

## 5.04 BUDESONIDE, Capsule (modified release) 3 mg, Entocort®, Emerge Health

### 1 Purpose of application

- 1.1 Authority Required (streamlined) listing for budesonide controlled ileal release capsules (budesonide from herein) for treatment of mild to moderate Crohn's disease (CD) affecting the ileum and/or the ascending colon. This is the first submission by Emerge Health for budesonide in this indication.
- 1.2 The requested basis for listing was a cost-utility analysis for budesonide compared with mesalazine.

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

Component	Description
Population	Adult patients with mild to moderate CD affecting the ileum and/or the ascending colon
Intervention	Budesonide (9 mg/day orally for 12 weeks, inclusive of 2-4 week dose tapering period)
Comparator	Mesalazine high dose 4 g/day orally
Outcomes	Remission (CDAI $\leq$ 150) and adverse events
Clinical claim	In patients with mild to moderate CD, budesonide is more effective than mesalazine at inducing remission, with less adverse events

Abbreviations: CD=Crohn's disease; CDAI=Crohn's Disease Activity Index  
Source: Table 10, p3 of the submission

### 2 Requested listing

- 2.1 The requested restriction is provided below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
<b>BUDESONIDE</b> Controlled ileal release capsules, 3 mg	90	2	\$ [REDACTED]	<b>ENTOCORT®</b> Emerge Health

<b>Category/Program</b>	Section 85 (general schedule)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	N/A
<b>Severity:</b>	Mild to moderate <del>Crohn's disease</del>
<b>Condition:</b>	<del>Mild to moderate</del> Crohn disease
<b>PBS Indication:</b>	Mild to moderate Crohn's disease <del>affecting the ileum and/or the ascending colon</del>
<b>Treatment phase:</b> <i>e.g. initial/continuing</i>	<del>Initial treatment for active</del> Crohn's disease

<b>Restriction:</b> <i>Section 85</i>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by a gastroenterologist
<b>Clinical criteria:</b>	<ul style="list-style-type: none"> <li>• <i>The condition must affect the ileum</i></li> <li>OR</li> <li>• <i>The condition must affect the ascending colon</i></li> <li>OR</li> <li>• <i>The condition must affect the ileum and ascending colon</i></li> <li>• <del>Patient must have mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon</del></li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Patient must have had a documented hypersensitivity reaction to a sulphonamide</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Patient must be intolerant to sulfasalazine</li> </ul>
<b>Population criteria:</b>	<ul style="list-style-type: none"> <li>• Patient must not have systemic or local bacterial, fungal or viral infections</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Patients must not have hypersensitivity to any of the ingredients</li> </ul>
<b>Foreword</b>	N/A
<b>Definitions</b>	N/A
<b>Prescriber Instructions</b>	<ul style="list-style-type: none"> <li>• When treatment with Entocort<sup>®</sup> capsules <del>this drug</del> is to be discontinued, the dose should be tapered from 9 mg <i>daily</i> to 0 mg daily over the last 2 to 4 weeks of therapy and not stopped abruptly</li> <li>• The total duration of therapy should be no more than 12 weeks in any single course</li> </ul>
<b>Administrative Advice</b>	None
<b>Cautions</b>	N/A
<b>Note</b>	<i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i>

2.2 Budesonide is a modified release formulation of budesonide and contains acid-stable 1 mm microgranules composed of an inner sugar core surrounded by a layer of budesonide in ethylcellulose (budesonide ECM™ layer) and an outer coating that dissolves at pH ≥ 5.5. The recommended dose of budesonide is 9 mg once daily. When treatment with budesonide is to be discontinued, the approved product information (PI) recommends dose tapering over the last 2 to 4 weeks of therapy, with the total duration of therapy not exceeding 12 weeks in any single course.

- 2.3 In Australia, the cost of budesonide (Entocort®) on the private market is \$202.69 per 90 capsules<sup>1</sup>. The PBAC noted that this is significantly lower than the price requested. The ESC noted that consumers report a large degree of variation in the private market price of budesonide with many paying more than \$202.69.
- 2.4 It was noted that another brand of enteric release budesonide capsules (Budenofalk®) is also marketed for CD in Australia as a private prescription medicine. Budenofalk® 3 mg capsules also deliver budesonide to the ileum and the ascending colon (i.e., same part of gastrointestinal tract (GIT) as Entocort®). The submission argued that this formulation would not be directly comparable to Entocort® given its release is triggered at a slightly higher pH (6.4 versus 5.5). Although the two products may not be bioequivalent, Budenofalk® would be a direct competitor for Entocort®. The private prescription price for 90 x 3mg capsules of Budenofalk® is \$132.99<sup>2</sup>.

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

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<sup>1</sup> Chemist Warehouse prices online, 2017, available from: <http://www.chemistwarehouse.com.au/buy/20266/Entocort-3mg-Capsules-90>, accessed 11 August 2017.

<sup>2</sup> Chemist Warehouse prices online, 2017, available from <http://www.chemistwarehouse.com.au/search?searchtext=budenofalk&searchmode=allwords>, accessed 14 August 2017.

### 3 Background

#### Registration status

- 3.1 TGA status at time of PBAC consideration: Budesonide was TGA registered in January 1998 for induction of remission in adult patients with mild to moderate CD affecting the ileum and/or the ascending colon. It is noted that in Australia, budesonide is not registered for use in maintenance of remission. It is registered for maintenance therapy in some countries (e.g., USA, Canada), but due to the risk of glucocorticoid side effects associated with prolonged use, guidelines do not recommend budesonide be used in this manner<sup>3,4</sup>.

### 4 Population and disease

- 4.1 CD is a chronic relapsing inflammatory condition of the GIT. Patients with mild to moderate disease of the ileum generally present with abdominal pain, weight loss, diarrhoea, and malabsorption. Patients with disease of the colon may present with symptoms similar to those with severe ulcerative colitis with structural disease obstructions. Patients suffer from chronic, intermittent symptoms. Patients are commonly diagnosed during adolescence, with peak manifestations between 20-24 years of age.

