrogel[®] gel, Metrosoa[®] gel, Rosiced[®] cream, Rozex[®] cream/gel, Zyomet[®] gel) and azelaic acid 15% gel (Finacea[®] gel).

Cost of relevant comparators

Drug		Dose Regimen	Cost per course (£) ^A
Ivermectin 10mg/g (1%) cream		Apply once daily for up to four months (assume 0.5g daily)	34
Metronidazole	Metrogel [®] 0.75% w/w gel	Apply twice daily for three to four months (assume 1g daily)	43 to 58
	Zyomet [®] 0.75% w/w gel	Apply twice daily for three to four months (assume 1g daily)	34 to 45
	Rozex [®] 0.75% w/w cream/gel	Apply twice daily for three to four months (assume 1g daily)	21 to 28
	Rosiced [®] 7.5mg/g cream	Apply twice daily for six to twelve weeks (assume 1g daily)	10 to 21
	Acea [®] 0.75% w/w gel	Apply twice daily for eight weeks (assume 1g daily)	14
Azelaic acid 15% gel		Apply 0.5g twice daily for several months ^B	28

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 01/09/15. Cost for Zyomet[®] gel from MIMS online 01/09/15. ^ACosts do not take account of repeated courses. ^BCosts are based on four months use.

Additional information: budget impact

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.

The gross impact on the medicines budget was estimated to be £24k in year 1 and £61k 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. It should be noted that the patient numbers may include patients with mild, moderate and severe disease.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. British Association of Dermatologists (BAD). Patient information leaflet: rosacea. August 2004; updated December 2014.
<http://www.bad.org.uk/for-the-public/patient-information-leaflets/rosacea> accessed 12 August 2015.
2. National Institute for Health and Care Excellence (NICE) Clinical knowledge summary: Rosacea. September 2012. <http://cks.nice.org.uk/rosacea> accessed 12 August 2015.
3. Galderma (UK) Ltd. Soolantra 10mg/g cream. Summary of product characteristics. Last updated 17 April 2015.
4. Taieb A, Ortonne JP, Ruzicka T, Roszkiewicz J, Berth-Jones J, Briantais P, et al. Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. *Br J Dermatol* (2015) 172: 1103–1110.
5. NCT01493947. CD5024 1% cream versus metronidazole 0.75% cream in papulopustular rosacea (PPR) study (ATTRACT) www.clinicaltrials.gov (accessed 200815).
6. **Commercial In Confidence*.
7. Stein L, Kircik L, Fowler J, Tan J, Draelos Z, Fleischer A, et al. Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol*. 2014 Mar;13(3):316-23.
8. NCT01493687. Phase 3 papulopustular rosacea study. www.clinicaltrials.gov (accessed 200815).
9. NCT01494467. Phase 3 papulopustular rosacea study. www.clinicaltrials.gov (accessed 200815).
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11. **Commercial In Confidence*
12. Primary Care Dermatology Society. Rosacea: papules, pustules and nodules. 13th July 2012; updated 27th November 2014.
<http://www.pcds.org.uk/clinical-guidance/rosacea#management> accessed 12 August 2015.
13. Scottish Dermatological Society. Dermatology referral and management pathway for rosacea. November 2010. <http://www.sds.org.uk/general-practioners.php> accessed 12 August 2015.

This assessment is based on data submitted by the applicant company up to and including 16 October, 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.