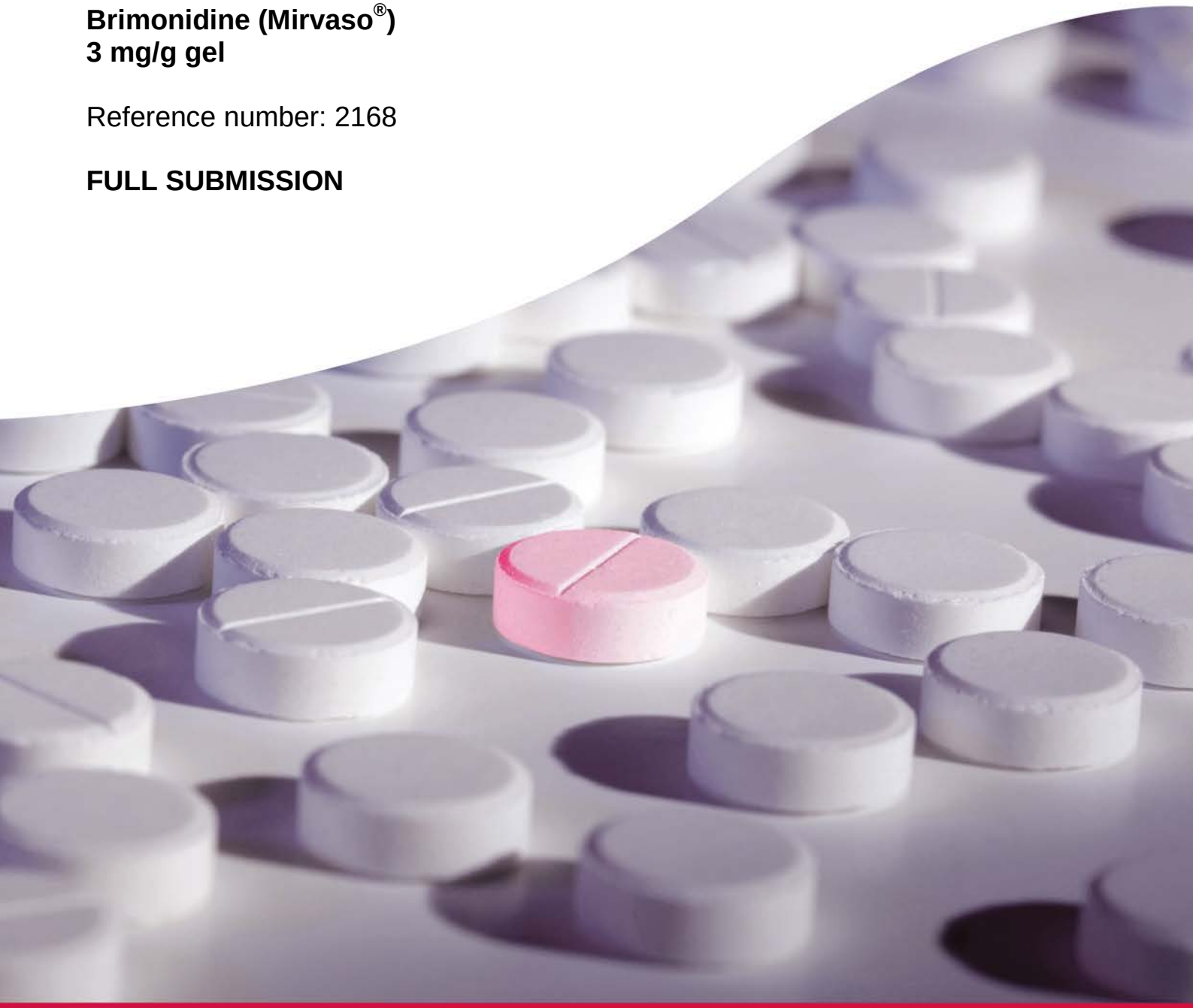
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Brimonidine (Mirvaso®) 3 mg/g gel

Reference number: 2168

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Brimonidine (Mirvaso®) 3 mg/g gel

This assessment report is based on evidence submitted by Galderma (UK) Ltd on 11 February 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Brimonidine (Mirvaso®) for the symptomatic treatment of facial erythema of rosacea in adult patients[2].
Dosing	One application per 24 hours, at a time suitable for the patient, for as long as facial erythema is present. Maximum daily recommended dose is 1 g of gel, containing 3.3 mg of brimonidine (equivalent to 5 mg of brimonidine tartrate), divided into five pea size amounts applied to the five areas of the face: forehead, chin, nose, and each cheek[2].
Marketing authorisation date	21 February 2014[2].