The submission proposed the place of therapy for budesonide is in mild to moderate CD, with budesonide replacing mesalazine. The PBAC considered that although it is likely budesonide will be used in first or second line treatment of mild to moderate CD, it is unlikely to displace mesalazine (see discussion in Comparator). The PBAC noted that based on the submission's clinician survey and Australian and international treatment guidelines examined during the evaluation, there is heterogeneity in clinician preference with respect to the use of aminosalicylates (5-ASA) drugs (i.e., sulfasalazine and mesalazine) in CD. Due to recent evidence indicating the poor efficacy of 5-ASAs in CD (Lim 2016 Cochrane review), some clinicians do not use 5-ASAs in clinical practice. However, some clinicians still try 5-ASAs first since they are generally well tolerated and may have some chemoprotective effects. The Pre-Sub-Committee Response (PSCR) (p1) argued that mesalazine is approved for use in CD and cited the Australian Guidelines for General Practitioners and Physicians for Inflammatory Bowel Disease (IBD), third edition 2013 (Andrews 2013) that recommend mesalazine. The PBAC noted that the Andrews 2013 guideline is due to be updated in 2017 and that 5-ASAs were not recommended by recent Australian guidelines (eTG July 2017 edition) while prednisolone (or a similar oral corticosteroid) and budesonide were.

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

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<sup>3</sup> Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J, Bloom S, IBD Section of the British Society of Gastroenterology, Guidelines for the management of inflammatory bowel disease in adults., Gut. 2011;60(5):571.

<sup>4</sup> Hanauer SB, Sandborn W, Practice Parameters Committee of the American College of Gastroenterology, Management of Crohn's disease in adults. Am J Gastroenterol. 2001;96(3):635.

## 5 Comparator

- 5.1 The submission nominated high dose mesalazine ( $\geq 4$  g/day) as the comparator, assuming all clinicians currently use 5-ASAs in first line therapy, trying sulfasalazine first, and progressing to mesalazine if intolerant (as per its PBS listing) or due to poor response (not PBS listed for this use). It was then assumed if budesonide is to be listed on the PBS it will be tried after sulfasalazine but before mesalazine.
- 5.2 The PBAC considered the submission's assumptions are not consistent with likely clinical practice. The PBAC noted that recent evidence suggests limited efficacy of 5-ASAs in CD (Lim 2016 Cochrane review) and that they were not recommended in recent Australian guidelines (eTG July 2017 edition) while prednisolone (or a similar oral corticosteroid) and budesonide were.
- 5.3 The PBAC also considered it is unlikely that budesonide will be used after sulfasalazine (but before mesalazine), since mesalazine (the active ingredient of sulfasalazine) is generally used in patients who are intolerant to sulfasalazine but would add little value if patients had already switched to budesonide from sulfasalazine due to poor efficacy. The PBAC noted that for patients who respond to sulfasalazine but have a tolerability issue, it is likely they would switch to mesalazine rather than budesonide (since they appeared to respond to this drug class).
- 5.4 The PBAC considered that within each class of drugs (i.e., 5-ASAs or corticosteroids), given the current PBS restrictions, it is likely patients will trial sulfasalazine then mesalazine, and prednisolone then private budesonide if there are tolerability issues. If budesonide is to be listed on the PBS as proposed, it is likely budesonide will be used before prednisolone since it has a better safety profile.
- 5.5 The pre-PBAC response (p1) acknowledged the complexity of CD treatment and the heterogeneity across available guidelines (Andrews 2013 vs eTG guidelines) and clinician preferences with respect to the use of 5-ASAs and oral corticosteroids. The pre-PBAC response (p1) concedes that budesonide will likely partly replace prednisolone in clinical practice but argues this would be in addition to mesalazine and hence it is not appropriate to disregard mesalazine as a relevant comparator altogether. However, the PBAC agreed with the ESC that, based on the likely clinical treatment algorithms and similar pharmacological action of budesonide and prednisolone, for most patients, the therapy most likely to be replaced by budesonide will be prednisolone (or similar oral systemic corticosteroid). Given some patients are also currently accessing budesonide (Entocort®) or Budenofalk® on the private market, a PBS listing of Entocort® will also likely replace private purchases of Entocort® and Budenofalk®.

*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 individuals (46), health care professionals (10) and organisations (1) 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 they have found this medicine beneficial for their condition with fewer side effects than oral corticosteroids. The health care professionals noted that many of their patients are unable to afford this medicine as a private prescription and listing on the PBS would be beneficial.
- 6.3 The PBAC noted advice received from Crohn's and Colitis Australia clarifying the likely use of budesonide in clinical practice. The PBAC specifically noted the advice that budesonide is recommended by professional representative bodies. The PBAC noted advice that the limited efficacy of 5-ASA agents in CD and the lack of subsidised topically acting oral corticosteroids means that most patients with mild to moderate CD in Australia receive systemic corticosteroids. These agents cause significant short and long term toxicity. The PBAC noted that this advice was supportive of the evidence provided in this submission.

