5.04 BUDESONIDE, Tablet 9 mg, Cortiment®, Ferring Pharmaceuticals Pty Ltd

1 Purpose of Application

1.1 The submission requested an unrestricted listing for budesonide colonic release tablets (budesonide CR), however the only evidence presented in the submission was for active mild to moderate ulcerative colitis (UC). The TGA approved indication is for "adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient or not tolerated". PBS listed 5-ASA (or 5-aminosalicylic acids) include sulfasalazine, mesalazine, olsalazine and balsalazide.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Mild to moderate ulcerative colitis where 5-ASA treatment is not sufficient or not tolerated
Intervention	Budesonide CR (Cortiment®) 9 mg prolonged-release tablets, daily oral administration
Comparator	Budesonide (Budenofalk®) 2 mg foam enema, daily rectal administration
Outcomes	Remission, mucosal appearance (endoscopy) subscore, and TEAEs
Clinical claim	In patients with mild to moderate active ulcerative colitis, budesonide CR 9 mg is as effective as budesonide 2 mg foam enema at inducing remission and achieving a mucosal appearance (endoscopy) subscore of 0 (UCDAI) or ≤ 1 (mMayo). Budesonide CR is non-inferior to budesonide foam enemas in terms of safety.

Abbreviations: 5-ASA = 5-aminosalicylic acids; CR = colonic release; mMayo = modified Mayo score; TEAEs = treatment emergent adverse events; UCDAI = ulcerative colitis disease activity index score
Source: p2 of the submission

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	Max №.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
CORTIMENT, colonic release oral tablets, 9 mg	30	3	$[redacted]	Ferring Pharmaceuticals Pty Ltd

Category / Program:	General Schedule
Restriction:	Unrestricted

2.1 The ESC noted that the recommended treatment duration in the TGA approved Product Information (PI) is for up to 8 weeks and that the requested 3 repeats would allow for up to 4 months of treatment. The ESC considered that this created a possible Quality Use of Medicines (QUM) issue, where patients may continue treatment beyond 8 weeks. The ESC considered that 1 repeat may be more appropriate. The Pre-PBAC response (p1) suggested providing more than one repeat would allow patients to commence treatment for a second flare immediately rather than waiting for an appointment with a gastroenterologist. The PBAC agreed with

the ESC advice that 1 repeat was more appropriate for this presentation to reduce the possibility of inappropriate treatment beyond 8 weeks.

2.2 The basis for the listing is a cost minimisation analysis against budesonide foam enema via an indirect comparison using placebo as the common comparator.

2.3 Budesonide CR is an orally administered but locally active treatment for UC. It has a delayed release formulation where the active ingredient is not released until the colon (i.e. pH>7). The recommended dosage regimen of budesonide CR is one 9 mg tablet once daily for up to eight weeks.

2.4 The PBAC considered that an unrestricted listing for this form of budesonide was not appropriate as it may result in use before 5-ASAs and use in Crohn's disease.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 Budesonide CR 9 mg was TGA registered on 31 August 2015 for induction of remission in adult patients with mild to moderate active UC where 5-ASA treatment is not sufficient or not tolerated.

3.2 Budesonide CR has not been previously considered by the PBAC.

4 Population and disease

4.1 UC is a condition that causes inflammation and ulceration beginning in the rectum and progressing proximally to involve the colon. Symptoms include bloody diarrhoea, abdominal pain, fever, rectal bleeding, fatigue, anaemia, loss of appetite, weight loss and loss of body fluids and nutrients. Symptoms may occur as intermittent attacks between periods of no symptoms (remission), although 5-10% of patients can experience symptoms all the time. The prevalence of UC in Australia is unknown, but it was estimated in 2013 that 75,000 Australians have inflammatory bowel disease which is a combination of Crohn's disease and UC (PWC report[1]), whilst in 2007 it was estimated there are approximately 33,000 Australians with UC (Access Economics report[2]).

4.2 Budesonide CR is an additional treatment option alongside other locally acting corticosteroids in patients with active mild to moderate UC who have had an inadequate response or are intolerant to 5-aminosalicylates (5-ASAs).

[1] PWC. Improving Inflammatory Bowel Disease care across Australia. March 2013. Available from https://www.crohnsandcolitis.com.au/site/wp-content/uploads/PwC-Report-2013-Executive-Summary.pdf , accessed 4 May 2017

[2] Access Economic. The Economic Costs of Crohn's Diease and Ulcerative Colitis. 9 June 2007 Available from https://www.crohnsandcolitis.com.au/site/wp-content/uploads/Deloitte-Access-Economics-Report.pdf , accessed 4/5/17

4.3 With an unrestricted listing, in clinical practice, there may be some use of budesonide CR as a first line treatment, either in place of or alongside 5–ASA, before the efficacy of 5-ASA can be fully ascertained. This would not concord with current best practice treatment guidelines.

4.4 The PBAC agreed with the Secretariat that a restricted benefit listing would be appropriate for budesonide CR.

5 Comparator

5.1 The submission nominated budesonide foam enema as the main comparator Hydrocortisone foam enema was nominated by the submission as a secondary comparator on the basis of being the most commonly used rectal corticosteroid for UC (10% Medicare sample analysis), however no comparative results of budesonide CR versus hydrocortisone were presented as the submission did not identify any directly or indirectly comparable trials. A course of treatment with hydrocortisone foam enemas is less expensive than with budesonide foam enemas.