2.0 DECISION CONTEXT

2.1 Background

Rosacea is a chronic relapsing disease of the facial skin, characterised by recurrent episodes of facial flushing, erythema, telangiectasia, papules and pustules[3,4]. It affects mainly fair skinned people, with a higher occurrence in women, and onset typically occurs between 30 to 50 years of age[4,5] (prevalence between 2% and 10% in Europe)[5]. The disease is commonly classified into four subtypes based upon clinical signs and symptoms[1,5]. Of these, erythematotelangiectatic rosacea is the most prevalent subtype, and is characterised by persistent central facial erythema[5]. Erythema is associated with permanent vasodilation of small vessels. The intensity of erythema may range from mild and transient to very severe forms[1,5]. It may worsen during the day and possible triggers include extreme weather, sunlight, strenuous exercise, stressful situations, spicy food, alcohol and hot drinks[3–5]. A second subtype, papulopustular rosacea, is also characterised by persistent central facial erythema, but also with episodic or persistent inflammation in the form of small to medium papules and pustules in a central facial distribution[5].

There are no approved pharmaceutical agents in Europe that directly target persistent facial erythema[3,4]. There are several treatments primarily targeted towards the papulopustular rosacea subtype that reduce inflammatory lesions through anti-inflammatory mechanisms[5]. They include local and systemic antibiotics (metronidazole and tetracyclines), topical azelaic acid, and isoflavonoid. Studies have, however, failed to demonstrate sufficient efficacy for these treatments for the more widespread generalised erythema that patients experience[4,6].

Management of erythema generally consists of lifestyle advice; this includes recommendations to frequently apply high-factor sunscreen, avoidance of triggers, the use of emollients and camouflage cream[3,4]. Laser therapy can be effective although improvement is not permanent[7]. Brimonidine (Mirvaso®) is the only treatment that targets a single symptom of rosacea; i.e. facial erythema[5]. It is a relatively selective

alpha-2 adrenergic receptor agonist with potent vasoconstrictive and vasostabilising activity[2,3,5].

The All Wales Medicines Strategy Group (AWMSG) appraise medicines within the whole of its licensed indication; however, the applicant company highlight that the patients covered by this submission are those who have moderate to severe persistent facial erythema associated with rosacea: in line with the patient cohort in the pivotal clinical studies[1].

2.2 Comparators

The company highlight that there are no approved pharmaceutical agents in Europe that directly target the persistent facial erythema of rosacea and therefore the primary comparator would be no pharmacological therapy. Metronidazole and azelaic acid gels however, are included in the cost-effectiveness analyses (although these treatments are assumed to have no treatment benefit for reducing erythema). From market research, the company highlight in their submission that it appears that metronidazole and azelaic acid are currently used in clinical practice despite both being off-label products lacking demonstrated efficacy (with a very limited evidence base) in the symptomatic treatment of facial erythema of rosacea[1]. Consequently, both agents were identified as secondary comparators for brimonidine and explored as part of a scenario analysis (see Section 4.1.1).

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Facial erythema of rosacea: brimonidine tartrate gel. Evidence Summary: new medicines (ESNM) 43 (2014)[3].
- Primary Dermatology Society. Clinical guidance: rosacea (2014)[7].
- NICE. Clinical Knowledge Summary: Rosacea (2012)[4].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of five phase III studies to evaluate the efficacy and safety of brimonidine gel in adult patients with moderate to severe erythema: two pivotal vehicle-controlled studies and three supportive studies[1]. The company also provided details of two phase II dose-finding studies, which are not discussed in relation to the clinical efficacy of brimonidine, but are included in the comparative safety section (see Section 3.3). The company conducted a systematic literature review to identify studies evaluating brimonidine: only the seven studies described above were identified[1].