### **Clinical trials**

- 6.4 The PBAC noted the submission was primarily based on one head-to-head trial comparing budesonide to mesalazine (Thomsen 1998). The submission also presented one trial comparing Budenofalk® to mesalazine (Tromm 2011) as supplementary evidence, and three trials comparing budesonide to placebo (Greenberg 1994; Tremaine 2002; Suzuki 2013) as secondary evidence. During the course of the evaluation, data were additionally extracted from two trials of budesonide versus prednisolone (Rutgeerts 1994; Campieri 1997). Details of the included trials are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Budesonide versus mesalazine</b>		
Thomsen 1998	CSR: 08-3027. Entocort® capsules (budesonide) versus oral SR Pentasa® (mesalazine), a controlled multicentre trial in patients with active Crohn's disease. Thomsen OO, Cortot A, Jewell D, et al. A comparison of budesonide and mesalamine for active Crohn's disease. Thomsen OO, Cortot A, Jewell D, et al. Budesonide and mesalazine in active Crohn's disease: A comparison of the effects on quality of life.	20 January 1998.  New England Journal of Medicine 1998; 339(6): 370–374.  American Journal of Gastroenterology 2002; 97(3): 649-653.
<b>Budesonide (Budenofalk® formulation) versus mesalazine</b>		
Tromm 2011	Tromm A, Bunganic I, Tomsova E, et al. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease.	Gastroenterology 2011; 140(2): 425-434.
<b>Budesonide versus placebo</b>		
Greenberg 1994	CSR: Study 08-3001. Oral budesonide in Crohn's disease. A dose finding placebo-controlled study. Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide for active Crohn's disease.	5 April 1994.  New England Journal of Medicine 1994; 331(13): 836-841.
Tremaine 2002	CSR: Study 08-3025. Budesonide controlled ileal release capsules once or twice daily in active Crohn's disease. A placebo-controlled study. Tremaine WJ, Hanauer SB, Katz S, et al. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: A randomized placebo-controlled study in the United States.	9 October 1998.  American Journal of Gastroenterology 2002; 97(7): 1748-1754.
Suzuki 2013	CSR: Study D9421C00002. A multicentre, double-blind, randomised, parallel-group, phase II study to assess efficacy and safety of D9421-C 9 mg and 15 mg versus placebo in Japanese patients with active Crohn's disease. Suzuki Y, Motoya S, Takazoe M, et al. Efficacy and tolerability of oral budesonide in Japanese patients with active Crohn's disease: A multicentre, double-blind, randomized, parallel-group phase II study.	8 October 2008.  Journal of Crohn's and Colitis 2013; 7(3): 239-347.
<b>Budesonide versus prednisolone</b>		
Rutgeerts 1994	Rutgeerts P, Lofberg R, Malchow H, et al. A comparison of budesonide with prednisolone for active Crohn's disease.	New England Journal of Medicine 1994; 331(13): 842-845.
Campieri 1997	Campieri M, Ferguson A, Doe W, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease.	Gut 1997; 41: 209-214.

Source: Table 20, pp25-27 of the submission

6.5 The key features of the randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome	Use in modelled evaluation	
<b>Budesonide versus mesalazine</b>							
Thomsen 1998 (primary trial versus mesalazine)	182	R, DB, MC, 16 weeks	Low	CDAI 200-400	Remission	Benefit in remission rates	
Tromm 2011 (Budenofalk® vs mesalazine)	309	R, DB, MC, 8 weeks	Low	CDAI 200-400	Remission	Not used	
<b>Budesonide versus placebo</b>							
Greenberg 1994	258	R, DB, MC, 8 weeks <sup>a</sup>	Low	CDAI $\geq$ 200	Remission	Not used	
Tremaine 2002	200	R, DB, MC, 8 weeks <sup>a</sup>	Low	CDAI 200-450			
Suzuki 2013	77	R, DB, MC, 8 weeks <sup>a</sup>	Low	CDAI $\geq$ 200; Japanese pts			
Meta-analysis	535	The evaluation pooled Tremaine 2002 and Suzuki 2013 (budesonide once daily dosing regimen), and Greenberg 1994 (budesonide twice daily dosing regimen)					
<b>Budesonide versus prednisolone</b>							
Rutgeerts 1994	176	R, DB, MC, 10 weeks <sup>b</sup>	Low	CDAI $\geq$ 200	Remission	Not used	
Campieri 1997	178	R, DB, MC, 12 weeks <sup>c</sup>	Low				
Meta-analysis	354	Included Rutgeerts 1994 and Campieri 1997					

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; R=randomised.

Source: compiled during the evaluation from trial publications.

<sup>a</sup> This 8-week duration excludes budesonide dose tapering after 8 weeks.

<sup>b</sup> The 10-week trial of Rutgeerts 1994 included the last 2 weeks of budesonide at a lower dose (dose tapering)

<sup>c</sup> The 12-week trial of Campieri 1997 included the last 4 weeks of budesonide at lower doses (dose tapering).

6.6 The total daily dose of budesonide administered in the included trials was mostly 9 mg per day, which is consistent with its PI. In terms of dosing frequency, it was noted that while most trials had administered budesonide as a once daily dose, in Greenberg 1994 the daily dose of budesonide (9 mg) was administered over two divided doses. Tremaine 2002 and Campieri 1997 also included separate trial arms where total daily dose of budesonide (9 mg) was administered in single or twice daily doses. In Tromm 2011, budesonide (Budenofalk®) was given either once or three times daily, thus permitting a comparison across the dosing regimens.

6.7 In Thomsen 1998, patients randomised to budesonide were treated with 9 mg/day for a total of 16 weeks. This does not match the dosing recommendations in the PI which is for a maximum treatment duration of 12 weeks, with dose tapering in the last 2-4 weeks of treatment. The submission (p107) acknowledged this difference and as a result it was proposed that the modelled economic evaluation should be based on the dosage recommendations in the PI. The PBAC considered that there are issues with this approach and it favoured budesonide in the modelled economic evaluation (See “Economic Analysis”).

### **Comparative effectiveness**

- 6.8 The clinically relevant outcome in CD is disease remission defined as a Crohn's Disease Activity Index (CDAI) score  $\leq 150$ . This was the primary outcome in all included trials and was relied upon by the submission for its clinical claim and the modelled economic evaluation. The results for remission after 8 weeks of treatment were compared across the included trials (including meta-analyses) and are summarised in Table 4.
- 6.9 The PBAC noted that the submission reasonably argued that the results of Thomsen 1998 trial (Entocort<sup>®</sup>) and Tromm 2011 (Budenofalk<sup>®</sup>) versus mesalazine should not be pooled, mainly because the trials had used different formulations of budesonide and mesalazine and also different dosages of mesalazine, with Tromm 2011 administering a higher daily dose (4.5 g/day versus 4 g/day in Thomsen 1998).
- 6.10 The submission however did pool results from the three included placebo controlled trials of budesonide (Greenberg 1994, Tremaine 2002 and Suzuki 2013). The budesonide dosing frequency had varied across the trials and this had an effect on the results of the analysis. Hence, Table 4 also splits the results of the meta-analyses by budesonide dosing frequency in the trials.