5.2 The PBAC considered budesonide foam enema to be the appropriate comparator as it contains the same active ingredient. The PBAC recalled that it had previously considered budesonide foam enemas to have a better safety profile than hydrocortisone foam enemas (PSD July 2013), and therefore considered a comparison versus budesonide foam enemas to be more informative.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from organisations (3), 'Crohn's & Colitis Australia', 'Gastroenterological Society of Australia – Australian Inflammatory Bowel Disease Association', 'Medical & Scientific Committee' and Health Professionals (2) via the Consumer Comments facility on the PBS website. The comments noted support for availability of this drug on the PBS and a hope from patients for an improved quality of life under treatment. The PBAC noted the advice, which included feedback from patients about how patients often find rectal therapies inconvenient or uncomfortable and some patients are unable to retain the enemas long enough for them to be effective, and therefore an alternative orally administered form would be welcomed. The health professionals noted that many of their patients are unable to afford this medication as a private prescription and listing on the PBS would be beneficial.

Clinical trials

6.3 The submission was based on an indirect comparison of three budesonide CR trials (CORE I, CORE II and CONTRIBUTE) with three budesonide foam enema trials (BUCF3001, BUCF3002 and Naganuma 2016), using placebo as common comparator.

6.4 Details of the trials presented in the submission are summarised in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Budesonide CR vs placebo trials		
CORE I	Efficacy and safety of new oral budesonide-MMX® (CB-01-02) 6 mg and 9 mg extended release tablet formulations in patients with mild or moderate, active ulcerative colitis. A multicenter, randomized, double-blind, double dummy, comparative study versus placebo, with an additional reference arm evaluating Asacol® 2400 mg (Clinicaltrials.gov: NCT00679432)	24 November 2011
	Sandborn WJ, Travis S, Moro L, et al. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: Results from the CORE I study.	Gastroenterology 2012; 143(5):1218–1226.
CORE II	Efficacy and safety of oral budesonide-MMX® (CB-01-02) 6 mg and 9 mg extended release tablets in patients with mild or moderate active ulcerative colitis. A multicentre, randomised, double-blind, double-dummy, comparative study versus placebo with an additional reference arm evaluating Entocort®EC (Clinicaltrials.gov: NCT00679380)	24 November 2011
	Travis SP, Danese S, KupcinskasL, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study.	Gut 2014; 63(3):433–441.
CONTRIBUTE	Rubin D, Russell C, William S, et al. O-001 budesonide MMX® 9 mg for inducing remission in patients with mild-to-moderate ulcerative colitis not adequately controlled with oral 5-ASAs.	Inflamm Bowel Dis. 2014; 20(Supplement1):S1
D'Haens 2010	Preliminary efficacy and safety study of a new extended release budesonide 9 mg tablets formulation in patients with moderate left-sided ulcerative colitis. Period I: randomised, double-blind, placebo-controlled, parallel-group, pilot multicentre efficacy study. Period II: open-labelled, pilot multicentre efficacy study.	26 May 2006
	D'Haens GR, Kovács A,Vergauwe P, et al. Clinical trial: preliminary efficacy and safety study of a new budesonide-MMX® 9 mg extended-release tablets in patients with active left-sided ulcerative colitis.	J Crohns Colitis 2010; 4(2):153–160.
budesonide foam enemas vs placebo trials		
BUCF3001 & BUCF3002 (combined publications)	Sandborn WJ, Bosworth B, Zakko S, et al. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis.	Gastroenterology 2015; 148(4):740-750.
Naganuma 2016	Naganuma M, Aoyama N, Suzuki Y, et al. Twice daily budesonide 2-mg foam induces complete mucosal healing in patients with distal ulcerative colitis.	J Crohns Colitis 2016; 828-836
Gross 2006	Gross V, Bar-Meir S, Lavy A, et al. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis.	Aliment Pharmacol Ther. 2005; 23:303-312
Bar-Meir 2003	S. Bar-Meir, H. H. Fidder, M. Faszczyk et al. Budesonide foam vs. hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis.	Diseases of the Colon and Rectum 2003; 46 (7):929-936

Source: p.26-27 of the submission

6.5 Key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration of follow-up	Within trial risk of bias	Patient population	Outcomes
Budesonide CR vs placebo					
CORE I	256	R, DB, 8 weeks	Low	Mild/Moderate UC	Remission^ & Mucosal appearance
CORE II	257	R, DB, 8 weeks	Low	Mild/Moderate UC	
CONTRIBUTE	458	R, DB, 8 weeks	Low	Mild/Moderate UC uncontrolled by 5-ASA	
Budesonide foam enema vs placebo					
Naganuma 2016	109	R, DB, 6 weeks	Low	Mild/Moderate UC	Remission^ & Mucosal appearance
BUCF3001/ BUCF3002 (Sandborn 2015)	165	R, DB, 6 weeks	Low	Mild/Moderate UC	

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised, UC = ulcerative colitis, 5-ASA = 5-aminosalicylic acid

^ Remission was defined differently in the two sets of trials.

