Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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budesonide, 3mg, gastro-resistant capsules (Budenofalk®) SMC No. (1043/15)

Dr Falk Pharma UK Ltd

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

Indication under review: autoimmune hepatitis.

SMC restriction: for use in non-cirrhotic patients who are intolerant of conventional oral corticosteroids (prednisolone) with severe corticosteroid-related side effects (actual or anticipated) such as psychosis, poorly controlled diabetes or osteoporosis

In a phase IIb study, a significantly greater proportion of patients with non-cirrhotic autoimmune hepatitis achieved complete biochemical remission and a reduction in predefined corticosteroid-specific side effects when treated with budesonide plus an immunosuppressant compared with an alternative corticosteroid plus an immunosuppressant.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Autoimmune hepatitis (AIH).

Dosing Information

Induction of remission (adults aged >18 years):
For the induction of remission (i.e. normalisation of elevated laboratory parameters) the recommended daily dose is one capsule (containing 3mg budesonide) three times daily (morning, midday and evening; corresponding to a total daily dose of 9mg budesonide).

Maintenance of remission (adults aged >18 years):
After achievement of remission the recommended daily dose is one capsule (containing 3mg budesonide) twice daily (one capsule in the morning and one capsule in the evening; corresponding to a total daily dose of 6mg budesonide).

If alanine aminotransferase and/or aspartate aminotransferase increase during maintenance treatment, the dose should be increased to three capsules per day (corresponding to a total daily dose of 9mg budesonide) as described for induction of remission.

In patients tolerant to azathioprine, treatment for induction and maintenance of remission with budesonide should be combined with azathioprine.

Treatment for maintenance of remission in AIH should be continued for at least 24 months. It might be terminated only if biochemical remission is constantly maintained and if no signs of inflammation are present in a liver biopsy.

The capsules containing the gastro-resistant granules should be taken about half an hour before meals, swallowed with plenty of fluid (e.g. a glass of water).

Product availability date

20 August 2010

Summary of evidence on comparative efficacy

Immunosuppressive therapy is used in the management of AIH to induce and maintain remission. The aim of remission is to reduce serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels to within the normal range (defined as complete biochemical remission). Corticosteroids induce remission; however, corticosteroid-related side effects often result in early drug withdrawal.[1,2] Budesonide is a synthetic glucocorticosteroid with a higher glucocorticoid receptor-binding activity than prednisolone. It inhibits mast cell function, strengthens cell membranes and reduces inflammation, and the systemic bioavailability of budesonide is reduced to 10% as a result of its high first-pass metabolism in the liver.[3]

The submitting company has requested that SMC considers this product when positioned for use in patients who decline or cannot tolerate corticosteroids (first line therapy) and are non-cirrhotic patients with severe (actual or anticipated) corticosteroid-related side effects such as psychosis, poorly controlled diabetes or osteoporosis.

Clinical evidence derives from a phase IIb, randomised, multicentre, active-controlled study to evaluate the safety and efficacy of budesonide (Budenofalk®) compared with prednisone, both in combination with azathioprine.[4,5] The study recruited patients aged 10 to 70 years with an acute diagnosis of AIH (based on the Alvarez score) in the absence of liver cirrhosis, and with serum ALT or AST levels ≥2 times the upper limit of normal (ULN). Two consecutive study segments, A and B, were each conducted for a six-month duration. In segment A, the double-blind phase, patients were randomised to treatment with azathioprine plus budesonide (n=103) or azathioprine plus prednisone (n=105). In weeks 1 and 2, patients received oral budesonide 3mg three times daily or oral prednisone 40mg daily. After two weeks, the budesonide dose was tapered to 3mg twice daily and the prednisone dose was tapered to 10mg daily in those with serum AST and ALT within the normal range (i.e. complete biochemical remission). Patients who had not achieved complete biochemical remission continued on the original dose regimen. Depending on serum AST and ALT levels at subsequent visits, the budesonide dose could be altered to 3mg twice daily or 3mg three times daily. The prednisone dose was tapered according to the fixed-dose regimen selected at the two-week visit (high-dose or low-dose regimen). Patients achieving biochemical remission at months three and six in segment A were eligible to transfer to segment B; those not achieving biochemical remission after six months were permitted to enter segment B at the discretion of the investigators. In segment B, the open-label phase, all patients (n=176) received azathioprine plus budesonide 3mg twice daily (upon biochemical remission) or three times daily. Azathioprine was given orally during both segments at a dose of 1 to 2mg/kg/day based on clinical judgement.