3.1 Pivotal studies

3.1.1 Studies 18140 and 18141

The design, methodology, inclusion/exclusion criteria and primary aim of studies 18140 and 18141 were identical[1,5,8]. The aim of these multicentre, randomised, double-blind, vehicle-controlled, parallel-group studies was to compare the efficacy and safety of brimonidine gel 0.33% with that of a vehicle gel for the treatment of moderate to severe facial erythema in adults ≥ 18 years of age. Moderate to severe erythema was defined as a grade 3 or 4 on both the Clinical Erythema Assessment (CEA) and Patient Self-Assessment (PSA) 0–4-point scales (see Glossary). Only patients with less than three facial inflammatory lesions were recruited and no other rosacea treatments were allowed. Patients were randomised 1:1 to apply brimonidine (n = 277) or vehicle gel (n = 276) once-daily for four weeks, followed by a four-week follow-up phase when no medication was applied[1,5,8].

The primary endpoint was a composite of success that was defined as a 2-grade improvement from baseline on both CEA and PSA scores between 3 and 12 hours post application on Days 1, 15, and 29[1,5,8]. The secondary endpoint was the 30-minute effect, defined as a 1-grade improvement from baseline on both CEA and PSA at 30 minutes post dosing on Day 1[1,5,8].

In both studies, brimonidine was statistically significantly more effective than vehicle gel in reducing moderate to severe erythema ($p < 0.001$): between 13% and 32% of patients in the brimonidine group showed 2-grade improvement on both CEA and PSA across all days and time points, compared to 0% and 11% of vehicle gel patients[1,5,8]. With regards to the secondary endpoint, brimonidine produced a statistically significant ($p < 0.001$) earlier effect compared to vehicle gel in both studies: approximately 28% of patients in the brimonidine group showed 1-grade improvement on both the CEA and PSA at 30 minutes post-dosing on day one compared to 5% to 7% of vehicle gel patients[1,5,8]. See Table 1 for full results.

Table 1. Primary and secondary endpoint results from study 18140 and study 18141

	Study 18140				Study 18141			
	Brimonidine gel 0.33% (ITT = 129)	Vehicle gel (ITT = 131)	p-value	Odds ratio (95% CI)	Brimonidine gel 0.33% (ITT = 148)	Vehicle gel (ITT = 145)	p-value	Odds ratio (95% CI)
Composite success at Day 1, Hour 3* n/N (%)	21/129 (16.3)	4/131 (3.1)	< 0.001	NC	29/148 (19.6)	0/145 (0)	< 0.001	NC
Composite success at Day 1, Hour 6* n/N (%)	30/129 (23.3)	3/131 (2.3)			44/148 (29.7)	3/145 (2.1)		
Composite success at Day 1, Hour 9* n/N (%)	25/129 (19.4)	5/131 (3.8)			27/148 (18.2)	1/144 (0.7)		
Composite success at Day 1, Hour 12* n/N (%)	17/129 (13.2)	4/130 (3.1)			20/148 (13.5)	2/144 (1.4)		
Composite success at Day 15, Hour 3* n/N (%)	32/128 (25.0)	4/128 (3.1)	< 0.001	NC	36/143 (25.2)	5/141 (3.5)	< 0.001	NC
Composite success at Day 15, Hour 6* n/N (%)	35/128 (27.3)	8/128 (6.3)			37/143 (25.9)	6/141 (4.3)		
Composite success at Day 15, Hour 9* n/N (%)	25/128 (19.5)	7/128 (5.5)			31/143 (21.7)	7/141 (5.0)		
Composite success at Day 15, Hour 12* n/N (%)	21/128 (16.4)	3/128 (2.3)			22/143 (15.4)	10/141 (7.1)		
Composite success at Day 29, Hour 3* n/N (%)	40/127 (31.5)	14/128 (10.9)	< 0.001	3.750 (2.100 to 6.696)	36/142 (25.4)	13/142 (9.2)	< 0.001	2.947 (1.687 to 5.148)
Composite success at Day 29, Hour 6* n/N (%)	39/127 (30.7)	12/128 (9.4)			36/142 (25.4)	13/142 (9.2)		
Composite success at Day 29, Hour 9* n/N (%)	33/127 (26.0)	13/128 (10.2)			25/142 (17.6)	15/142 (10.6)		
Composite success at Day 29, Hour 12* n/N (%)	29/127 (22.8)	11/128 (8.6)			30/142 (21.1)	14/142 (9.9)		
Composite success at Day 1, 30 minutes post-dosing† n/N (%)	36/129 (27.9)	9/131 (6.9)	< 0.001	4.751 (2.220 to10.168)	42/148 (28.4)	7/145 (4.8)	< 0.001	7.448 (3.256 to 17.037)