Source: compiled during the evaluation

6.6 The dosage regimens used in the budesonide CR trials were consistent with the dosage recommended in budesonide CR's approved PI (i.e., 9 mg once daily for 8 weeks). For the budesonide foam enema trials, while the dosage regimen used in Naganuma 2016 (i.e. 2mg daily for 6 weeks) was consistent with the approved Australian dose of budesonide foam enema of 2mg daily for 6-8 weeks, the dosage used in BUCF3001 and 3002 of 2mg twice daily for 2 weeks then once daily for 4 weeks differed.

6.7 There are a number of differences between the two sets of trials:

- Different scoring algorithms for disease severity: The definition of mild to moderate UC adopted for the inclusion criteria differed both with respect to i) the disease scoring algorithms used (i.e., modified Mayo score (mMAYO) for the budesonide foam trials and the UC disease activity indexes (UCDAI) for the budesonide CR trials), and ii) the cut off values used. However, the UCDAI and the mMAYO score appear to be reasonably similar and capture similar disease domains, although the inter-observer variability in scoring between indices is unknown.
- Anatomical extent of disease: The budesonide CR trials generally permitted enrolment of patients with more extensive anatomical disease covering the full anatomical spectrum of UC (from the large intestine to the rectum), whereas the budesonide foam enema trials were limited to patients with UC affecting the rectum (proctitis) or the rectum and sigmoid colon but not involving the descending colon (proctosigmoiditis). To address this, the submission conducted a post hoc analysis of CORE I and CORE II using results of patients with proctitis or proctosigmoiditis only.
- Prior use of 5-ASA: All patients in CONTRIBUTE have had prior treatment with 5-ASA versus only 50 to 75% of patients enrolled in CORE I and II, BUCF3001 and BUCF3002. 87% of patients in Naganuma 2016 had prior 5-ASA. Patients with prior use of 5-ASA may be more treatment resistant.

- Concomitant 5-ASA: All patients in CONTRIBUTE were taking concomitant 5-ASA, which contrasted with trials CORE I and II where 5-ASA use was not permitted. Approximately 55% of the population enrolled in BUCF3001 and 3002 were taking 5-ASA versus approximately 87% concomitant 5-ASA use in Naganuma (2016).
- Trial duration: efficacy analyses were reported after 8 weeks of treatment for budesonide CR whereas in the budesonide foam enema trials results were reported after 6 weeks of treatment.

6.8 Further, 19/128 (15%) and 40/129 (31%) of patients randomised to the budesonide CR and placebo respectively in CORE II were excluded from its efficacy analyses due mainly to: i) violations in good clinical practice (GCP) at four clinical sites, and ii) the lack of histological evidence of active UC in randomised patients. This is a potential concern as it affects the power of the trial to detect a meaningful difference. Although a post hoc sensitivity analysis conducted by the trial investigators found the trial conclusions to remain reasonably consistent when the excluded patients were reincorporated as non-responders, the exclusion of such a large proportion of patients would significantly reduce the statistical power of the trial and bias the indirect comparison towards the null.

Comparative effectiveness

6.9 The main outcomes relied on by the submission were remission and mucosal appearance or endoscopic scores (which was a sub-score on the disease algorithms). These are relevant outcomes in UC. As well as presenting an analysis comparing the trial based definitions of remission for UC, the submission presented a post-hoc analysis that adjusted the remission definitions of CORE I and CORE II (the only trials which the sponsor has individual patient data) in an attempt to align the definitions with those used in the budesonide foam enema trials. It was argued that the definition for remission used in CORE I and CORE II was more stringent than in the budesonide foam enema trials.

6.10 In a sensitivity analysis for the indirect comparison, the results from Naganuma 2016 were excluded. The submission claimed this was because the definition of remission in this trial was different to that in BUCF3001/BUCF3002. During the evaluation this was not considered an appropriate justification since the trial definition of remission for CORE I, CORE II and CONTRIBUTE were also different to that used in BUCF3001 and BUCF3002. Further, the definition of remission in Naganuma 2016 is likely to be more stringent than the definition in BUCF3001/BUCF3002, with the only difference being measurement in the stool frequency subscore. BUCF3001/BUCF3002 required a stool frequency subscore of an improvement or no change from baseline whilst Naganuma 2016 required a subscore of 0 or an increase of ≥ 1 from baseline.

6.11 In an effort to make the trial populations more consistent with the budesonide foam trials, the submission also conducted a subgroup analysis of the trial results by extent of anatomical involvement as CORE I and II had enrolled patients with more anatomically involved disease compared to the budesonide CR trials (see paragraph 6.7).

6.12 The submission did not nominate a non-inferiority margin for interpretation of the results of the indirect comparison. Instead it argued that statistical non-significance alone should be sufficient to justify a claim of non-inferiority and that non-inferiority margins that may be nominated for head to head non-inferiority trials would be too onerous as the confidence intervals from results of indirect comparisons would be wider. The ESC disagreed noting that an indirect comparison introduces additional error and uncertainty. As stated in Section 2.4.5 of the Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee Version 5.0, "…a lack of statistically significant difference between the proposed medicine and the comparator does not adequately establish non-inferiority" instead, "It is common practice to require that the confidence limits of the difference in treatment effect do not include an a priori stated clinically meaningful difference favouring the comparator".