Segment A was completed by 90% (n=92/102) of patients in the budesonide group and 84% (n=88/105) of patients in the prednisone group. Two patients in each of the treatment groups were excluded from the intention-to-treat (ITT) population for analysis of the primary outcome due to protocol violations (budesonide group n=100; prednisone group n=103). Of the 180 patients who completed segment A, 176 patients progressed to segment B and received budesonide; these patients were analysed according to the treatment they initially received in segment A. One patient in the original budesonide group and two patients in the original prednisone group were excluded from the ITT population due to protocol violations (budesonide group n=88; prednisone group n=85).

The primary outcome was complete response to therapy, defined as complete biochemical remission (i.e. serum AST and ALT within the normal range) at the patient's last visit of segment A, and the absence of predefined corticosteroid-specific side effects (i.e. moon face, acne, buffalo hump, hirsutism, striae, diabetes, glaucoma, and increased intraocular pressure) throughout segment A.

The composite primary outcome was achieved in 47% (n=47/100) of patients in the budesonide group, and in 18% (n=19/103) of patients in the prednisone group within the ITT population (97.5% confidence interval [CI], lower limit: 16.2%; $p<0.001$). At the end of segment A, complete response in both male and female patients was significantly higher in the budesonide group compared with the prednisone group. In the budesonide and prednisone groups, respectively, complete response in male patients was achieved in 57% (n=17/30) versus 6.7% (n=1/15) ($p<0.001$) and in female patients was achieved in 43% (n=30/70) versus 20% (n=18/88) ($p<0.01$).

Secondary outcomes included complete biochemical remission and the occurrence or absence of corticosteroid-specific side effects. Within the ITT population, complete biochemical remission at six months was achieved in 60% (n=60/100) of patients in the budesonide group, and in 39% (n=40/103) of patients in the prednisone group (97.5% CI lower limit: 7.7%; $p<0.001$).

There was no significant difference in complete response by the end of segment B (when all patients received budesonide) between patients who initially received budesonide or prednisone in segment A. Complete response at 12 months (the end of segment B) was achieved by 55% (n=95/173) of patients overall, and the proportions in patients who initially received budesonide or prednisone were 51% (n=88/173) and 49% (n=85/173) respectively.

Summary of evidence on comparative safety

Within the budesonide (n=102) and prednisone (n=105) populations, respectively, treatment-emergent adverse events included weight gain (5.9% versus 19%), headache (12% versus 7.6%), mood alterations (9.8% versus 7.6%), muscular weakness (4.9% versus 7.6%), hypertension (2.9% versus 6.7%), and insomnia (1.0% versus 4.8%).[4]

Predefined corticosteroid-specific side effects were moon face, acne, hirsutism, skin striae, buffalo hump, diabetes, increased intraocular pressure and glaucoma and these events were reported in the ITT population. During segment A there was an absence of corticosteroid-specific side effects in 72% (n=72/100) of patients in the budesonide group versus 47% (n=48/103) in the prednisone group (97.5% CI lower limit: 12.3%; p<0.001). Predefined side effects occurring less frequently in the budesonide group (n=100) compared with the prednisone group (n=103) were moon face (10% versus 42%), acne (8% versus 15%), skin striae (2% versus 3.9%), and buffalo hump (1% versus 3.9%). Hirsutism (9% versus 2.9%) and diabetes (4% versus 0%) were reported in a greater proportion of patients in the budesonide group than in the prednisone group. Two of the four reports of diabetes were established as pre-existing and one was classed as a transient elevation of glycosylated haemoglobin.

Among those patients who switched from prednisone to budesonide in segment B, there was an almost 40% reduction in the occurrence of commonly associated corticosteroid-specific side effects by completion of the segment at month 12 (start of segment B 45% n=39/87; end of segment B 26% n=23/87; p<0.002).

