Public Summary Document

Product: Budesonide, foam enema, 2 mg, Budenofalk®
Sponsor: Orphan Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission requested an Unrestricted benefit listing for ulcerative colitis.

2. Background

Budesonide foam enema had not previously been considered by the PBAC

3. Registration Status

Budesonide foam enema was TGA registered on 12 June 2012 for the treatment of active rectal and rectosigmoid disease in ulcerative colitis.

4. Listing Requested and PBAC's View

Unrestricted benefit

5. Clinical Place for the Proposed Therapy

Ulcerative colitis causes chronic inflammation of the large intestine (colon) and rectum, as well as causing ulcers in the lining of the rectum and colon. It is one of a group of diseases called inflammatory bowel disease. About half of patients with ulcerative colitis have symptoms up to 4 stools per day, possibly bloody; with pulse, temperature, haemoglobin concentration and erythrocyte sedimentation rate (ESR) normal. There is no cure, but medications can reduce inflammation and ease the symptoms, sometimes for long periods of remission. The aim of treatment of ulcerative colitis is to induce remission in active disease and to maintain remission and prevent relapse.

The submission proposed that the place in therapy of budesonide is as an alternative treatment option to prednisolone for patients requiring treatment with a topical (locally acting) corticosteroid.

6. Comparator

The submission nominated prednisolone enema 31.25 mg/100 mL (equivalent to 25 mg prednisolone) as the comparator. The submission also presented data for secondary comparators, hydrocortisone foam and mesalazine.

The PBAC agreed that the choice of prednisolone enema was appropriate. The PBAC noted that the PBS-listed dose of prednisolone enema is different to that in the submission, at 20 mg/100 mL.

7. Clinical Trials

The submission presented a primary comparison directly comparing efficacy and safety of budesonide with prednisolone, based on three studies – Danielsson 1987, the Danish Budesonide Study Group (DBSG) 1991 and Lofberg 1994. One safety study, Thomsen 1994 was also presented. The PBAC noted that the clinical trials presented were old and the trial participant numbers were small.

The PBAC noted that the submission also presented two supplementary comparisons comparing budesonide with hydrocortisone (Bar-Meir 2013 and Tarpila 1994) and 5-aminosalicylic acid (Lamers 1991 and Lemann 1995). A comparison between budesonide foam enema and liquid enema [Gross 2006 (BUF-9/UCA)] was also presented in the submission.

The details of the published trials presented in the submission are shown below:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Danielsson 1987	Danielsson A et al. A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis.	*Scandinavian Journal of Gastroenterology* 1987; 22(8): 987-992.
Danish Budesonide Study Group 1991	The Danish Budesonide Study Group (DBSG). Budesonide enema in distal ulcerative colitis. A randomized dose-response trial with prednisolone enema as positive control.	*Scandinavian Journal of Gastroenterology* 1994; 26(12): 1225-1230
Lofberg 1994	Lofberg R et al. Budesonide versus prednisolone retention enemas in active distal ulcerative colitis.	*Alimentary Pharmacology & Therapeutics* 1994; 8(6): 623-629.
Thomsen 1994	Thomsen O et a. A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis.	*European Journal of Gastroenterology & Hepatology* 1994; 6: 507-511.

8. Results of Trials

The submission presented results for endoscopic response/improvement as the key clinical outcome for demonstrating non-inferiority. The submission claimed that 10-15% differences in endoscopic response for absolute difference and 12-20% for relative difference was considered non-inferior in the published literature.

The PBAC recalled that remission was previously accepted as the key patient-relevant outcome when assessing rectal preparations for ulcerative colitis. However, the PBAC noted the sponsor's advice in the Pre-Sub-Committee Response (PSCR) that the term 'disease remission' has been neither defined nor validated and multiple terms are used including "clinical remission", "registration remission", and "complete or deep remission"(Cooney,

Warren et al. 2007). The PSCR further suggested that there were no data linking clinical remission to improvement in long-term health outcomes and that endoscopic response (an improvement of greater than or equal to 1 in score) was more closely linked with improvements in longer term health outcomes, including milder disease and less need for surgery. The PBAC considered this was reasonable.

The PBAC noted the results of the meta-analysis of the Danielsson 1987 and Lofberg 1994 trials for endoscopic response/improvement over 4 weeks. The PBAC agreed that the results of the meta-analysis (RR: 1.15 [95% CI: 0.97, 1.37], RD: 0.11 [95% CI: -0.03, 0.25]) demonstrate budesonide was non-inferior to prednisolone in achieving an endoscopic response.

In terms of endoscopic remission over 4 weeks, PBAC noted that the results for Danielsson 1987 and Lofberg 1994 were divergent and the confidence intervals for the pooled result were very wide (RR: 1.13 [95% CI: 0.35, 3.65], RD: 0.08 [95% CI: -0.30, 0.46]) and exceeded the 10-15% non-inferiority margins. The results did not adequately demonstrate non-inferiority. The PBAC noted that a demonstration of statistical non-inferiority would require a larger sample size.