*Primary endpoint: 2-grade improvement
†Secondary endpoint: 1-grade improvement
CI: confidence interval; ITT: intention-to-treat; n/N: number of patients; NC: not calculated.

3.2 Supportive studies

3.2.1 Active-controlled study 10219

The aim of this multicentre, randomised, controlled, double-masked, active-controlled, two-period crossover design study was to compare the efficacy and safety of brimonidine gel 0.33% versus azelaic acid gel 15%, in patients ≥ 18 years of age with moderate to severe facial erythema (grade 3 or 4 on both CEA and PSA) and with fewer than six facial inflammatory lesions[1]. Patients received 15 days of treatment with brimonidine once daily (n = 35) or azelaic acid gel twice daily (n = 35) in random sequence with a three to seven day washout between the treatment periods. The primary endpoint was a composite of success defined as a 2-grade improvement from baseline on both CEA and PSA at six hours post dose at the end of each treatment period. A significant carryover effect from period one to period two was observed, therefore, only data from the first period was used for the efficacy analysis. Significantly more patients treated with brimonidine achieved a 2-grade improvement at 6 hours on day 15 in period one compared to those treated with azelaic acid gel (14.3% versus 5.7% respectively, $p < 0.001$)[1].

3.2.2 Quality of life study 29107

The aim of this multicentre, randomised, double-blind, vehicle-controlled, parallel-group study was to compare patient-reported outcomes of brimonidine tartrate 0.5% gel versus vehicle gel, in patients ≥ 18 years of age with severe facial erythema with a PSA score of 4 and a CEA score of 3 or 4 at baseline, and with more than five facial inflammatory lesions[1,9]. Patients received eight days of treatment with brimonidine (n = 48) or vehicle gel (n = 44) once daily. Patient reported outcomes were assessed using the Dermatology Life Quality Index (DLQI), Facial Redness questionnaire, EQ-5D-3L questionnaire, patient satisfaction questionnaire, and a semi-structured interview. Safety and efficacy (2-grade improvement on CEA and PSA) of the two treatment regimens were also evaluated[1,9].

After eight days of treatment, there was a similar improvement ($p = 0.4817$) in DLQI score for both treatment groups compared with baseline[1,9]. The EQ-5D-3L showed a slight improvement in 'pain/discomfort' and 'anxiety/depression' domains in the brimonidine group compared to vehicle gel group. In the Facial Redness questionnaire, the percentages of patients who provided positive response were higher in the brimonidine group than in the vehicle gel group for most of the questions. The patient satisfaction questionnaire showed that significantly more patients in the brimonidine group than in the vehicle gel group were satisfied overall with the treatment ($p = 0.0065$) and satisfied with the improvement in their facial redness ($p = 0.0009$).

3.2.3 Long-term study 18142

The aim of this one-year, open-label, non-comparative study of brimonidine gel 0.33% applied once daily in 499 patients with moderate to severe facial erythema was to assess the long-term safety and efficacy of the treatment[2,10]. There was no restriction on the number of inflammatory lesions: 29% of patients received concomitant treatment for the lesions. Daily reductions in erythema for the first month of use (as measured with the CEA and PSA scales) were similar to those observed in the two pivotal studies (see Section 3.1), and those reductions were achievable for up to 12 months with no apparent loss of effect over time[2,10].

