Scottish Medicines Consortium

azelaic acid 15% gel (Finacea®) No. (359/07)

Valeant Pharmaceuticals Ltd

9 March 2007

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

azelaic acid 15% gel (Finacea®) is accepted for use within NHS Scotland for the topical treatment of papulopustular rosacea**.**

It shows equivalent efficacy at a lower cost compared to another topical preparation used for rosacea.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

For the topical treatment of papulopustular rosacea.

Dosing information

Finacea 15% Gel should be applied sparingly to the affected skin areas twice a day (in the morning and in the evening) and massaged gently into the skin. Approximately 0.5 g = 2.5 cm of gel is sufficient for the entire facial area.

Occlusive dressing or wrappings should not be used, and hands should be washed after applying the gel.

Significant initial therapeutic effects have been observed after 4 – 8 weeks of treatment although to obtain optimum results, it has been used over several months, in accordance with the clinical outcome.

Product availability date

18th September 2006

Summary of evidence on comparative efficacy

Azelaic acid is a dicarboxylic acid. The exact mechanism by which azelaic acid interferes with the pathogenic events in rosacea is unknown but it may exert an anti-inflammatory effect by inhibition of the generation and action of reactive oxygen species and indirectly by inhibition of inflammatory mediators by follicular bacteria.

A double-blind study recruited 251 patients ≥ 18 years with moderate facial papulopustular stage 2 rosacea, defined as 10-50 inflamed facial papules and/or pustules, persistent erythema and telangiectasia. Following the washout period they were not permitted to receive any concurrent therapy that could affect the course of rosacea during the study. Patients were randomised equally to apply twice daily topical azelaic acid 15% gel or metronidazole 0.75% gel in the morning and evening to the face for 15 weeks. The primary efficacy endpoint was the change in inflammatory lesion count from baseline to last available visit, with last observations carried forward for missing data. This was assessed in the intent–to-treat (ITT) population, which included all randomised patients who received study medication. The trial was completed by 227 patients. Azelaic acid gel was associated with a significantly greater mean reduction in lesion count than metronidazole gel: 12.9 vs. 10.7. The mean lesion count was reduced from a baseline of 18.1 lesions to 4.5 at endpoint in the azelaic acid group and from 19.4 to 7.6 lesions in the metronidazole group. Thus, the mean reductions in inflammatory lesions (73% vs. 56% respectively) were also significantly greater with azelaic acid. Also facial erythema was significantly improved with azelaic acid compared to metronidazole: (56% vs. 42% respectively). With both mean lesion count and severity of erythema, the effectiveness of metronidazole gel plateaued at 8 weeks, whereas the effectiveness of azelaic acid demonstrated progressive improvement throughout the trial. Neither treatment showed any significant clinical improvement in telangiectasia.

The investigators' global assessment and rating of overall improvement showed a significant therapeutic advantage for azelaic acid. The patients' rating of overall improvement was consistent with the investigators' assessment and both treatments were rated as having high cosmetic acceptability.

An investigator-blinded study recruited 160 patients ≥ 18 years with moderate rosacea, defined as 8-50 papules, pustules and nodules, with no greater than 2 facial nodules. After washout of existing treatments for rosacea, they were randomised equally to apply topical metronidazole 1% gel (a formulation that is not licensed in the UK) once daily or azelaic acid 15% gel twice-daily for 15 weeks. The primary objective was to show non-inferiority in terms of median reduction in inflammatory lesion counts from baseline to week 15. This was assessed in both the ITT and per protocol (PP) populations with last observation carried forward method for missing data. The trial was completed by 136 patients. In the ITT population median decreases in inflammatory lesion counts were not significantly different in the treatment groups: 80% and 77% in the azelaic acid and metronidazole groups, respectively. In the PP population, the results were similar in both groups: 85% and 80%, respectively. Results were also similar between treatment groups for the success rate, erythema scores and in the efficacy and tolerability based on analysis of the patient questionnaires.

Summary of evidence on comparative safety

In the first active-comparator study, treatment-related facial skin signs and symptoms such as skin dryness, scaling, itching, oedema, burning and stinging were reported by 26% (n=32/124) and 7% (n=9/127) of patients in the azelaic acid and metronidazole groups, respectively. Adverse effects were generally mild-to-moderate in severity. Due to treatment-related adverse events, 3% of patients receiving azelaic acid and no patients receiving metronidazole discontinued treatment. Dose reductions were necessary in 4% and 2% of patients in the azeliac acid and metronidazole groups respectively. Local tolerability of their respective treatment was reported as ‘good’ or ‘acceptable despite minor irritation’ in 89% and 96% of azelaic acid and metronidazole-treated patients, respectively. No serious or systemic adverse events were reported in either treatment group and there were no reports of phototoxic or photoallergic reactions.