6.13 In the literature, non-inferiority margins used for risk difference of remission of active disease ranged between 10-15%. This is also consistent with the non-inferiority margin presented in the budesonide foam enema submission (p.3, budesonide foam enema PSD 2013) and was previously accepted by the PBAC.

6.14 The within trial, meta-analysis and indirect comparison results for remission based on the individual trial definitions and the adjusted definitions are summarised in Table 4 and 5 respectively. Results for mucosal appearance (endoscopy subscore) are presented in Table 6. A discussion of the results is presented in the Clinical Claim section below.

6.15 The ESC noted several factors which may impact the exchangeability/transitivity across the budesonide CR and budesonide foam trials. These included differences in the number of patients previously and concomitantly treated with 5-ASAs and the extent of anatomical disease involvement, which limit the reliability of the indirect comparison. The ESC noted the remission rates for the placebo groups of the foam trials were substantially higher than for the placebo groups of the oral trials.

6.16 The PSCR (p3) claimed that the lower percentage of patients who had prior use of 5-ASA in the foam studies biased the analysis against the oral therapy. The ESC noted that when comparing the most closely matched studies for this variable, CONTRIBUTE (oral) and Naganuma 2016 (foam) studies, there were still substantial differences in placebo response rates (7.5% oral vs 20.4% foam).

Table 4: Trial, subgroup, meta-analyses and indirect comparison results for the outcome of remission (based on the individual trial definitions)

Trial ID	Budesonide n/N (%)	Placebo n/N (%)	Relative risk RR (95% CI)	Risk difference RD (95% CI)	Odds ratio OR (95% CI)
Budesonide CR trials Wk 8 results					
CORE I[1]	22/123 (17.9)	9/121 (7.4)	**2.40 (1.15,5.01)**	**0.10 (0.02,0.19)**	**2.71 (1.19,6.16)**
CORE II[1]	19/109 (17.4)	4/89 (4.5)	**3.88 (1.37,10.99)**	**0.13 (0.05,0.21)**	**4.49 (1.47,13.72)**
CONTRIBUTE[2]	30/230 (13.0)	17/228 (7.5)	**1.75 (0.99,3.08)**	**0.06 (0.00,0.11)**	**1.86 (1.00,3.48)**
Meta-analysis	71/462 (15.4)	30/438 (6.8)	**2.19 (1.45,3.31)**	**0.09 (0.04,0.13)**	**2.42 (1.53,3.81)**
CORE I and CORE II subgroup analyses by extent anatomical involvement					
Whole trial[3]	40/230 (17.4)	13/204 (6.4)	**2.73 (1.50,4.96)**	**0.11 (0.05,0.17)**	**3.09 (1.60,5.97)**
Proctosigmoiditis or Distal colitis	32/145 (22.1)	11/144 (7.6)	**2.89 (1.52,5.51)**	**0.14 (0.06,0.22)**	**3.42 (1.65,7.10)**
Extensive UC or pancolitis	8/85 (9.4)	2/60 (3.3)	2.82 (0.62,12.83)	0.06 (-0.02,0.14)	3.01 (0.62,14.72)
Budesonide foam enema trials Wk 6 results					
BUCF3001[4]	51/133 (38.3)	34/132 (25.8)	**1.49 (1.04,2.14)**	**0.13 (0.01,0.24)**	**1.79 (1.06,3.03)**
BUCF3002[4]	59/134 (44.0)	33/147 (22.4)	**1.96 (1.37,2.80)**	**0.22 (0.11,0.32)**	**2.72 (1.62,4.55)**
Naganuma 2016[5]	28/55 (50.9)	11/54 (20.4)	**2.50 (1.39,4.50)**	**0.31 (0.14,0.48)**	**4.05 (1.74,9.46)**
Meta-analysis(all trials)	138/322 (42.9)	78/333 (23.4)	**1.83 (1.41,2.39)**	**0.20 (0.11,0.29)**	**2.49 (1.64,3.78)**
Meta-analysis (excluding Naganuma)	110/267 (41.2)	67/279 (24.0)	**1.71 (1.31,2.24)**	**0.17 (0.08,0.26)**	**2.21 (1.47,3.33)**
Indirect comparisons budesonide CR vs budesonide foam enema					
Using all trial results			1.20 (0.73, 1.95)	**-0.11 (-0.21,-0.01)**	0.97 (0.52,1.80)
excluding the results of Naganuma 2016			1.28 (0.78, 2.10)	-0.08 (-0.18, 0.02)	1.10 (0.59,2.02)
Proctosigmoiditis/distal colitis only			1.58 (0.79, 3.17)	-0.06 (-0.18, 0.06)	1.37 (0.59,3.18)
Proctosigmoiditis/distal colitis only and excluding Naganuma 2016			1.69 (0.84,3.40)	-0.03 (-0.15, 0.09)	1.55 (0.47,5.05)

Abbreviations: CI = confidence interval; CR = colonic release, df = degrees of freedom; n = number of patients with event; N = total number of patients in group

Text in bold indicate statistically significant differences

1 Defined as stool frequency, rectal bleeding, mucosal appearance = 0, physician rating = 0 or 1, endoscopic index score ≥ 1 point reduction from baseline and UCDAI score ≤ 1

2 Defined as stool frequency, rectal bleeding, mucosal appearance = 0, physician rating = 0 or 1 and UCDAI score ≤ 1

3 2 patients in budesonide CR and 6 patients in placebo group did not have anatomical involvement data

4 Defined as stool frequency of improvement or no change, rectal bleeding =0, mucosal appearance ≤ 1 on the mMAYO score

5 Defined as stool frequency = 0 or decrease of ≥ 1 from baseline, rectal bleeding =0, mucosal appearance ≤ 1 on the mMAYO score

Source: Table 2.6-1, p81, Table 2.6-2, p82, Table 2.6-6, p86, Table 2.6-7,p87, Table 2.6-8, p89 Table 2.6-10, p93, Table 2.6-11, p 95 of the submission.