**Table 4: Results of remission rate at 8 weeks (including meta-analyses) across the trials**

Trial ID	Budesonide n/N (%)	Comparator n/N (%)	Budesonide versus comparator		
			RR (95% CI)	RD (95% CI)	OR (95% CI)
<b>Budesonide 9mg/d versus mesalazine</b>					
<b>- Budesonide given once daily</b>					
Thomsen 1998 (Entocort®)	63/93 (67.7)	37/89 (41.6)	<b>1.63 (1.23, 2.16)</b>	<b>0.26 (0.12, 0.40)</b>	<b>2.95 (1.61, 5.41)</b>
Tromm 2011 <sup>c</sup> (Budenofalk®)	51/76 (67.1)	95/153 (62.1)	1.08 (0.88, 1.32)	0.05 (-0.08, 0.18)	1.25 (0.70, 2.22)
<b>- Budesonide given TID<sup>b</sup></b>					
Tromm 2011 <sup>c</sup> (Budenofalk®)	56/78 (71.8)	95/153 (62.1)	1.16 (0.96, 1.39)	0.10 (-0.03, 0.22)	1.55 (0.86, 2.81)
<b>Budesonide 9 mg/day<sup>a</sup> versus placebo</b>					
<b>- Budesonide given once daily (Entocort®)</b>					
Tremaine 2002	37/80 (46.3)	13/41 (31.7)	1.46 (0.88, 2.42)	0.15 (-0.03, 0.32)	1.85 (0.84, 4.09)
Suzuki 2013	6/26 (23.1)	3/26 (11.5)	2.00 (0.56, 7.16)	0.12 (-0.09, 0.32)	2.30 (0.51, 10.41)
Meta-analysis	43/106 (40.6)	16/67 (23.9)	1.52 (0.95, 2.44)	0.13 (0.00, 0.27)	1.94 (0.96, 3.91)
<b>- Budesonide given BD<sup>b</sup> (Entocort®)</b>					
Greenberg 1994 <sup>a</sup>	31/61 (50.8)	13/66 (19.7)	<b>2.58 (1.49, 4.45)</b>	<b>0.31 (0.15, 0.47)</b>	<b>4.21 (1.92, 9.26)</b>
Tremaine 2002	41/79 (51.9)	13/41 (31.7)	<b>1.64 (1.00, 2.69)</b>	<b>0.20 (0.02, 0.38)</b>	<b>2.32 (1.05, 5.13)</b>
Meta-analysis	72/140 (51.4)	26/107 (24.3)	<b>2.03 (1.30, 3.16)</b>	<b>0.26 (0.14, 0.38)</b>	<b>3.13 (1.75, 5.61)</b>
<b>- Submission's approach in pooling all three placebo-controlled trials</b>					
Greenberg 1994 <sup>a</sup>	31/61 (50.8)	13/66 (19.7)	<b>2.58 (1.49, 4.45)</b>	<b>0.31 (0.15, 0.47)</b>	<b>4.21 (1.92, 9.26)</b>
Tremaine 2002	37/80 (46.3)	13/41 (31.7)	1.46 (0.88, 2.42)	0.15 (-0.03, 0.32)	1.85 (0.84, 4.09)
Suzuki 2013	6/26 (23.1)	3/26 (11.5)	2.00 (0.56, 7.16)	0.12 (-0.09, 0.32)	2.30 (0.51, 10.41)
Meta-analysis	74/167 (44.3)	29/133 (21.8)	<b>1.92 (1.30, 2.83)</b>	<b>0.20 (0.08, 0.33)</b>	<b>2.73 (1.58, 4.72)</b>
<b>Budesonide 9 mg versus prednisolone</b>					
<b>- Budesonide given once daily</b>					
Rutgeerts 1994	46/88 (52.3)	57/88 (64.8)	0.81 (0.63, 1.04)	-0.13 (-0.27, 0.02)	0.60 (0.33, 1.09)
Campieri 1997	35/58 (60.3)	35/58 (60.3)	1.00 (0.74, 1.34)	0.00 (-0.18, 0.18)	1.00 (0.48, 2.10)
Meta-analysis	81/146 (55.5)	92/146 (63.0)	0.89 (0.72, 1.09)	-0.07 (-0.19, 0.05)	0.74 (0.45, 1.21)
<b>- Budesonide given BD<sup>b</sup></b>					
Campieri 1997	26/61 (42.6)	35/58 (60.3)	0.71 (0.49, 1.01)	-0.18 (-0.35, 0.00)	0.49 (0.24, 1.01)

Source: Tables 46-48, 52, pp78-81, 96 of the submission; p843 of Rutgeerts (1994); p211 of Campieri (1997).

Abbreviations: CI = confidence interval; n = number of participants with event; N = total participants in group, RR=relative risk, RD=risk difference, OR=odds ratio, BD=twice daily, TID=three times daily

<sup>a</sup> The budesonide dose of 9 mg per day was administered twice daily in Greenberg 1994.

<sup>b</sup> Not TGA-approved dosing frequency.

<sup>c</sup> p=0.001 for noninferiority of budesonide versus mesalazine. Mesalazine dose in Tromm 2011 was higher than Thomsen 1998 at 4.5g/day.

### Budesonide versus mesalazine

6.11 The PBAC noted that statistically significantly more patients treated with budesonide (Entocort®) achieved remission at Week 8 compared to mesalazine in Thomsen 1998; RD (95% CI): 0.26 (0.12, 0.40). The PBAC noted that Tromm 2011, however, found no significant differences in remission between budesonide (Budenofalk®) at 9 mg total daily dose versus mesalazine 4.5 g/day; RD (95% CI): 0.05 (-0.08, 0.18). The lower 95% CI was also within the trial's pre-specified non-inferiority margin of -10%, indicating the two treatments to be non-inferior.

6.12 The pre-PBAC response (p2) reiterates the PSCR (p2) argument that the differences in the outcomes reported by Thomsen 1998 and Tromm 2011 may be attributable to differences related to the formulation and dose of agents evaluated in the trials. The pre-PBAC response (p2) further argues the results from Thomsen 1998 are most pertinent to the submission as the trial examined the exact formulation of budesonide for which PBS listing is sought. However, the PBAC noted that as acknowledged by the submission (p11), recent meta-analyses indicate mesalazine to be of limited efficacy for induction of remission in CD, particularly at lower doses.