The PBAC noted the results of the meta-analysis for the secondary comparators. The Committee noted that the results of the endoscopic response were similar between budesonide and hydrocortisone (RR: 1.27 [95% CI: 1.02, 1.57], RD: 0.12 [95% CI: 0.01, 0.23]) but did not demonstrate non-inferiority against 5-aminosalicylic acid (RR: 0.87 [95% CI: 0.73, 1.04], RD: -0.10 [95% CI: -0.23, 0.03]).

In the comparative study of budesonide foam and liquid enema, the submission claimed there was greater patient preference for the foam formulation of budesonide. This was demonstrated with 83% (95% CI: 80, 86) of patients in the Gross 2006 (BUF-9/UCA) trial reporting a preference for the foam. The trial achieved its primary outcome of demonstrating non-inferiority on the basis of 15% non-inferiority margin in the stratified per protocol group. The submission's claim of non-inferior effectiveness between the foam and enema formulations was based only on the results for the per protocol population.

With regards to comparative harms, the PBAC noted that the trials presented in the submission contain limited information on adverse events. Based on the data from the trials, adverse events did not appear to be common with 4-8 week use of budesonide. Budesonide did not appear to have a higher risk of adverse events than the comparator drugs.

The PBAC also noted that the results of a random effects meta-analysis of morning plasma cortisol level over 4 weeks were in favour of budesonide (mean difference: 181.44 [95% CI: 133.71, 229.16]). The submission claimed that reduced cortisol suppression with budesonide was considered to be a key safety benefit.

9. Clinical Claim

The submission described budesonide foam enema as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over prednisolone enema.

The PBAC accepted the submission's claim of non-inferior effectiveness and that endoscopic response was an appropriate clinical outcome. The Committee considered that the evidence presented in the submission supported the claim of non-inferiority of budesonide foam enema compared with prednisolone enema in terms of achieving an endoscopic response. The PBAC agreed that this outcome was more closely linked with improvements in longer term health outcomes including milder disease and less need for surgery.

The PBAC accepted the submission's claim of superior safety in comparison to prednisolone and agreed that the claim was adequately supported.

The PBAC noted the submission's claim of greater patient preference to the foam preparation was adequately supported.

10. Economic Analysis

The submission presented a cost-minimisation analysis comparing budesonide foam enema with prednisolone enema based on the dose observed in the clinical trials, not including any additional costs or cost offsets. The PBAC agreed that a cost minimisation analysis was appropriate for a claim of non-inferiority (equivalence) with prednisolone.

The submission claimed that budesonide 2 mg was equi-effective to prednisolone 31.25 mg (trial dose, equivalent to 25 mg prednisolone). The PBAC noted that the doses of budesonide and prednisolone used in the trials were not entirely consistent with the proposed budesonide and PBS listed prednisolone. The submission did not present any calculation of equi-effective dose despite inconsistencies in doses, however the sponsor's PSCR proposed an equi-effective dose of 20 mg prednisolone with 2 mg budesonide. The PBAC accepted this dose equivalence.

11. Estimated PBS Usage and Financial Implications

The PBAC considered that the submission's estimates of usage were quite low as budesonide was assumed to displace 100% of prednisolone market, and only 10% of the current 5-aminosalycilic acid and hydrocortisone market. The PBAC considered that this was a possible underestimation as it is likely that a higher displacement rate will occur with hydrocortisone because of budesonide's better safety profile.

The submission's estimated net cost of listing of budesonide was less than $10 million per over five years. The PBAC noted that the actual net cost to PBS/RPBS is lower than the submission's estimate using the revised cost-minimisation calculation, and results in a net saving over 5 years of less than $10 million. The small saving was due to the assumed 10% replacement of mesalazine.

The financial implications are to be further verified

12. Recommendation and Reasons

The PBAC recommended listing of budesonide foam enema as an Unrestricted benefit for treatment of ulcerative colitis on a cost-minimisation basis with prednisolone enema. The accepted equi-effective doses are budesonide 2 mg and prednisolone 20 mg.

The PBAC accepted endoscopic response as the patient-relevant primary outcome. The Committee considered that the evidence presented in the submission supported the claim of non-inferiority of budesonide foam enema compared with prednisolone enema in terms of achieving an endoscopic response. The PBAC agreed that this outcome was more closely linked with improvements in longer term health outcomes including milder disease and less need for surgery. The PBAC noted that the evidence presented supported the claim of superiority of budesonide compared with prednisolone in terms of safety (reduced cortisol suppression).

The PBAC therefore accepted the submission's claim of non-inferior effectiveness and superior safety of budesonide foam enema compared with prednisolone enema.

The PBAC considered that the submission's estimates of usage were likely underestimated as it is likely that a higher displacement rate in the hydrocortisone market will occur because of budesonide's better safety profile.

The PBAC advised that, under Section 101 (3BA) of the *National Health Act,* that budesonide enema should be treated as interchangeable on an individual patient basis with prednisolone enema and hydrocortisone enema.

The PBAC considered that budesonide foam enema is suitable for inclusion in the list of medicines for prescribing by nurse practitioners within collaborative arrangements.

Outcome:
Recommended

Recommended Listing

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer	
BUDESONIDE				
Foam enema 2 mg per application each pressurised container sufficient for 14 applications, 2 cans	2	1	Budenofalk	Orphan Australia

Unrestricted benefit

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor had no comment.