Summary of clinical effectiveness issues

AIH is a chronic inflammatory liver disease which can result in cirrhosis, liver failure and death if left untreated. All age groups can be affected; however, women are three to four times more likely to be affected than men. Most cases have no identifiable cause. Diagnosis is usually by identification of biochemical, immunological, and histological features, and the exclusion of other possible liver conditions. The key laboratory findings of AIH include elevated serum ALT and AST activity, raised serum immunoglobulins, negative viral hepatitis serum tests, and high levels of circulating autoantibodies. Achieving serum AST and ALT within the normal range (defined as complete biochemical remission) is generally agreed as the aim of remission. Long-term treatment goals aim to reduce the risk of relapse, death from liver disease or transplantation, and treatment-related adverse events. Current guidelines recommend first-line treatment of AIH with prednisolone plus azathioprine; budesonide plus azathioprine may be considered in non-cirrhotic patients intolerant of prednisolone with severe (actual or anticipated) corticosteroid-related side effects such as psychosis, poorly controlled diabetes or osteoporosis. Second-line treatment options for AIH include tacrolimus, ciclosporin, mycophenolate mofetil, deflazocort and ursodeoxycholic acid.[1]

The submitting company has requested that SMC considers budesonide when positioned for use in patients who decline or cannot tolerate corticosteroids (first line therapy) and are non-cirrhotic patients with severe (actual or anticipated) corticosteroid-related side effects such as psychosis, poorly controlled diabetes or osteoporosis. Use of budesonide in patients with severe (actual or anticipated) corticosteroid-related side effects is consistent with the British Society for Gastroenterology guidelines on AIH.[1]

In the phase IIb study, the composite primary outcome of complete response to therapy and the absence of predefined corticosteroid-specific side effects was achieved in significantly more patients in the budesonide group compared with the prednisone group. The blinded phase of the study was only conducted for the first six months in segment A. However, patients were eligible to enter segment B if they achieved biochemical remission after three months; the number of patients who completed six months of double-blind treatment is therefore unknown. Bias may have been introduced into the analysis of study outcomes at month 12 as a result of the open-label design of segment B. Current guidelines advise treating AIH for at least two years, and for at least twelve months after normalisation of transaminases; however, the study was only conducted for one year, and there is a lack of long-term data on the use of budesonide in the treatment of AIH. It is also not explicitly clear how all patients were accounted for between segments A and B, and there was no measure of the impact of the study outcomes on the patients' quality of life.

The prednisone group had a significantly higher proportion of female patients than the budesonide group (85% [n=89/105] versus 70% [n=71/102]) and, therefore, the budesonide group had almost double the number of male patients (30%, n=31/102) compared with the prednisone group (15%, n=16/105).[4] As AIH is more prevalent in women, this imbalance could have potentially biased the results.

Budesonide would offer an alternative licensed corticosteroid treatment for patients with AIH but information on switching patients from prednisone/prednisolone to budesonide is lacking. In patients with AIH, serum ALT and AST should be monitored at regular intervals in order to adjust the dose of budesonide accordingly.[6]

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing budesonide (Budenofalk®) to budesonide (Entocort®) in patients with AIH who decline or cannot tolerate corticosteroids (first line therapy) and are non-cirrhotic patients with severe (actual or anticipated) corticosteroid-related side effects such as psychosis, poorly controlled diabetes or osteoporosis.

No direct or indirect comparative data were presented against budesonide (Entocort®) to support equivalence of outcomes as necessary for a cost-minimisation analysis. However, given that the comparison is between two budesonide products at the same dose via the same administration schedule, it is considered reasonable to assume that outcomes would be equivalent without having comparative data.

The analysis was based on drug acquisition costs only. It was presented to show the average annual costs, with the average based across a treatment duration of 30 months, 6 months of which used an initiation dose of 9mg/ day and the remainder a dose of 6mg/ day for each treatment.