3.3 Comparative safety

Evidence of the safety and tolerability of brimonidine gel was provided by safety analyses and adverse event (AE) reporting from the five phase III studies (described in Section 3.1 and Section 3.2) and two phase II dose finding studies[1]. In five of the studies, the proportion of patients reporting at least one AE ranged from 20.5% (vehicle gel group in the quality of life study) to 39.7% (azelaic acid gel 15% group in the active-controlled study). In the two remaining studies, one reported the highest rate of 61.2% (long-term study) and one (a dose finding study) did not assess AEs[1].

In the long-term study, 34 AEs were reported by 21 patients in the brimonidine group. Of these, a total of 31.0% of reported AEs were considered to be related to brimonidine (the majority were mild/moderate transient and self-limiting dermatological events). Serious AEs were reported in 8.9% of patients in the long-term study; none were deemed to be linked to brimonidine[1]. Across studies, the most common brimonidine-related AEs reported were flushing (1.4% to 9.1%); erythema (3.4% to 6.5%), rosacea (1.4% to 3.6%), and skin irritation (2.3% to 3.1%). Discontinuations due to brimonidine were reported in three studies[8,9,11]. In all but one study, the range was one to two patients: in the long-term study, 67 (14.9%) patients discontinued the therapy, with the discontinuation deemed to be linked to brimonidine[1].

The Committee for Medicinal Products for Human Use (CHMP) concluded that the safety profile of brimonidine gel is benign with mainly local AEs; these were considered to be common AEs for other topically applied medicinal products and therefore do not raise further concerns to those already known[5].

3.4 AWTTC critique

- Brimonidine is indicated for all adult patients with non-transient erythema of rosacea: the indication does not specify severity of the condition. However, only evidence relating to the use of brimonidine for the symptomatic treatment of moderate to severe facial erythema of rosacea in adult patients has been provided.
- Efficacy endpoints for the treatment of rosacea are not clearly established[5]. Therefore, the applicant company developed the CEA and PSA scales that were used as co-primary endpoints in the phase III studies. It should be acknowledged that both the CEA and the PSA are scales that are based on subjective judgments and not objective measures. However, CHMP state that considering the type of condition and the intended use of the product (symptomatic reduction of erythema rather than curative treatment), assessments made by the patients are of relevance[5]. CHMP state that these scales are sufficiently described and validated for their intended purpose[5].
- Erythema and flushing are included in the clinical symptomatology of rosacea, and therefore CHMP state that it is difficult to assess if these symptoms are due to lack of efficacy or true AEs[5]. A case report published in 2014, suggested that this reaction constitutes rebound dilation of the capillaries caused by down-regulation of alpha-2 adrenergic receptors following use of brimonidine, and as such directly opposes the goal of the therapy[12].
- Although brimonidine has a transient effect on erythema, it does not alter the course of the disease or have any effect on other features of rosacea, such as telangiectasia or inflammatory papules[3]. It does not need to be used daily and some patients may only use brimonidine on days when they feel their appearance is particularly important[3].
- Concomitant use of brimonidine with other medicinal products for the treatment of inflammatory lesions of rosacea has not been systematically investigated[2,5]. However, in the long-term study (18142), the efficacy and safety of brimonidine was not affected by the concomitant use of cosmetics or other medicinal products (e.g. topical metronidazole, topical azelaic acid, and oral tetracyclines including low dose doxycycline) for the treatment of inflammatory lesions of rosacea in the concerned subpopulation[2,10].
- Patients are advised that it is important to ensure that lifestyle recommendations, such as using high-factor sunscreen and avoiding trigger factors, have been optimised before brimonidine is considered, and that these are continued throughout treatment with brimonidine[3].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) comparing brimonidine gel against no pharmacological therapy for the treatment of persistent, moderate to severe facial erythema of rosacea[1]. As the licensed indication for brimonidine gel does not specify severity of erythema as a condition of use[2], the company's economic evidence is effectively restricted to a subpopulation of rosacea sufferers meeting the licensed indication. Comparisons against topical metronidazole and azelaic acid have been conducted as scenario analyses, as explained under section 2.2.

