Scottish Medicines Consortium

beclometasone dipropionate 5mg tablets (Clipper®) No. (166/05)
Trinity-Chiesi Pharmaceuticals

8 April, 2005 *(Issued August 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

Beclometasone dipropionate (Clipper®) is not recommended for use within NHS Scotland for the treatment of mild to moderate ulcerative colitis in active phase as add-on therapy to 5-ASA containing drugs. The clinical and cost effectiveness against standard practice have not been demonstrated.

This advice is based on an assessment carried out in April 2005.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Beclometasone dipropionate 5mg tablets (Clipper®)

Licensed indication under review

For the treatment of mild to moderate ulcerative colitis in active phase, as add-on therapy to 5-ASA containing drugs, in patients not responding to 5-ASA therapy in active phase.

Dosing information under review

5mg daily swallowed whole in the morning. Therapy cycles of not more than four weeks are recommended.

UK launch date

Expected September 2005

Comparator medications

Prednisolone. The aminosalicylates form the basis of drug therapy but oral beclometasone dipropionate is advocated in addition to this. A modified release form of oral budesonide is also available but is only licensed for Crohn's disease.

Cost per treatment period and relevant comparators

Basic NHS costs for 28 days treatment (one course of therapy with beclometasone dipropionate).

Drug	**Dose**	**Cost/28 days**
Beclometasone dipropionate (Clipper®)	**5mg daily**	**£60.00**
Prednisolone (drug tariff)*	40mg daily	£5.44

Prednisolone is likely to be initiated at a dose of 40mg daily which will be reduced gradually according to severity and patient response. The duration of prednisolone therapy is likely to be 4 to 8 weeks.

Summary of evidence on comparative efficacy

The efficacy of beclometasone dipropionate was assessed during clinical trials using the Disease Activity Index (DAI). The DAI is a scoring system (0-12), which measures the severity of each of four clinical and endoscopic parameters (stool frequency, rectal bleeding, mucosal appearance and physician's rating of disease activity) on a scale of 0 to 3.

The submission presented details of two phase II, dose-ranging studies as well as two phase III studies. The key efficacy data comes from the results of these two phase III studies: one in comparison with mesalazine and one, as the licence, in combination with mesalazine. Both studies enrolled out-patients with extensive or left-sided mild to moderately active ulcerative colitis (baseline DAI score >3 and <10). The primary endpoint of both studies was the proportion of patients with a reduction from baseline to week 4 in the DAI score of at least 3 points. Secondary endpoints included the proportion of patients achieving clinical remission, defined as have a DAI score <3, and histological results.

The first study, which did not reflect the licence since it used monotherapy, was a single-blinded study comparing beclometasone dipropionate (5mg daily, n=90) with mesalazine (2.4g daily, n=87) over a 4-week study period. Eligible patients were not allowed treatment with corticosteroids, mesalazine or sulfasalazine in the month prior to or during the study. The ITT population comprised 73 beclometasone dipropionate patients and 80 mesalazine patients who were evaluable in terms of DAI. The primary endpoint, of a reduction in the DAI of $\geq$ 3, occurred in 15% (11/73) beclometasone dipropionate and 11% (9/80) mesalazine patients (p=ns). There was also no significant difference between treatments in terms of the secondary endpoint of clinical remission (63% of both groups). Biopsy scores were significantly reduced from baseline in both groups (p<0.001), with 33% of beclometasone dipropionate and 35% of mesalazine patients showing histological remission..

The second study, which reflects the licence, was a double-blind comparison of beclometasone dipropionate (5mg daily) plus mesalazine (2.4g daily) (n=58) with placebo plus mesalazine (2.4g daily) (n=61). Eligible patients were not allowed treatment with corticosteroids for one month prior to the study, or mesalazine >3.2g daily or sulfasalazine >2g daily for two weeks prior to the study and during the 4-week study period. The primary endpoint, of a reduction in the DAI of $\geq$ 3, occurred in 17% (10/58) of beclometasone dipropionate and 16% (10/61) of placebo patients (p=ns). Clinical remission was achieved in more beclometasone dipropionate treated patients (59% versus 34% of placebo treated patients, p=0.021). Both treatments resulted in significant improvements in histological assessment from baseline (p<0.001) with no difference between treatments. The intestinal mucosa was described as "normalised" in 31% of beclometasone dipropionate and 16% of placebo patients.