Overall, the PBAC considered the claim of superior effectiveness versus mesalazine to be uncertain.

#### Budesonide versus placebo

- 6.13 The submission's meta-analyses of budesonide versus placebo had pooled results from all budesonide treatment arms (irrespective of dosing frequency). The pooled results showed a significant difference between budesonide and placebo in terms of remission at Week 8; RD (95% CI): 0.20 (0.08, 0.33). The PBAC noted that this conclusion changed when these were disaggregated and instead pooled based on dosing frequency of budesonide
- 6.14 Using the TGA-approved dosing frequency of budesonide 9 mg/day administered once daily, the results of all placebo-controlled trials did not find any significant differences in remission rates at Week 8 between budesonide and placebo; RD (95% CI): 0.13 (0.00, 0.27). In trials that used twice daily dosing regimens of budesonide at the same total daily dose of 9 mg (Greenberg 1994 and Tremaine 2002) there were however significantly more patients treated with budesonide twice daily dosing that achieved remission at Week 8 compared to placebo RD (95% CI): 0.26 (0.14, 0.38).
- 6.15 The PSCR (p3) argued it is reasonable to pool results from these trials as undertaken in the submission's meta-analysis as all have at least one budesonide arm in which a daily dose of 9 mg was administered and it was only these arms from each trial that were selected for pooling in the meta-analysis. In addition, the PSCR (p3) argued that a similar approach to that used in the submission's meta-analysis was used in a recent Cochrane review (Rezaie 2015), and the conclusion was that after 8 weeks of treatment, 9 mg budesonide was significantly more effective than placebo for induction of clinical remission of CD (RR 1.93, 95% CI 1.37 to 2.73).

#### Budesonide versus prednisolone

- 6.16 The PBAC noted that after 8 weeks of treatment, although the trials did not find any significant differences between budesonide and prednisolone treated patients in remission rates, the results favoured prednisolone, with more patients treated with prednisolone attaining remission in each trial. The pooled meta-analysis for the once daily budesonide versus prednisolone estimated a risk difference (RD) (95% CI): -0.07 (-0.19, 0.05). For the comparison of the twice daily dosing of budesonide versus prednisolone in Campieri 1997, the difference was also nearing statistical significance, with 42.6% and 60.3% of patients treated with budesonide and prednisolone respectively attaining remission, RD (95% CI): -0.18 (-0.35, 0.00). The lower 95% CIs indicate that budesonide could potentially be up to 19% or 35% less effective than prednisolone in induction of remission (depending on dosing regimen).

### **Comparative harms**

#### Budesonide versus mesalazine

- 6.17 The PBAC noted that in Thomsen 1998, there were no significant differences between budesonide and mesalazine treated patients in adverse events (AEs), serious AEs, and patients discontinuing due to AEs. However, the proportions of patients with severe AEs and discontinuation due to lack of efficacy and AEs were significantly lower in

those treated with budesonide compared to mesalazine (RD (95% CI): -0.12 (-0.23, -0.01) and -0.25(-0.38, -0.13), respectively). The PBAC considered that on balance the claim of superior safety versus mesalazine was supported.

#### Budesonide versus prednisolone

- 6.18 The PBAC noted that in the trials of budesonide versus prednisolone (Rutgeerts 1994, Campieri 1997), a lower proportion of patients treated with budesonide experienced corticosteroid-associated AEs compared to prednisolone patients. In Rutgeert 1994, patients treated with budesonide experienced significantly fewer total corticoid related AEs, including significant differences in the incidence of moon face, acne and swollen ankles. For Campieri 1997, although the rate of corticosteroid related AEs were lower in budesonide treated patients, the difference was not statistically significant, except for the incidence of moon face. The PBAC considered that the reductions in AEs demonstrated may be particularly advantageous in certain patient groups such as those with diabetes or low bone density.
- 6.19 Plasma cortisol response as a physiological measure of systemic glucocorticoid effect beyond the GIT was also studied in both Rutgeerts 1994 and Campieri 1997. The results suggest that adrenal suppression was greater during treatment with prednisolone than budesonide.
- 6.20 The effect of treatment on blood glucose control was also reported in Rutgeerts 1994. The study found a greater effect of prednisolone on blood glucose levels compared to budesonide: during the 10 week treatment period, mean fasting blood glucose concentration was increased significantly from 4.6 to 5.4 mmol per litre in the prednisolone group versus 4.5 to 4.6 mmol per litre in the budesonide group ( $p < 0.001$ ).

#### **Benefits and harms**

- 6.21 The PBAC considered that prednisolone (or a similar oral corticosteroid) is a more appropriate comparator for budesonide than mesalazine. A summary of the comparative benefits and harms for budesonide versus prednisolone is presented in the table below.

Table 5: Summary of comparative benefits and harms for budesonide and comparator

<b>Benefits: Remission at Week 8</b>						
Trials	Budesonide	Comparator	RR(95% CI)	Events/100 patients*		RD(95% CI)
				Budesonide	Comparator	
<b>BUDESONIDE VERSUS PREDNISOLONE</b>						
Rutgeerts 1994	46/88	57/88	0.81 (0.63, 1.04)	52.3	64.8	-0.13 (-0.27, 0.02)
Campieri 1997	35/88	35/88	1.00 (0.74, 1.34)	60.3	60.3	0.00 (-0.18, 0.18)
<b>Harms</b>						
Trials	Budesonide	Comparator	RR (95% CI)	Events/100 patients*		RD (95% CI)
				Budesonide	Comparator	
<b>BUDESONIDE VERSUS PREDNISOLONE</b>						
<b>Proportion of patients with corticosteroid-related AEs</b>						
Rutgeerts 1994	29/88	48/88	<b>0.60 (0.42, 0.86)</b>	33.0	54.5	<b>-0.22 (-0.36, -0.07)</b>
Campieri 1997	29/58	34/58	0.85 (0.61, 1.19)	50.0	58.6	-0.09 (-0.27, 0.09)

\* Maximum duration of exposure: Rutgeerts 1994 = 10 weeks; Campieri 1997 = 12 weeks.