Table 5: Trial, subgroup, meta-analyses and indirect comparison results for the outcome of remission (using adjusted remission definition for CORE I and CORE II trials)

Trial ID	Budesonide CR n/N (%)	Placebo n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)	Odds ratio 95% CI)
Whole trial population					
CORE I	[redacted]				
CORE II					
Meta-analysis					
CORE I and CORE II by extent of anatomical involvement					
Whole trial	[redacted]				
Proctosigmoiditis or Distal colitis					
Extensive or pancolitis					
Budesonide foam enema					
BUCF3001	51/133 (38.3)	34/132 (25.8)	**1.49 (1.04,2.14)**	**0.13 (0.01,0.24)**	**1.79 (1.06,3.03)**
BUCF3002	59/134 (44.0)	33/147 (22.4)	**1.96 (1.37,2.80)**	**0.22 (0.11,0.32)**	**2.72 (1.62,4.55)**
Naganuma 2016	28/55 (50.9)	11/54 (20.4)	**2.50 (1.39,4.50)**	**0.31 (0.14,0.48)**	**4.05 (1.74,9.46)**
Meta-analysis	138/322 (42.9)	78/333 (23.4)	**1.83 (1.41,2.39)**	**0.20 (0.11,0.29)**	**2.49 (1.64,3.78)**
Meta-analysis (excluding Naganuma)	110/267 (41.2)	67/279 (24.0)	**1.71 (1.31,2.24)**	**0.17 (0.08,0.26)**	**2.21 (1.47,3.33)**
Indirect comparisons budesonide CR vs budesonide foam enemas					
budesonide CR (CORE I & II) vs budesonide foam enema (all trials)			[redacted]		
budesonide CR (CORE I & II) vs budesonide foam enema (excluding Naganuma 2016)					
Proctosigmoiditis/distal colitis (CORE I & II) for budesonide CR vs budesonide foam enema (all trials)					
Proctosigmoiditis/distal colitis CORE I & II for budesonide CR vs budesonide foam enema (excluding Naganuma 2016)					

Abbreviations: CI = confidence interval; CR = colonic release, df = degrees of freedom; n = number of patients with event; N = total number of patients in group

Text in bold indicate statistically significant differences

* A post-hoc analysis

\+ A secondary outcome

Source: Table 2.6-3, p83, Table 2.6-6, p86, Table 2.6-7,p87, , Table 2.6-12, p97, Table 2.6-13, p 99, of the submission.

Table 6: Trial, subgroup, meta-analyses and indirect comparison results for the outcome of improvement in mucosal subscores (based on the individual trial definitions of either mucosal appearance subscore = 0 or endoscopy subscore ≤ 1)

Trial ID	Budesonide n/N (%)	Placebo n/N (%)	Relative risk RR (95% CI)	Risk difference RD (95% CI)	Odds ratio OR (95% CI)
Budesonide CR Wk8					
CORE I[1#]	[redacted]				
CORE II[1#]	[redacted]				
CONTRIBUTE[1]	[redacted]				
Meta-analysis	[redacted]				
CORE I and CORE II by extent of anatomical involvement[#]					
Whole trial [1]	[redacted]				
Proctosigmoiditis or Distal colitis[1]	[redacted]				
Extensive or pancolitis [1]	[redacted]				
Budesonide foam enema Wk6					
BUCF3001[2]	74/133 (55.6)	57/132 (43.2)	**1.29 (1.01,1.65)**	**0.12 (0.01,0.24)**	**1.65 (1.02,2.68)**
BUCF3002[2]	75/134 (56.0)	54/147 (36.7)	**1.52 (1.17,1.98)**	**0.19 (0.08,0.31)**	**2.19 (1.36,3.53)**
Naganuma 2016[2]	38/55 (69.1)	25/54 (46.3)	**1.49 (1.07,2.09)**	**0.23 (0.05,0.41)**	**2.59 (1.18,5.67)**
Meta-analysis	187/322 (58.1)	136/333 (40.8)	**1.42 (1.21,1.66)**	**0.17 (0.10,0.25)**	**2.00 (1.46,2.73)**
Indirect comparisons budesonide CR versus budesonide foam enemas					
Using all include trials			[redacted]	[redacted]	[redacted]
budesonide CR vs budesonide foam enema (excluding Naganuma 2016)			[redacted]	[redacted]	[redacted]
Proctosigmoiditis/distal colitis subgroup of CORE I & II vs budesonide foam enema (all trials included)			[redacted]	[redacted]	[redacted]
Proctosigmoiditis/distal colitis subgroup of CORE I & II vs budesonide foam enema (excluding Naganuma 2016)			[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; CR = colonic release, df = degrees of freedom; n = number of patients with event; N = total number of patients in group

Text in bold indicate statistically significant differences

1 defined as UCDAI mucosal appearance subscore = 0

2 defined as mMayo endoscopy subscore ≤ 1

post hoc analysis

Source: Tables 2.6-4 and 2.6.5, p84, Table 2.6-21, p110, Table 2.6-14, p102, Table 2.6-15, p 104 of the submission.