The analysis is based on a one-year Markov model, in which patients are assigned to health states in a weekly cycle according to the severity of erythema: clear to almost clear (Health State 1: HS1), mild erythema (Health State 2: HS2) or moderate to severe erythema (Health State 3: HS3). All patients commence treatment in HS3, with probabilities of transitioning to other erythema severity states in subsequent cycles determined by pooled composite end point data (assessment by clinicians using the CEA scale, and patients using the PSA scale), assessed at four weeks in the two phase III studies (18140 and 18141). No therapy (and the assumed lack of metronidazole and azelaic acid efficacy) is represented by the placebo arms of the studies. Patients who transition to a less severe state (HS1 or 2) during the first four weeks are assumed to remain on treatment, with transition probabilities assumed to remain constant over the whole year. Those who do not transition to HS1 or 2 in the first four weeks are assumed to discontinue and switch to no therapy.

Medication costs are based on British National Formulary (BNF) list prices[13]. The base case analysis assumes 0.5 g of brimonidine gel is applied each day. For the comparison against metronidazole, it is assumed that 75% of patients would use a gel formulation and 25% a cream. Other medical costs include GP and dermatologist consultations, which are costed using published unit costs. Based on Scottish expert opinion, the company assumes that patients in HS1, HS2 and HS3 would on average have 0.25, 0.5 and 0.75 GP consultations per month, respectively, irrespective of treatment received. Furthermore, based on hospital episode statistics for any skin-related problems in England and Wales, 2006–2007[14], 6.1% of GP visits for those in HS3 are assumed to result in referral to a dermatologist, equivalent to 0.09 dermatology appointments per month. AEs are not considered in the analysis.

Utility values to reflect health-related quality of life associated with each erythema severity state are based on a published study of quality of life in people with acne (HS1 0.89, HS2 0.87 and HS3 0.84)[15].

4.1.2 Results

The results of the base case analysis are presented in Table 2. Over a one year time horizon of analysis, use of brimonidine resulted in an incremental cost per quality-adjusted life year (QALY) gained versus no therapy of £10,455, based on an increase in total costs of £104 and a gain of 0.00991 QALYs.

Table 2. Base case CUA results over a one year time horizon[1].

	Brimonidine	No therapy
Total costs	£487	£382
Total QALYs	0.86380	0.85389
ICER (Cost/QALY gained)	**£10,629/QALY gained**	
Probability cost effective at WTP £20,000/QALY*	79.20%	
Probability cost effective at WTP £30,000/QALY*	88.11%	

*From probabilistic sensitivity analyses.

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay per QALY gained.

One-way sensitivity analyses indicate the model outputs are most sensitive to the assumed utility values and ongoing probabilities of brimonidine reducing the severity of erythema from week five onwards. Within the range of their 95% confidence intervals (CIs), the incremental cost per QALY gained for the HS3 utility values ranged from £5,902 to £45,712, and for HS1 and HS2 utility values ranged £6,652 to £24,404. The 95% CI for transition probabilities with brimonidine treatment in cycles from week five onwards generated estimates in the range £4,401 to £27,116 per QALY gained. Probabilistic sensitivity analysis indicates the probability of the incremental cost per QALY gained falling below £20,000 as 79% and below £30,000 as 88%; however, there is a large spread of values on the cost-effectiveness plane, reflecting significant uncertainty.

In scenario analyses comparing brimonidine against metronidazole and azelaic acid gels, the incremental costs per QALY gained were £5,528 and £5,372, respectively. In these analyses, metronidazole and azelaic acid gels are assumed to have no treatment benefit for reducing erythema, and so reflect only greater costs compared with no treatment. A range of other scenario analyses have explored alternative time horizons and use of only clinician or only patient assessment of efficacy, and appear to have little impact on the base case estimates of cost-effectiveness.

4.1.3 AWTTC critique

The economic model relates only to patients with moderate to severe erythema, with few pustular lesions. The company considers the primary comparator to be no therapy, as other topical agents are used to treat pustular lesions rather than erythema per se.