In terms of the cost-minimisation analysis, based on an average annual cost, the following results were presented:

Medicine	Average annual cost
Budesonide (Budenofalk®) 3mg capsules	£602.25
Budesonide (Entocort®)	£794.97

On the basis of these calculations, budesonide (Budenfalk®) would be preferred on cost-minimisation grounds as it was associated with an average saving of £192.72 (24% cheaper).

Given the simplicity of the analysis, no sensitivity analysis was presented. SMC clinical experts have suggested that the duration of the initiation phase of treatment may be shorter than the 6 months assumed, but adjusting for this would not alter the finding that budesonide (Budenofalk®) would be the preferred treatment on cost-minimisation grounds.

The key weakness with the analysis related to the lack of data comparing the two medicines to show equivalent efficacy, but it would seem appropriate to accept that outcomes would be the same. Given this, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

Guidelines on the management of autoimmune hepatitis (AIH) have been published by the British Society of Gastroenterology (2011).[1] Immunosuppressive therapy should be offered to those with AIH and moderate/severe inflammation (i.e. one or more of serum AST >5 times normal, serum globulins >2 times normal, liver biopsy showing confluent necrosis); in the absence of this criteria, those patients presenting with symptoms, established cirrhosis, or younger patients should also be considered for treatment. Prednisolone, alone or in combination with azathioprine, produces a fall in transaminases that resolve clinical symptoms and improve liver function. Prednisolone (30mg/day, reducing to 10mg/day over 4 weeks) plus azathioprine (1mg/kg/day) form the primary treatment of AIH. Up to 1mg/kg/day of prednisolone as an initial dose are often used. Higher doses of prednisolone and azathioprine, or alternatively tacrolimus, may be used in slow/non-responders. Budesonide plus azathioprine may be considered in non-cirrhotic patients intolerant of prednisolone with severe (actual or anticipated) steroid-related side effects such as psychosis, poorly controlled diabetes or osteoporosis. Prednisone alone or in combination with mycophenolate can be considered in patients intolerant of azathioprine. Treatment should continue for at least two years and at least 12 months after normalisation of transaminases.

Additional information: comparators

Prednisolone, budesonide (Entocort® CR)*.

*Off-label indication for the treatment of AIH.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Budesonide (Budenofalk®)	**6 to 9mg orally per day**	**546 to 820**
Budesonide (Entocort® CR)*	6 to 9mg orally per day	720 to 1081
Prednisolone	30mg orally per day for one week; 25mg orally per day for one week; 20mg orally per day for one week; 15mg orally per day for one week; 5 to10mg orally per day	14 to 29

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 23/01/15. Costs do not include initial induction period. *Off-label indication for the treatment of AIH.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 194 in year 1 rising to 253 in year 5 with an estimated uptake rate of 50% in year 1 and 90% by year 5. The gross impact on the medicines budget was estimated to be £58k in year 1 and £137k in year 5. As another drug was assumed to be displaced (Entocort®), the net medicines budget impact is estimated to be a saving of £18k in year 1 and a saving of £43k in year 5. These figures are based on the average annual cost used in the economic analysis.

References

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

1. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) Guidelines for management of autoimmune hepatitis. Gut 2011; 60(12):1611-1629

2. Manns M, Czaja A, Gorham J, Krawitt E, Vergani-Mieli G, Vergani D et al. Diagnosis and management of autoimmune hepatitis. American Association for the Study of Liver Diseases (AASLD) Guideline. Hepatology 2010; 51(6):1-31

3. Wiegand J, Schuler A, Kanzler S, Lohse A, Beuers U Kreisel W et al. Budesonide in previously untreated autoimmune hepatitis. Liver International 2005; 25:927-934

4. Manns M, Woynarowski M, Kreisel W, Lure, Y, Rust C, Zuckerman E et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology 2010; 139:1898-1206

5. NCT00838214. Budesonide 3x3mg/d versus prednisone in active autoimmune hepatitis. www.clinicaltrials.gov accessed 13/01/15.

6. Dr. Falk Pharma UK Ltd. Budenofalk 3mg gastro-resistant capsules. Summary of product characteristics. Last updated September 2010.

This assessment is based on data submitted by the applicant company up to and including 09 March 2015.

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.