6.17 The ESC noted the non-inferiority margin previously accepted by the PBAC of 10-15% for absolute difference in remission was not met for budesonide CR versus budesonide foam enema. For remission based on the individual trial definitions, an additional 9% of patients treated with budesonide CR compared with placebo achieved remission, whereas with the budesonide foam enema an additional 20% of patients achieved remission. Based on the indirect comparison, the difference in remission rates of 11% between budesonide formulations was statistically significant (95% CI: -0.21, -0.01).

6.18 The ESC noted that the PSCR (p3) proposed a non-inferiority margin for relative differences (eg relative risk (RR)) of 12-20%, based on that proposed in the budesonide foam PBAC submission. The ESC noted that based on risk differences the point estimates from the indirect comparisons favoured the foam formulation whereas based on relative measures the point estimates favoured the oral formulation. This reflected the much lower remission rates in the placebo groups for the oral trials. However, for most of the indirect comparisons the lower 95% confidence interval for the relative risk was less than 0.8 and hence the proposed 20% non-inferiority margin for the relative difference was not met.

6.19 The PBAC noted the ESC advice above, and the pre-PBAC response proposing a non-inferiority margin based on the CORE I, II and CONTRIBUTE studies of [redacted] for endoscopic remission and [redacted] for overall remission. The PBAC did not consider the proposed wider non-inferiority margins to be reasonable, and that the exchangeability issues across the trials limited the reliability of the indirect comparisons.

Comparative harms

6.20 Overall, compared to placebo, treatment with budesonide CR or budesonide foam enema was associated with more adverse events but these events are likely to be mild in nature. The indirect comparison between the two budesonide formulations on comparable outcomes did not find any statistically significant differences with respect to adverse events.

6.21 One adverse event of special interest in the budesonide CR trials was glucocorticoid side effects (such as moon face, striae rubrae, flushing, fluid retention, mood changes, sleep changes, insomnia, acne and hirsuitism) and morning plasma cortisol (as measure of adrenal suppression) given budesonide CR is an oral treatment. This was measured in CORE I and CORE II, and overall, there was no significant difference between budesonide CR and placebo in the incidence of glucorticoid related signs or symptoms however there were significant differences in cortisol levels (mean difference (95% CI): CORE I [redacted] nmol/L ([redacted]) and CORE II: [redacted] nmol/L [redacted]). Nonetheless, the lower morning cortisol levels in patients treated with budesonide CR were still within normal ranges after 8 weeks of treatment with budesonide CR in CORE I and CORE II.

Clinical claim

6.22 The submission claimed that budesonide CR is non-inferior to budesonide foam enema in efficacy and safety. The ESC considered the non-inferiority safety claim to be adequately supported. However, the ESC did not consider the claim of non-inferiority for efficacy was adequately supported because:

- There were significant differences between the trials used in the indirect comparisons that affected exchangeability, including: the extent of anatomical disease (more severe for budesonide CR trials), the use of concomitant 5-ASA (taken concurrently in CONTRIBUTE, not allowed in CORE I and II and permitted in Naganuma 2016, BUCF3001 and 3002), prior use of 5-ASA (100% in CONTRIBUTE versus 50 to 75% in CORE I and II, BUCF3001 and BUCF3002 and 87% in Naganuma 2016) and the timing of trial assessments (Week 8 for budesonide CR and Week 6 for budesonide foam enema trials). Consequently, the placebo response rates differed significantly across the trials, with much higher placebo responses noted for the enema trials (≈23% for budesonide foam enema trials versus ≈7% and [redacted]% for budesonide CR trials when using the trial defined and adjusted definitions of remission and 40% for budesonide enema trials versus [redacted]% for budesonide CR trials for the outcome of mucosal appearance). Such differences reaffirm that the

transitivity may have been violated and hence the results of the indirect comparison may not be reliable.

- A non-inferiority margin was not nominated by the submission. The PBAC has previously considered a non-inferiority margin of 10-15% to be reasonable for absolute difference in remission in UC. If this margin was to be adopted for this submission, then none of the indirect comparison results except for the outcome of trial defined remission when comparing the post hoc results from patients with Proctosigmoiditis/distal colitis CORE I & II for budesonide CR vs budesonide foam enema (excluding Naganuma 2016) would satisfied this criterion, as the lower 95% confidence interval for the indirect comparison results consistently exceeded the 15% margin.
- The submission's conclusion of non-inferiority focused on results expressed in the relative risk (RR) statistic which favoured budesonide CR. Unlike RR, risk differences (RD) generally do not favour budesonide CR, with a significantly lower proportion of patients attaining remission with budesonide CR versus budesonide foam enemas (RD (95%CI): -0.11(-0.21, -0. 01)).
- The ESC noted using a non-inferiority margin of 12-20% for the RR, as proposed in the PSCR (p3), only 1 of the 4 comparisons using the individual trial definitions of remission met this criterion (the post-hoc analysis using only patients with Proctosigmoiditis/distal colitis and excluding Naganuma 2016, indirect RR=1.69, 95% CI 0.84,3. 40). With the adjusted remission definition for the CORE I and CORE II trials none of the comparisons met this criterion.
- For the subgroup of patients with extensive UC or pancolitis, the results of the subgroup analysis of CORE I and CORE II trials also did not find any significant differences in remission between budesonide CR and placebo treated patients, however the size of the subgroup is likely to be under powered to detect any statistically significant differences.

