Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

budesonide 3mg gastro-resistant capsule (Budenofalk®) SMC No. (828/12)

Dr Falk Pharma

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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

budesonide gastro-resistant capsule (Budenofalk®) is accepted for use within NHS Scotland.

Indication under review: symptomatic relief of chronic diarrhoea due to collagenous colitis.

budesonide (Budenofalk®) provides symptomatic improvement of diarrhoea associated with collagenous colitis compared with placebo.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Symptomatic relief of chronic diarrhoea due to collagenous colitis.

Dosing Information

3mg three times daily. The duration of treatment should be limited to eight weeks. Treatment should not be stopped abruptly, but withdrawn gradually (i.e. reduced to two capsules daily for one week, then one capsule daily for one week, then stopped).

Product availability date

28 June 2004

Summary of evidence on comparative efficacy

Collagenous colitis is an inflammatory disease of the colon characterised by chronic or recurrent watery, non-bloody diarrhoea, normal looking colonic mucosa on endoscopy, but a thickened subepithelial collagen layer and a lymphoplasmocytic infiltrate.[1] Budesonide (Budenofalk®) is a corticosteroid formulated in capsules containing granules coated with Eudragit to protect it from gastric juices. The granules dissolve at pH ≥6.4, releasing budesonide in the lower gastro-intestinal tract where it is thought to produce a local anti-inflammatory effect before undergoing extensive (almost 90%) first-pass metabolism.[2,3] It is the first medicine licensed for treatment of collagenous colitis.[2] A licence extension for budesonide in the treatment of chronic diarrhoea due to collagenous colitis was granted in 2004, but there was no Scottish Medicines Consortium (SMC) assessment at that time. The current submission is being assessed in parallel with an abbreviated submission for a new 9mg granule formulation of budesonide.

A double-blind study equally randomised 28 patients with collagenous colitis and chronic symptoms of at least eight weeks' duration to budesonide (Budenofalk®) 3mg three times daily or placebo for eight weeks. The primary endpoint assessed at week eight in the intention-to-treat population was clinical response, defined as at least a 50% reduction in the number of bowel movements in the previous seven days compared to baseline. The number of clinical responders in the budesonide (Budenofalk®) group was significantly greater than in the placebo group: 57% (8/14) versus 21% (3/14). At the end of double-blind treatment, nine of the eleven non-responders in the placebo group received open-label budesonide (Budenofalk®) 3mg three times daily for eight weeks and a clinical response was achieved by 78% (7/9). Histologically, there were no significant differences between groups in subepithelial collagen band thickness. All patients in the budesonide (Budenofalk®) group had a reduction of infiltrate in the lamina propria, with 9 of 13 patients achieving complete normalisation and 4 patients showing a partial response. The effects were greater than in the placebo group, where 4 of 12 patients had a partial response and 8 patients had no response.[1]

There are some placebo-controlled, double-blind studies of another budesonide formulation in collagenous colitis. Budesonide (Entocort®), is a capsule formulation that is similar to budesonide (Budenofalk®), in that it releases budesonide in the lower gastro-intestinal tract. Budesonide (Entocort®) capsules contain granules coated to protect them from gastric juices, which dissolve at pH>5.5 and, thereafter, a matrix of ethylcellulose with budesonide controls the release of the drug in a time-dependent manner.[4] These studies provide supportive evidence of the therapeutic benefits associated with administration of budesonide locally to the lower gastro-intestinal tract.[5-8]

A Cochrane review pooled data from the budesonide (Budenofalk®) study described previously and two double-blind, placebo-controlled studies of budesonide (Entocort®). It noted that 94 patients with collagenous colitis were enrolled in the three trials, of whom 47 were randomised to budesonide and 47 to placebo. Clinical response was achieved in 81% (38/47) of budesonide- and 17% (8/47) of placebo-treated patients. The pooled odds ratio for response to therapy was 12.32 (95% confidence interval (CI): 5.53 to 27.46) and the absolute risk reduction was 64% (95% CI: 48% to 79%). The number needed to treat with budesonide rather than placebo to achieve a clinical response was two. The review noted that histological definitions of improvement with therapy in the three trials were generally based on subjective criteria and varied between trials. Therefore, a decision was made not to combine the histological data for analysis.[9]

Summary of evidence on comparative safety

Budesonide (Budenofalk®) is associated with adverse effects typical of a corticosteroid. It undergoes extensive (almost 90%) first-pass metabolism and so the incidence of adverse effects with budesonide (Budenofalk®) is considerably lower (around half) that associated with clinically equivalent doses of oral prednisolone.[2]

Summary of clinical effectiveness issues

The treatment of collagenous colitis is generally symptomatic with anti-diarrhoeal agents such as loperamide and bismuth subsalicylate or with aminosalicylates. Budesonide (Budenofalk®) is the only treatment specifically licensed for this condition.

The results from the single placebo-controlled trial of budesonide (Budenofalk®) demonstrating a reduction in bowel movements were significant and appear clinically relevant (57% versus 21%). Five patients (approximately 18%) in the study population (three in the budesonide (Budenofalk®) group and two in the placebo group) did not reach the entry criterion of a minimum of 21 stools per week at baseline. If these patients are excluded from analysis of the primary endpoint, clinical response rates in the respective groups are 73% (8/11) versus 25% (3/12).[2] These figures may better represent expected benefits in practice.[1]

The study results support the initial management of the condition, but do not address long-term issues such as prevention of relapse. The Summary of Product Characteristics for budesonide (Budenofalk®) recommends that treatment duration should be limited to eight weeks.[2]

Budesonide (Entocort®) appears to be the relevant comparator, as the other medicines used to treat collagenous colitis would be used either in milder disease (i.e. anti-diarrhoeal agents such as loperamide) or in more severe disease (i.e. immunosuppressants such as azathioprine).