The model categorises patients into health states based on the probabilities of achieving subjective improvements in erythema severity over four week study periods, and then extrapolates these over one year. The model is very sensitive to the assumed transition probabilities with brimonidine treatment over this period of extrapolation. Brimonidine treatment is estimated by the model to improve health-related quality of life compared with no therapy and secondary comparators, which are considered to have no treatment benefit for erythema. The model is very sensitive to the assumed improvements in health-related quality of life with reduced erythema severity, and these are based on quality of life measured in patients with acne, rather than the quality of life data collected in the phase III studies in which there were no discernible improvements with brimonidine treatment over placebo.

As mentioned previously, the scenario analyses comparing brimonidine against topical metronidazole and azelaic acid assume these comparators have no efficacy against erythema and so simply reflect additional costs over no therapy; however, in practice, it is plausible that brimonidine could be used in addition to, rather than instead of, these agents[5]. These scenario analyses would therefore appear to have limited informative value.

Collectively, the base case analysis and scenario analyses appear subject to considerable uncertainty, and it is therefore not clear the analyses would reflect the cost effectiveness of the use of brimonidine in practice.

Key limitations and uncertainties in the economic evidence include:

- There is a lack of long-term comparative data for brimonidine gel, and the model extrapolates treatment benefits from four-week trials over a whole year.
    - The model is very sensitive to the assumed transition probabilities with brimonidine treatment from week five onwards, with the 95% CI generating incremental costs per QALY gained in the range £4,400 to £27,000.
- The phase III studies found no discernible improvements in health-related quality of life with brimonidine treatment compared with placebo, possibly because quality of life at baseline in patients recruited to the studies was not poor, and uncertainty in the relevance of generic measures to a condition like rosacea[5]. The model assumes quality of life data measured in patients with acne, which results in quality of life improvements with brimonidine over comparators.
    - The model is very sensitive to the assumed utility values attached to health states, with the 95% CIs generating incremental costs per QALY gained in the range of £5,900 to £45,700.
- The costs of brimonidine assumed in the base case model are subject to uncertainty:
    - The model assumes brimonidine costs based on patients using 0.5 g per day as observed in the longer term clinical trial[10]. Alternative dosing could significantly impact on the estimated cost-effectiveness of brimonidine, and has not been explored.
    - The model assumes that all patients who do not achieve an improvement in erythema from HS3 (moderate or severe) to HS2 (mild) or HS1 (almost clear or clear) by week four will discontinue brimonidine treatment. Removal of the assumption of discontinuation at four weeks for patients who do not achieve at least mild erythema increases the base case incremental cost per QALY estimate to £16,708; however, assuming continued use for a year when no benefit is achieved would also seem improbable.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on a published estimated prevalence of subtype 2 rosacea (papulopustular rosacea) in Ireland of 2.7%[16] and company data on file (not verified), the company estimates a prevalence of subtype 1 (vascular erythema) rosacea of 3.9%[1]. Of these, only 27% are estimated to be diagnosed, and of those the company suggests 40.86% attend physician consultation, of which 39.1% receive treatment. Applying these figures to the adult population of Wales, the company estimates there to be 3,160 adults treated for subtype 1 rosacea in Wales.

Based on a UK observational study of incident cases of rosacea[17], and assuming 76.55% of rosacea cases are subtype 1, the company estimates an annual increase in prevalence of 1.08% in year two, rising to 4.31% in year five. Uptake is estimated to be 12.71% in year one, rising to 59.87% in year five.

As brimonidine is anticipated to reduce the number of patients with moderate to severe erythema, it is assumed that the number of GP and dermatologist visits would be

reduced, as per the economic model in Section 4. The company has included reduced costs of GP and dermatologist visits in its budget impact estimates.

5.1.2 Results

The company reports the net budget impact in Wales in each of the next five years as in Table 3.