Abbreviations: RD = risk difference; RR = risk ratio

Source: Compiled during the evaluation.

6.22 On the basis of direct evidence presented by the submission, over 10-12 weeks treatment duration, for every 100 patients treated with budesonide (9 mg/day) in comparison to prednisolone (40 mg/day initially with dose tapering from week 3):

- It is unlikely that any additional patients will attain disease remission; but
- Approximately 22 fewer patients will experience corticosteroid related AEs (indicated by Rutgeerts 1994 trial).

### **Interpretation of clinical evidence**

6.23 The submission claimed budesonide 9 mg once daily to be superior to mesalazine 4g/day in terms of effectiveness and safety. The PBAC considered that mesalazine as the nominated comparator was inappropriate based on current clinical practice. Prednisolone (or a similar oral corticosteroid) is considered by the PBAC as a more appropriate comparator for budesonide.

6.24 The PBAC noted that based on evidence from the two trials of budesonide versus prednisolone examined during the evaluation (Rutgeerts 1994, Campieri 1997), budesonide 9 mg administered once daily was not statistically significantly different from prednisolone 40 mg/day over 8 weeks in induction of CD remission, but the results did favour prednisolone; RD (95% CI): -0.07 (-0.19, 0.05). The lower 95% CI (-0.19) was also outside of the nominated non-inferiority margin of -10% from Tromm 2011. The PBAC noted that in terms of safety, the trial evidence suggests budesonide to be superior to prednisolone, particularly in terms of glucocorticoid associated AEs.

### **Economic analysis**

#### **Cost-utility analysis versus mesalazine**

6.25 The submission presented a stepped economic evaluation versus mesalazine, based on results of Thomsen 1998 and implementing a modelled evaluation. The type of economic evaluation presented was a cost-utility analysis. Table 6 summarises the key components of the economic evaluation. The PBAC considered that the modelled

economic evaluation versus mesalazine was uninformative for decision making as prednisolone (or a similar oral corticosteroid) was a more appropriate comparator. The PBAC noted an indicative cost-minimisation analysis versus prednisolone was conducted during the evaluation (see Cost-minimisation analysis versus prednisolone).

**Table 6: Summary of model structure and rationale**

Component	Summary
Time horizon	8 and 12 weeks in the model base case versus 16 weeks in primary trial (Thomsen 1998). The model therefore did not extrapolate beyond the trial evidence and was limited to costs and consequences associated with one episode of CD flare up only.
Outcomes	Remission; quality-adjusted life years.
Costs	The only costs considered in the model were drug costs for mesalazine and budesonide.
Methods used to generate results	Decision tree model. The model transition probabilities derived from Thomsen 1998. The model structure is considered simplistic, illustrating the outcomes of treatment limited to a single episode of CD flare up.
Health states	Remission (CDAI $\leq$ 150); Active CD (CDAI $>$ 150). Patients started in the "Active CD" health state and can only achieve remission at Weeks 2, 4 and 8 (i.e. matching data points from Thomsen 1998). Patients could also move back to the "Active CD" health state given the trial data used.
Utilities	Sourced from Gregor 1997 in the literature. 0.92 for remission and 0.81 for active CD.
Cycle length	2 weeks up to Week 4; then 4 weeks (patients can move between health states at Weeks 2, 4, 8, 12) The ESC noted that the model assumed that transitions began at each 2-week cycle and hence allowed more time to be spent in remission. The ESC considered that this approach favours budesonide.
Transition probabilities	Informed by the proportions of patients in remission at Weeks 2, 4 and 8 (Thomsen 1998).

Source: Attachment 13 of the submission: Entocort economic model.

6.26 The submission presented (i) an 8-week analysis (ii) a 12-week analysis with dose tapering for budesonide and (iii) a 12-week analysis with no dose tapering. Key drivers of the model are presented in Table 7. The PBAC noted the results were very sensitive to the assumed remission rates for both treatments and drug costs.

**Table 7: Key drivers of the model**

Description	Method/Value	Impact
Remission rates	Taken from primary trial (Thomsen 1998). This contrasted with results of Tromm 2011 which showed no significant difference between budesonide (Budenofalk®) and mesalazine 4.5 g/day. Comparative efficacy between budesonide and mesalazine appeared to be highly dose dependent (see Interpretation of Clinical Evidence).	High, favours budesonide
Cost of mesalazine	Base case used the weighted average cost, weighted by current PBS utilisations of each formulation/brand of mesalazine. Cost offsets associated with Mesasal® was the greatest, however, it is unlikely Mesasal® will be the most substituted since its PI does not recommend doses above 1.5 g/day.	High, favours budesonide
Cost of budesonide	70.5% of the model's estimated savings for budesonide (versus mesalazine) came from the reduced treatment costs in the 4 week dose tapering phase (halving treatment costs). If clinicians should opt for a shorter 2 week dose tapering duration, then this would significantly increase cost of budesonide therapy.	High, favours budesonide

Source: compiled during the evaluation based on the results of Attachment 13 of the submission: Entocort economic model.

6.27 Table 8 summarises the results of the stepped economic evaluation.

**Table 8: Results of the stepped economic evaluation**

Step and component	Budesonide	Mesalazine	Increment
<b>Step 1: trial-based costs<sup>a</sup> and outcomes over 8 weeks<sup>b</sup></b>			
Costs	████████	████████	████████
Proportion of period in remission	34.0%	26.8%	7.2%
Incremental cost/extra % of 8-week period in remission			Dominant
<b>Step 2: trial-based costs<sup>a</sup> and outcomes over 12 weeks<sup>b</sup></b>			
Costs	████████	████████	████████
Proportion of period in remission	45.2%	31.9%	13.3%
Incremental cost/extra % of 12-week period in remission			Dominant
<b>Step 3: include dose tapering for budesonide</b>			
Costs	████████	████████	████████
Proportion of period in remission	45.2%	31.9%	13.3%
Incremental cost/extra % of 12-week period in remission			Dominant
<b>Step 4: trial evidence transformed to QALYs (12-week analysis)</b>			
Costs	████████	████████	████████
QALY	0.1984	0.1950	0.0034
Incremental cost/QALY gained			Dominant

Source: Derived from Attachment 13 of the submission: Entocort economic model, with adjustments as below.