6.23 The ESC considered that an alternate conclusion to the proposed clinical claim might be, there is insufficient evidence to support that budesonide CR is non-inferior to budesonide foam enema in terms of remission and mucosal appearance (or endoscopic sub-score) in patients with mild to moderate active UC based on a non-inferiority margin of 15% for the risk difference or 20% for the relative risk.

6.24 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.25 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.26 The submission presented a cost minimisation analysis of budesonide CR against budesonide foam enema. The ESC noted that this would only be appropriate if the PBAC considers that budesonide CR is non-inferior in efficacy to budesonide foam.

6.27 The equi-effective doses were estimated to be budesonide CR 9 mg orally once daily for 8 weeks versus budesonide foam enema 2 mg/25mL administered rectally once daily for 8 weeks. While the dosage for budesonide CR was based on the clinical trial doses, the dose regimen assumed for budesonide foam enema was based on the maximum dose recommended in its PI, which differed to the dosage used in the clinical trials. The number of doses recommended in the PI was 56 doses over 8 weeks compared to 56 doses over 6 weeks in BUCF3001 and BUCF3002 and 42 doses over 6 weeks in Naganuma 2016.

6.28 A comparison of budesonide CR with budesonide foam enema is presented in Table 7.

Table 7: Comparison of cost of budesonide CR and budesonide foam enema

Drug	Max quantity	Dosage[1]	DPMQ	Cost/daily dose	Cost/course
Budesonide CR	30	1 daily up to 8 weeks	$[redacted]	$[redacted]	$[redacted][a]
Budesonide Foam 2 mg/20mL	28 applications	1 daily 6-8 weeks	$188.11	$6.72	$282.17-$376.22

Abbreviations: CR=colonic release

[1] Doasage as per PI.

[a] Based on [redacted] tablets whereas [redacted] packs would be [redacted] tablets at a cost of $[redacted].

Source: Constructed during evaluation using information in the submission, PBS schedule online and relevant product information

6.29 The ESC noted that budesonide CR is priced lower than the foam due to the assumed different treatment durations (56 days versus 42 days respectively).

6.30 The PBAC considered that the cost minimisation approach presented in the submission was not informative as non-inferiority of budesonide CR to budesonide foam enema was not adequately supported by the clinical data presented.

Drug cost/patient/8 week course: $[redacted]

6.31 The cost per course was based on the DPMQ for 56 doses over 8 weeks of treatment. For [redacted] packs of [redacted] tablets the cost per 2 months of treatment is $[redacted]. Comparatively, the cost for two boxes of budesonide foam enema, sufficient for 56 doses over 8 weeks, is $[redacted]. The requested maximum and number of repeats would provide up to four (16 week) courses of budesonide CR. The PBAC considered one repeat providing up to two (8 week) courses would be more appropriate in any recommended listing.

Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC. A market share approach was used by the submission for the financial estimates. The submission assumed that the introduction of budesonide CR would not grow the market and any market growth will be based on usage patterns of existing rectal corticosteroids. This assumption may not be appropriate, it is possible that budesonide CR will additionally grow the UC market since it is the first orally delivered but locally active corticosteroid for UC. Patients who may have been reluctant to use rectal treatments may be more willing to start treatment with an oral agent.

6.33 The submission conducted a review of a 10% Medicare sample to determine how many scripts for rectal corticosteroids are being used for UC compared to other conditions. The methods used are likely to have overestimated the use of rectal corticosteroids for UC. However, different values were used in the estimate presented and the reasons for this deviation were not explained. A sensitivity analysis using the values obtained from the 10% Medicare sample analysis was conducted during evaluation.

6.34 Table 8 summarises the financial estimates presented by the submission.

Table 8: Summary of financial impact and change in prescription numbers for listing budesonide CR

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Projected Total PBS/RPBS prescriptions for ulcerative colitis (no budesonide CR)						
Budesonide foam enema						
Hydrocortisone foam enema						
Prednisolone liquid enema						
Total						
Budesonide CR uptake/substitution from existing therapy						
Budesonide foam enema						
Hydrocortisone foam enema						
Prednisolone liquid enema						
Budesonide CR						
Cost to PBS and RPBS (net copayments)						
Budesonide foam enema	-$	-$	-$	-$	-$	-$
Hydrocortisone foam enema	-$	-$	-$	-$	-$	-$
Prednisolone liquid enema	-$	-$	-$	-$	-$	-$
Total cost offsets	-$	-$	-$	-$	-$	-$
Budesonide CR	$	$	$	$	$	$
Net financial impact PBS/RPBS	$	$	-$	-$	-$	-$
MBS changes	$0	$0	$0			
Net financial impact	$	$	-$	-$	-$	-$

Source: table 4.2-1, p129, table 4.2-4, p131, tables 4.2-7 and 4.3-1, p133, table 4.3-4, p135, table 4.4-1, p136 and 4.5-2, p137 of the submission.