In the second active-comparator study 6 patients (7.4%) treated with metronidazole 1% gel had moderate to severe stinging and burning as their worst score, compared with 9 patients (11.8%) treated with azelaic acid 15% gel. Additionally, 12 patients (14.8%) had moderate scaling in the metronidazole group compared with 7 patients (9.2%) in the azelaic acid group. No statistical differences in terms of worst score for dryness and itching were found between the two treatment groups. In the metronidazole 1% gel group, 41 patients (50.0%) reported adverse events versus 29 patients (37.2%) in the azelaic acid 15% gel group, with 7 and 2 adverse events related to treatment in the respective groups. One adverse event (rosacea flare) in one patient treated with metronidazole 1% gel led to discontinuation of the study medication.

Summary of clinical effectiveness issues

There was no information from comparative trials about the effect of azelaic acid gel on patients’ quality of life. However, in the second active-comparator study, where a patient questionnaire was administered, the proportion of patients who felt better about themselves and were satisfied or very satisfied with their outcome was similar between treatment groups.

The licence for azelaic acid gel is for treatment of papulopustular rosacea and is not restricted to any particular grade of severity. All studies specified patients with moderate rosacea in their inclusion criteria therefore there are no data for patients with mild or severe disease.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis which estimated the average annual cost of azelaic acid gel compared to topical metronidazole for the treatment of papulopustular rosacea. The manufacturer estimated that treatment with azelaic acid gel would result in cost savings of £10.08 per patient per year compared to metronidazole (Rozex) and £29.78 compared to metronidazole (Metrogel).

The appropriate comparator was used in the analysis. Another azelaic acid treatment was considered but was not used as a comparator as it is not the main treatment for rosacea and is only licensed for the treatment of acne. The clinical data showed that azelaic acid had at least equivalent efficacy to metronidazole and the cost per day is lower. Therefore, a cost minimisation analysis seemed appropriate.

No sensitivity analysis was carried out, although the costs of two different brands of metronidazole (Rozex and Metrogel) were included and the results were presented for azelaic acid compared to both brands. The economic analysis showed that azelaic acid was cost saving compared to metronidazole and as such the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest group Submission was not made.

Additional information: guidelines and protocols

Rosacea- Prodigy Knowledge Guidance: whole review. Last revised July 2005.

The Centre for Change and Innovation within NHS Scotland has produced a Rosacea Patient Pathway (April 2005). This lists primary care options for management of rosacea as: topical therapy with metronidazole, clindamycin or erythromycin or a 2-3 month course of an oral tetracycline or erythromycin.

Additional information: comparators

Metronidazole 0.75% gel and cream are the only topical treatments licensed in the UK for treatment of rosacea. Systemic therapy, including oral antibiotics, are an alternative to topical therapy in some patients.

Additional information: costs

Preparation	Dose regimen	Cost per eight weeks (£)[a]
Azelaic acid (Finacea) 15% gel	Apply twice daily	**14.96**
Metronidazole (Acea) 0.75% gel	Apply twice daily	19.90
Metronidazole (Zyomet) 0.75% gel	Apply twice daily	24.00
Metronidazole (Rosex) 0.75% gel	Apply twice daily	30.56
Metronidazole (Rozex) 0.75% cream	Apply twice daily	30.56
Metronidazole (Metrogel) 0.75% gel	Apply twice daily	39.80
Metronidazole (Metrosa) 0.75% gel	Apply twice daily	39.80

[a] - Cost based on using 0.5g per dose for 8 weeks

Additional information: budget impact

The manufacturer estimated a net saving from using azelaic acid instead of metronidazole (Rozex) of £2,788 in year 1 rising to £17,663 in 2011. The budget impact estimates were based on 388 patients in year 1 and 2,030 patients in year 5. The manufacturer assumed that the market penetration will be 5% in year 1 rising to 30% in year 5.

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.

This assessment is based on data submitted by the applicant company up to and including 16 January 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

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

Elewski BE, Fleischer AB, and Pariser DM. (2003). A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea. Arch Dermatol 139, 1444-1450.

Wolf JE Jr, Kerrouche N, Arsonnaud S. Efficacy and safety of once daily metronidazole 1% gel compared with twice-daily azelaic acid 15% gel in the treatment of rosacea. Cutis.77(4 Suppl):3-11,2006 Apr.