<sup>a</sup> DPMQs have been used.

<sup>b</sup> Adjusted for movement to remission health state at end of period.

6.28 The submission's analysis estimated that budesonide treatment will dominate mesalazine for induction of remission in mild to moderate CD. This was driven both by the large cost offsets for mesalazine and the assumed superior efficacy of budesonide versus mesalazine. As discussed in paragraph 6.11, the results of Tromm 2011 instead suggested budesonide to be non-inferior to mesalazine 4.5 g/day, if there was no difference in efficacy between budesonide and mesalazine then the only impact would be a cost saving of -\$████████ with budesonide based on the submission's estimates.

6.29 The submission included univariate and multivariate sensitivity analysis and additional analyses were conducted during the evaluation. The results were sensitive to the assumed costs for mesalazine, varying dramatically across different brands of mesalazine in both the 8-week and 12-week analyses without dose tapering. In the 8-week analysis, assuming a 25% reduction in remission rate for budesonide and assuming budesonide will only replace the least costly formulation/brand of mesalazine, then mesalazine was less costly than budesonide but with more QALYs, i.e. dominated by mesalazine. The model was also sensitive to the assumption of a 4-week budesonide dose tapering phase; this assumption greatly reduced the costs associated with budesonide treatment (contributing to 70.4% of the estimated cost savings versus mesalazine). The PI also recommends dose tapering over 2 weeks, which will increase the costs associated with budesonide.

### Cost-minimisation analysis versus prednisolone

6.30 The PBAC noted that a cost-minimisation analysis was conducted versus prednisolone during the evaluation to illustrate the uncertain cost effectiveness of budesonide at its requested price. The analysis should be considered indicative only, since the clinical results discussed in paragraph 6.16 indicate that budesonide might be inferior to prednisolone for induction of remission at week 8 (remission rates were not statistically significantly different between the two treatments, but the results favoured prednisolone with the lower 95% CI -0.19 exceeding the non-inferiority

margin of 10% used in Tromm 2011). The PBAC noted a cost-minimisation analysis is also not able to take into account the costs and consequence of the superior safety profile of budesonide compared with prednisolone. The PBAC considered that, as outlined in paragraph 6.18, the reduction in AEs demonstrated in trials of budesonide versus prednisolone may be particularly advantageous in certain patient groups which may allow offsets against the higher price of budesonide.

- 6.31 The treatment doses compared for budesonide and prednisolone, over a 12-week course were estimated from the trial doses, and consisted of: budesonide 9 mg/day for 8 weeks, then tapered to 6 mg/day for 2 weeks then 3 mg/day for 2 weeks versus prednisolone 40 mg/day for 2 weeks then tapered to 30 mg/day after 2 weeks and then continuously reducing each week by 5 mg per week until reaching 5 mg/day after 9 weeks, patients then stayed on this dose for 3 weeks.
- 6.32 The estimated cost of budesonide versus prednisolone over a 12-week treatment period for a CD flare up is summarised in Table 9. The analysis estimated cost for prednisolone assuming leftover tablets dispensed in a pack for prednisolone will be discarded (with wastage) or will be used for a later flare up (without wastage). AEMP prices were used in the cost comparisons.

**Table 9: Cost of budesonide versus prednisolone over 12 weeks (based on AEMPs)**

Resource item	Pack size	Max Qty.	DPMQ	AEMP	Source (PBS item no)	AEMP per tablet / capsule	No. tablets / capsules per 12 weeks	No. packs per 12 weeks	Cost per 12 weeks
<b>With wastage (assumed leftover tablets dispensed in a pack for prednisolone will be discarded)</b>									
Prednisolone 25 mg tablets	30	1	\$15.37	\$3.98	1916W	\$0.13	42	2	\$7.96
Prednisolone 5 mg tablet	60	1	\$14.09	\$2.79	1917X	\$0.05	140	3	\$8.37
Total cost of prednisolone (with wastage)									<b>\$16.33</b>
Budesonide 3 mg capsules	90	1	████████	████████ <sup>a</sup>	Proposed	████████	210	3	████████
<b>Without wastage (assuming leftover tablets dispensed for prednisolone will get re-used at another flare up)</b>									
Prednisolone 25 mg tablets	30	1	\$15.37	\$3.98	1916W	\$0.13	42	1.4	\$5.57
Prednisolone 5 mg tablet	60	1	\$14.09	\$2.79	1917X	\$0.05	140	2.3	\$6.51
Total cost of prednisolone (with no wastage)									<b>\$12.08</b>
Budesonide 3 mg capsules	90	1	████████	████████ <sup>a</sup>	Proposed	████████	210	2.3	████████

Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = Dispensed price maximum quantity, Max Qty. = maximum quantity. Source: compiled during the evaluation based on PBS prices and trial dosages  
 a The PB11 form states that the AEMP is \$████████, this corresponds to DPMQ of \$████████.

- 6.33 The PBAC noted that the results of the cost-minimisation analysis illustrate that the cost of budesonide at the proposed AEMP price is much higher than the cost of prednisolone, i.e., cost of \$16.33 for prednisolone versus \$████████ for budesonide over 12 weeks of treatment, assuming wastage (i.e. leftover tablets from supply will be discarded rather than used for a later flare up). The cost of budesonide based on the current requested price is therefore at least ██████ times higher than the cost of prednisolone. The AEMP for budesonide would need to be reduced to at least \$████████ to be close to the cost of treatment with prednisolone (assuming wastage). Even if the costs of managing AEs are factored in, it is unlikely that budesonide would be cost effective against prednisolone at the proposed price.