The evidence base for budesonide (Budenofalk®) in this indication is very limited, with more evidence available from studies of the budesonide (Entocort®) formulation, which is not licensed for collagenous colitis. The latter studies provide evidence that budesonide administered to the lower gastro-intestinal tract is effective in this condition. The Cochrane review made no distinction between the two budesonide preparations in the pooled analysis of its effects in collagenous colitis.

SMC clinical experts advise that budesonide (Budenofalk®) has been routinely used for this condition for several years at the disease stage when corticosteroid therapy is considered appropriate. Some

clinicians consider that there is no distinction between budesonide (Budenofalk®) and the similar budesonide (Entocort®) formulation.

Summary of comparative health economic evidence

The submitting company presented a simple cost analysis to show only the drug acquisition costs of budesonide (Budenofalk®) 9mg/day and a range of other treatments; budesonide (Entocort®) 9mg/day, loperamide hydrochloride, mesalazine and azathioprine. No formal economic evaluations were presented in the submission as the company did not provide any evidence of the relative efficacy of the various medicines compared to budenoside (Budenofalk®). However, in subsequent correspondence, the submitting company requested that the cost analysis versus budesonide (Entocort®) be considered as a cost-minimisation analysis on the basis of an assumption of broadly equivalent outcomes between the treatments. The time horizons for the costings varied between 5 days and 6 months. SMC clinical experts have indicated that budesonide is a relevant comparator treatment and, for this analysis, the two medicines were compared over 1 day, 8 week and 6 month time horizons. It should be noted, however, that the dosing information for budesonide (Budenofalk®) indicates that treatment should be limited to 8 weeks.

The results of a comparison with budesonide (Entocort®) are shown below.

Treatment	**Cost per patient per day**	**Cost per patient per 8 weeks**	**Cost per patient per 6 months***
Budesonide (Entocort®)	£2.97	£166.32	£362.34
Budesonide (Budenofalk®)	£2.25	£126.00	£275.50
Saving with Budenofalk®	£0.72	£40.32	£86.84

*this treatment duration is outwith the licence, which limits treatment to 8 weeks.

On the basis of these results, budesonide (Budenofalk®) was the least expensive therapy, and thus would be the preferred treatment on cost-minimisation grounds.

Against the other potential comparators, using the costs above, budesonide (Budenofalk®) was more expensive than some regimens but cheaper than others, as shown below:

- Azathioprine: £25.20 to £113.34 for 3 months (men) and £18.90 to £97.20 (women)
- Mesalazine: £177.10 to £281.75 for 12 weeks
- Loperamide hydrochloride: £1.60 to £8.40 for 5 days.

However, no evidence was presented about the relative efficacy of these treatments compared to budesonide (Budenofalk®) to allow them to be considered in a cost-minimisation analysis.

No sensitivity analysis was presented given the limited nature of the cost analysis and the variables it contained. The analysis did not consider any potential differences in relapse rates.

The main weakness was that the cost-minimisation analysis versus the alternative budesonide preparation (Entocort®) was based on assumed equivalence rather than formal data and, for the remainder of the comparisons, only simple cost analyses rather than formal economic evaluations were presented. Despite this, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

No other medicine has a licence specifically for the treatment of chronic diarrhoea due to collagenous colitis.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Budesonide (Budenofalk®)	**3mg three times daily**	**126**
Budesonide (Entocort®)*	9mg daily	166

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 18 September 2012. An eight-week course has been used to calculate costs.
* Budesonide (Entocort®) is not licensed for use in collagenous colitis.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 1,897 in year 1 rising to 2,001 in year five with an estimated uptake rate of 25% in year 1 and 45% in year 5. The gross impact on the medicines budget was estimated to be £60k in year 1 and £113k in year 5. The submitting company has assumed savings in displaced medicine from current off-label prescribing of Entocort® for this indication. On this basis, the net medicines budget impact is expected to be as £52k in year 1 and £39k in year 5, given assumed displacement rates of 10% in year one rising to 50% by year 5.

References

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

1. Baert F, Schmit A, D'Haens G et al. Budesonide in Collagenous Colitis: A double-blind placebo-controlled trial with histologic follow-up. Gastroenterology 2002; 122: 20-25.

2. Dr Falk Pharma. Summary of product characteristics for Budenofalk 3mg gastro-resistant capsule.

3. Medicines Healthcare Products Regulatory Agency. Public assessment report for Budenofalk 9mg gastro-resistant granules. Procedure no: UK/H/2778/001/DC. UK Licence no: 08637/0020.

4. Food and Drug Administration. US labeling for Entocort.

5. Bonderup K, Hansen JB, Birket-Smith L et al. Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. Gut 2003; 52: 248–51.

6. Miehlke S; Heymer P, Bethke B et al. Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicenter trial. Gastroenterology 2002; 123: 978-84.

7. Bonderup K, Hansen JB, Teglbjærg PS et al. Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo controlled trial. Gut 2009; 58; 68-72.

8. Miehlke S, Madisch A, Bethke B et al. Oral Budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2008; 135: 1510–16.

9. Chande N, McDonald JWD, MacDonald JK. Interventions for treating collagenous colitis: a Cochrane Inflammatory Bowel Disease Group systematic review of randomized trials. American Journal of Gastroenterology 2004; 99: 2459-65.

This assessment is based on data submitted by the applicant company up to and including 14 November 2012.

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. 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.