Table 3. Company estimates of net cost implications associated with use of brimonidine[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	3,160	3,242	3,325	3,410	3,495
Uptake (%)	12.71%	19.51%	34.15%	49.45%	59.87%
Treated patients	402	633	1,135	1,686	2,092
Costs without brimonidine available in NHS Wales					
Medication	£154,923	£150,123	£153,768	£157,446	£161,157
GP visits	£1,025,715	£1,036,137	£1,061,294	£1,086,680	£1,112,294
Dermatologists	£179,469	£176,891	£181,186	£185,520	£189,892
Total	£1,360,106	£1,363,150	£1,396,248	£1,429,646	£1,463,344
Costs with brimonidine available in NHS Wales					
Medication	£209,621	£235,578	£306,979	£384,606	£442,667
GP visits	£1,004,255	£1,003,363	£1,002,534	£999,558	£1,004,328
Dermatologists	£168,805	£160,670	£152,105	£142,402	£136,459
Total	£1,382,681	£1,399,611	£1,461,618	£1,526,567	£1,583,454
Total Budget impact	**£22,575**	**£36,461**	**£65,370**	**£96,921**	**£120,110**

No sensitivity and scenario analyses have been provided regarding budget impact estimates.

5.1.3 AWTTC critique

- The company's estimates of eligible patient numbers rely on company data on file, which are not verifiable.
- Estimates of uptake are subject to uncertainty as in all budget impact analyses.
- The budget impact estimates include cost savings associated with reduced GP and dermatologist visits which, unless GP and dermatologist appointments were to be cancelled, would not be realised as cost savings in practice. The budget impact for NHS Wales would therefore be greater if these assumed cost-offsets were removed and the net costs were based on the medication costs in the model (approximately £55,000 in year 1, rising to £280,000 in year 5).
- Brimonidine may be used in addition to alternative topical treatments, rather than instead of[5]. Collectively, the company's estimates of the net budget impact of use of brimonidine in NHS Wales are subject to considerable uncertainty.

5.2 Comparative unit costs

Brimonidine is the only agent licensed specifically for the treatment of erythema in rosacea. In patients who respond, it would be used on an ongoing continual basis. Other topical treatments include metronidazole and azelaic acid, which are aimed at treating papules and pustules rather than erythema per se, and would generally be used as a course of treatment rather than on an ongoing continual basis. Comparative costs based on BNF list prices[13] are included in Table 4 for illustration only; it is likely that in practice brimonidine could be used in addition to, rather than instead of these agents[5].

Table 4. Illustrative costs of topical treatments for rosacea/erythema

Product	Example regimen	Costs
Brimonidine 0.33% gel (Mirvaso®)	Apply 0.5 g to 1 g (max) daily, ongoing	£205 to £410 per year
Metronidazole 0.75% gel (Rozex®)	Apply twice daily (assuming 1 g daily) for 8–9 weeks	£20 for 8–9 week course
Azelaic acid 15% gel (Finacea®)	Apply twice daily (assuming 1 g daily) for e.g. 6–12 months*	£52–97 for e.g. 6–12 months
This table does not imply therapeutic equivalence of the drugs or regimens. See respective Summaries of Product Characteristics (SPC) for full details[2,18,19]. *Finacea® gel SPC notes the gel can be used over several months in accordance with the clinical outcome[18]. Assume 6–12 months treatment as an example only.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, brimonidine (Mirvaso®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

The company do not anticipate that brimonidine (Mirvaso®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6–12 months:

- The quality of life study 29107, described in section 3.2.2, has been completed; however, results are yet to be published.
- An in use study of brimonidine (Mirvaso®) is currently recruiting with an estimated study completion date of April 2015 (trial identifier: NCT02249065)[20]. The study is designed to assess the signs and symptoms of rosacea without treatment and during treatment with brimonidine gel, characterise the lifestyle impact and patient satisfaction of treatment and gain a better understanding of real-world use of brimonidine.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 2 and 3 March 2015
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Clinical Erythema Assessment (CEA) and Patient Self-Assessment (PSA)

The CEA and PSA provide scores of erythema, defined as follows: CEA: 0 = clear skin with no signs of erythema; 1 = almost clear, slight redness; 2 = mild erythema, definite redness; 3 = moderate erythema plus marked redness; and 4 = severe erythema plus fiery redness. PSA: 0 = no redness; 1 = very mild redness; 2 = mild redness; 3 = moderate redness; and 4 = severe redness[2,11].

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