### **Drug cost/patient/course**

- 6.34 The estimated cost for budesonide was \$████████ based on DPMQ, assuming a total duration of 12 weeks (inclusive of a 4-week dose tapering period at an average dose of

4.5 mg/day). Compared with \$957.22 (based on DPMQ) for mesalazine over 12 weeks at an assumed dose of 4 g/day. The evaluation noted this is a weighted average cost across PBS listed mesalazine preparations weighted by their utilisations. The cost of mesalazine is likely to be less than what was estimated in the submission. Mesasal®, the most expensive PBS listed preparation, is unlikely to be substituted as its PI does not recommend doses above 1.5 g/day.

### Estimated PBS usage & financial implications

6.35 This submission was not considered by DUSC. The submission used an epidemiological approach with the number of patients with CD estimated from prevalence and incidence estimates from Australian studies. As the incidence of new cases of CD is small relative to prevalent cases, prevalent cases are considered sufficient for estimation of the eligible population in this case, and this was adjusted during the evaluation.

Table 10: Estimated use and financial implications

	2017 Year 1	2018 Year 2	2019 Year 3	2020 Year 4	2021 Year 5	2022 Year 6
<b>Estimated extent of use</b>						
Number of patients treated <sup>b</sup>						
Number of units (packs) dispensed <sup>a</sup>						
<b>Estimated financial implications of budesonide</b>						
Cost to PBS/RPBS <sup>c</sup>						
Copayments						
Cost to PBS/RPBS less copayments						
<b>Estimated financial implications for mesalazine</b>						
Cost to PBS/RPBS <sup>d</sup>						
Copayments						
Cost to PBS/RPBS less copayments <sup>e</sup>						
<b>Net financial implications</b>						
Net cost to PBS/RPBS						
Net cost to MBS						
Net cost to PBS/RPBS/MBS						

<sup>a</sup> Assuming 7 units (packs) per year as estimated by the submission; based on assumption of 3 episodes per year and dosage of 9mg/day during the first 8 weeks and 4.5mg/day for the next 4 weeks.

<sup>b</sup> Using only prevalence; incidence was excluded.

<sup>c</sup> Assumed DPMQ of \$ [redacted] calculated from the quoted ex-man price in the PB11 form.

<sup>d</sup> Assuming 3 episodes per year and mesalazine dosage of 4 g/day for a duration of 12 weeks per episode.

<sup>e</sup> Revised numbers by correcting an error, i.e., subtracting co-payment costs for mesalazine from total cost of mesalazine, instead of effectively adding co-payment costs for mesalazine onto the total cost of mesalazine as done in the submission.

Source: constructed during the evaluation based on Excel file Entocort Financial Table Workbook

6.36 At year 6, the estimated number of patients was less than 10,000 per year and the net saving to the PBS would be less than \$10 million. The net savings to the PBS over the 6 year period was estimated to be less than \$10 million.

6.37 Critically, the submission's estimates assumed budesonide will only replace mesalazine. The PBAC considered this was unreasonable as budesonide is more likely to replace oral prednisolone (or a similar oral corticosteroid) if it is listed on the PBS as requested. This has significant impact on the financial estimates. Instead of net savings, it is very likely that listing of budesonide will lead to significant net costs to the PBS. Cost offsets associated with displacing prednisolone would be negligible compared to the large cost offsets assumed for mesalazine by the submission. The

net cost to the PBS for the first 6 years of listing would be approximately \$30 – \$60 million rather than the estimated cost saving of approximately less than \$10 million .

*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 capsule (modified release) 3 mg for treatment of mild to moderate CD affecting the ileum and/or the ascending colon on the basis that the nominated comparator was not appropriate, and that cost-effectiveness against the appropriate comparator had not been established.
- 7.2 The PBAC noted the submission proposed the place of therapy of budesonide is in mild to moderate CD. The PBAC agreed with the submission that budesonide is likely to be used in first or second line treatment of mild to moderate CD. However, the PBAC considered the submissions assumption that 5-ASAs will be used first, with budesonide tried after sulfasalazine but before mesalazine, unlikely to reflect current clinical practice.
- 7.3 The PBAC noted that 5-ASAs such as mesalazine were previously used in CD and in 2013 were included in Australian guideline recommendations. However, the PBAC noted that the 2013 guideline is due to be updated in 2017. The PBAC also noted that evidence on lack of efficacy of 5-ASAs in CD had emerged in recent years (Lim 2016 Cochrane review) and that they were not recommended by recent Australian guidelines (eTG July 2017 edition) while oral corticosteroids and budesonide were. The PBAC considered that while the survey of five gastroenterologists presented in the submission indicates some use of 5-ASAs may continue, the recommendations of current Australian guidelines (eTG July 2017 edition) are more likely to reflect contemporary clinical practice.
- 7.4 The PBAC considered that mesalazine as the nominated comparator was inappropriate based on current clinical practice. Prednisolone (or a similar oral corticosteroid) is considered by the PBAC as a more appropriate comparator for budesonide as it is the treatment most likely to be replaced in practice.
- 7.5 The PBAC considered that in terms of efficacy budesonide may be slightly inferior to prednisolone but that in terms of safety, the trial evidence suggests budesonide to be superior to prednisolone, particularly in terms of glucocorticoid associated AEs.
- 7.6 A cost-minimisation analysis versus prednisolone was conducted during the evaluation. The PBAC considered the results of this analysis highlighted the substantial price difference between budesonide and prednisolone but noted that offsets related to the superior safety profile of budesonide compared with prednisolone were unable to be factored into such an analysis.
- 7.7 The PBAC considered it was unreasonable for the submissions financial estimates to assume budesonide would only replace mesalazine as it is more likely to replace prednisolone (or a similar oral corticosteroid). The PBAC concluded that at the proposed price, a budesonide listing would likely be associated with a significant cost to the PBS rather than the cost saving estimated in the submission.

- 7.8 The PBAC proposed that any future submission would need to clearly establish the place in therapy for budesonide based on contemporary guidelines and clinical practice. The PBAC considered that prednisolone would be an appropriate comparator in such a submission as this is the treatment most likely to be replaced in clinical practice.
- 7.9 The PBAC noted that this submission is eligible for an Independent Review.

**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**

The sponsor had no comment.