6.35 The redacted table above shows that at year 6 the estimated number of patients was 10,000 – 20,000 and the net savings to the PBS would be less than $10 million.

6.36 The submission assumed that one budesonide CR script will replace one budesonide foam enema/hydrocortisone foam enema or one prednisolone liquid enema script. This is inappropriate given the differences in recommended treatment regimens, particularly treatment duration (1-2 doses daily for 2-3 weeks (1-2 scripts) for hydrocortisone foam enema, 1 dose daily for 2-4 weeks (1 script) for prednisolone liquid enema and 1 tablet daily for 8 weeks for budesonide CR (2 scripts)). The ESC agreed that the different dosing durations had not been appropriately accounted for in the proposed financial estimates. The PBAC noted the pre-PBAC response (p3), which stated that prednisolone enema treatment may continue after the initial 2-4 weeks and therefore 2 scripts is "not unreasonable". The PBAC did not accept this claim and noted the wording of the prednisolone enema PI on dosing that "use of one enema nightly on retiring for two to four weeks, treatment may be continued in patients showing progressive improvement but it should not be persisted with if the response has been inadequate."

6.37 Sensitivity analyses using the proportion of patients using rectal corticosteroids for UC from the 10% Medicare sample analysis and altering the substitution of prednisolone liquid enema to account for a shorter treatment duration (assume that 2 scripts of budesonide CR per 8 week course will substitute for 1 script of prednisolone liquid for a 4 week course to be consistent with the PIs) is presented in Table 9. The PBAC noted that this had the effect of switching the estimated financial implication to the government from a net saving to a net cost due to an increase in the cost of budesonide CR.

Table 9: Sensitivity analysis around financial estimates of net cost to government

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case (88%, 73%, 69%)[1]	$[redacted]	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Using 10% sample proportions for patients with ulcerative colitis (88%, 67%, 70%)[1]	$[redacted]	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Base case (1:1 budesonide CR:prednisolone enema)	$[redacted]	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Assume 2:1 budesonide CR:prednisolone enema	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[1] Proportion reported for assumed budesonide foam enema, hydrocortisone foam enema and prednisolone liquid enema use for ulcerative colitis respectively

Source: Constructed during evaluation

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of budesonide colonic release (CR) tablets on the PBS for the treatment of ulcerative colitis as the clinical data did not support a claim of non-inferior effectiveness against budesonide foam enemas.

7.2 The PBAC considered that an unrestricted listing would not be appropriate for the CR oral form of budesonide as patients are required to be treated after a 5-ASA or be intolerant to a 5-ASA and an unrestricted PBS listing may result in use before 5-ASAs and use in Crohn's disease. A Restricted Benefit listing for mild to moderate UC in patients for whom 5-ASA is not sufficient or tolerated, would be more appropriate.

7.3 The PBAC considered that budesonide foam enema was the most appropriate comparator for the CR tablets as they contain the same active ingredient and budesonide foam enema has a better safety profile than hydrocortisone foam enema.

7.4 The PBAC considered the indirect comparison between budesonide CR tablet and budesonide foam enema was unreliable. The PBAC noted the transitivity issues between the clinical trials used in the indirect comparison, including the extent of anatomical disease, the use of concomitant 5-ASA and the timing of trial assessment. There were different placebo response rates across the trials and the conclusion of non-inferiority varied depending on whether an absolute or a relative measure for outcomes was used. These issues reduced the reliability of the indirect comparison.

7.5 The PBAC recalled that it had previously considered a non-inferiority margin of 10-15% to be reasonable for absolute difference in remission in ulcerative colitis. The indirect comparison did not meet this non-inferiority margin. The PBAC noted the pre-PBAC response (pp1-2) argued that this non-inferiority margin is based on power calculations for head-to-head comparisons and instead proposed a clinically meaningful non-inferiority margin as a proxy for a MCID use the method described by Massacesi[3]. This resulted in non-inferiority margins based on the CORE I, II and CONTRIBUTE studies of [redacted] and [redacted] for endoscopic remission and overall remission respectively. However, PBAC considered this did not resolve the exchangeability issues as demonstrated by the different placebo rates of remission.

7.6 The PBAC did not accept that budesonide CR was non-inferior to budesonide foam enemas for efficacy as it was not supported by the data.

7.7 The PBAC considered that non-inferiority for comparative safety was reasonable.

7.8 The PBAC considered that due to the lack of non-inferiority to the foam enema form the cost minimisation approach and financial implications presented in the submission were uninformative.

7.9 The PBAC noted that this submission may be eligible for an Independent Review because it is for a new form of a PBS listed drug.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Ferring is disappointed that the PBAC decided not to recommend CORTIMENT® (budesonide) for the treatment of active ulcerative colitis. Patient bodies and HCPs have indicated that there is a clinical need for additional (orally delivered) therapies, such as CORTIMENT, that have demonstrated to be effective and well tolerated. Ferring will therefore continue to work with the PBAC to ensure that Australian patients with active ulcerative colitis have access to CORTIMENT.

[3] 1 http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154161.pdf