There are no comparative data with other corticosteroids.

Summary of evidence on comparative safety

During the study in which beclometasone dipropionate was used in combination with mesalazine, the incidence of reported adverse events was 3.4% compared with 6.5% in the patients treated with mesalazine alone. However in this, and each of the other phase II and III studies, beclometasone dipropionate was associated with a significant reduction in plasma cortisol levels from baseline to week 4. Although the mean plasma cortisol level remained within the normal range (5-25μg/dl) at the end of each study, a proportion of patients (up to 25% at the proposed dose in each study) had levels below the lower limit (<5μg/dl). No clinical consequences were reported as a result of these effects on cortisol.

Summary of clinical effectiveness issues

Data from the phase III studies have shown that beclometasone dipropionate was as effective as mesalazine and more effective than placebo as add-on therapy to mesalazine in terms of clinical remission but no more effective in the primary endpoint of clinical improvement.

Both studies are limited by a relatively short duration of 4 weeks. This seems particularly relevant to the effects of adrenal suppression. During studies, beclometasone dipropionate was associated with reduction in plasma cortisol levels in up to 25% of patients and although this resulted in no clinical consequences during the study period, there was no longer-term follow-up of these patients.

The lack of direct comparison with prednisolone in terms of efficacy and safety makes the relative place of beclometasone dipropionate difficult to determine. Current guidelines recommend that prednisolone should generally be given in a course with dose reduction over eight weeks and how this compares to the maximum of four weeks therapy recommended in the licence for beclometasone dipropionate remains to be seen.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing oral beclometasone dipropionate with prednisolone, using a five-state Markov chain model. The clinical evidence came from meta-analyses of two trials (n=148) of oral beclometasone dipropionate and four trials (n=91) of prednisolone. Disease related utilities came from a peer reviewed published article: a disutility of 0.3 was assumed for side effects.

The incremental cost effectiveness ratio (ICER) for use of oral beclometasone dipropionate was £44,140 per QALY. A Monte Carlo simulation indicated a 43% probability of an ICER of less than £30,000. The results show that the use of oral beclometasone dipropionate is not cost effective.

Budget impact

The manufacturer forecasts additional direct costs of £10,113 in year 1, rising to £74,839 in year 5, assuming the treatment of approximately 100 patients in 2005, rising to 760 patients in 2009.

Guidelines and protocols

The British Society of Gastroenterology issued «*Guidelines for the management of inflammatory bowel disease in adults»* in 2004. These recommend the use of prednisolone for patients with active left-sided or extensive ulcerative colitis when either a prompt response is required or for patients with mild to moderate active disease when mesalazine (2-4g daily) has not been successful. In patients with active distal disease, oral prednisolone is recommended for patients failing to improve on a combination of oral mesalazine (2-4g daily) with either topical mesalazine or topical corticosteroids. The guidelines recommend a 40mg daily dose of prednisolone reduced gradually according to severity and patient response. Reductions over 8 weeks are generally considered appropriate, as anything more rapid can be associated with early relapse.

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 ***30 July 2007.***

Drug prices are those available at the time of SMC assessment.

References. Any references shaded grey are additional to those supplied with the submission.

Campieri M, Adamo S, Valpiani D et al. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. Aliment Pharmacol Ther 2003; 17: 1471-1480.

Rizzello F, Gionchetti P, D'Arienzo A et al. Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. Aliment Pharmacol Ther 2002; 16: 1109-1116.

Carter MJ, Lobo AJ, Travis SPL on behalf of the IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004; 53 (Suppl V) v1-v16.