

7.11 BUDESONIDE

Capsule (modified release) 3 mg, Entocort[®], Emerge Health Pty Ltd

1 Purpose of Application

- 1.1 The minor resubmission sought an Authority Required (STREAMLINED) listing for budesonide controlled ileal release capsules (budesonide from herein) for the treatment of mild to moderate Crohn's disease (CD) affecting the ileum and/or the ascending colon. In November 2017, the PBAC did not recommend the listing of budesonide for this indication on the basis that mesalazine as the nominated comparator was inappropriate based on current clinical practice (paragraph 7.1 and 7.4, budesonide Public Summary Document (PSD), November 2017). The minor resubmission proposed a mixed comparator (mesalazine and prednisolone).

2 Requested listing

- 2.1 The minor resubmission requested the following new listing based on advice provided by the PBAC at the November 2017 meeting.
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
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BUDESONIDE Oral, 3 mg modified release capsule	90	2	\$ [REDACTED]	Entocort® Emerge Health
Category/Program	Section 85 (general schedule)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Severity:	Mild to moderate			
Condition:	Crohn's disease			
PBS Indication:	Mild to moderate Crohn's disease			
Restriction:	<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			
Treatment criteria:	Must be treated by a gastroenterologist			
Clinical criteria:	The condition must affect the ileum, OR The condition must affect the ascending colon, OR The condition must affect the ileum and ascending colon.			
Population criteria:	Patient must not have systemic or local bacterial, fungal or viral infections AND Patients must not have hypersensitivity to any of the ingredients			
Prescriber Instructions	When treatment with this drug 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. The total duration of therapy should be no more than 12 weeks in any single course.			
Administrative Advice	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.			

- 2.3 The minor resubmission proposed 'must be treated by a gastroenterologist' as the treatment criteria. The PBAC noted that the restrictions for mesalazine and prednisolone do not include this criterion and considered that it should be removed from the proposed budesonide restriction.
- 2.4 The PBAC noted that the proposed population criteria could also apply to all other oral corticosteroid preparations but are not currently included in the restrictions for these medicines. The PBAC considered the proposed population criteria could be removed. In addition, the PBAC considered the proposed prescriber instruction stating 'When treatment with this drug is to be discontinued, the dose should be tapered from 9 mg daily to 0 mg daily over the last 2 to 4 weeks of therapy and not stopped abruptly' is not required to administer the listing and could be removed.

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

3 Background

- 3.1 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^{1,2}.
- 3.2 Budesonide in this presentation was previously considered by the PBAC at its November 2017 meeting.
- 3.3 The PBAC did not recommend the listing of budesonide on the basis that mesalazine as the nominated comparator was inappropriate based on current clinical practice. Prednisolone (or a similar oral corticosteroid) was considered by the PBAC as a more appropriate comparator for budesonide as it is the treatment most likely to be replaced in practice. The PBAC considered that the cost-effectiveness against an appropriate comparator had not been established (paragraph 7.1 and 7.4, budesonide PSD, November 2017).
- 3.4 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 (paragraph 7.8, budesonide PSD, November 2017).

4 Population and disease

- 4.1 The PBAC in November 2017 noted that the submission proposed the place of therapy of budesonide to be 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 aminosalicylates (5-ASAs, i.e. sulfasalazine and mesalazine) will be used first, with budesonide tried after sulfasalazine but before mesalazine, unlikely to reflect current clinical practice (paragraph 7.2, budesonide PSD, November 2017).
- 4.2 At that time, the PBAC noted that 5-ASAs such as mesalazine were previously used in CD and in 2013 were included in Australian guideline recommendations. 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

¹ 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.

² 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.

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 (paragraph 7.3, budesonide PSD, November 2017).

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

5 Comparator

- 5.1 The minor resubmission nominated both mesalazine and prednisolone as comparators. The November 2017 submission nominated mesalazine as the sole comparator.
- 5.2 The minor resubmission provided an updated version of the Gastroenterological Society of Australia (GESA) guidelines (2017). The resubmission stated (p23) that recommendations of 5-ASA use in CD had been retained in the newly-published 2017 GESA guidelines. The 2017 GESA guidelines focus on inflammatory bowel disease (IBD), of which CD and ulcerative colitis (UC) are the two most common forms. With respect to 5-ASAs, the guidelines state “These agents are more useful in UC than CD, and are the mainstay of maintaining remission in UC. This first-line therapy is typically also used to treat mild-to-moderate symptoms of active colonic IBD.... These agents are more effective for colonic (as opposed to small bowel) disease. While they do relieve acute symptoms in mild to moderate colitis, their main use is for long-term maintenance of remission.” The PBAC noted that the 2017 GESA guidelines state topically acting, oral steroids such as budesonide are helpful for mild ileal or ileocolonic CD and are associated with less reduction in bone mineral density and other systemic adverse events (AEs) than prednisolone.
- 5.3 The minor resubmission also provided an updated version of the eTG guidelines (updated in March 2018). The 2018 eTG guidelines state “In contrast to UC, 5-ASAs and rectal therapy have a limited role in CD.” The PBAC noted that the eTG guidelines emphasised the role of corticosteroids in induction therapy for mild to moderate CD. The PBAC also noted the eTG guidelines recommended that consideration be given to using budesonide for ileocaecal disease, particularly for patients with a history of AEs to systemic corticosteroids or precautions to their use (e.g. diabetes).
- 5.4 The pre-PBAC response argued that while the 2017 GESA guidelines do state that 5-ASAs are “more useful in UC than CD”, they do not exclude the use of 5-ASAs in CD nor do they recommend against the use of 5-ASAs in CD. Similarly, the pre-PBAC response argued the 2018 eTG guidelines suggest that there is some use of 5-ASAs in CD.
- 5.5 The PBAC recalled that in its previous consideration of budesonide (November 2017) it had considered that mesalazine as the nominated comparator was not

appropriate. At that time, the PBAC considered prednisolone a more appropriate comparator for budesonide.

- 5.6 The PBAC maintained the view that a comparison wholly against mesalazine was not appropriate. However, the PBAC agreed with the pre-PBAC response that contemporary Australian guidelines acknowledge a role for 5-ASAs such as mesalazine in CD. Moreover, the PBAC considered that there was a subset of patients who would be treated with mesalazine instead of prednisolone as the AE profile of the latter would prohibit a trial or ongoing use in clinical practice. The PBAC therefore accepted the nomination of a mixed comparator (mesalazine and prednisolone).

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 as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from one individual via the Consumer Comments facility on the PBS website. The comment described the side effects experienced when taking prednisolone (including weight gain, skin atrophy, insomnia and steroid-induced diabetes) and how fewer side effects were experienced when the individual was switched to budesonide. The comment also reported that a shorter taper period was required for budesonide compared to prednisolone.
- 6.3 The PBAC recalled that input from 46 individuals, 10 health care professionals and 1 organisation was received via the Consumer Comments facility on the PBS website for the November 2017 budesonide submission. The PBAC specifically recalled the advice received from Crohn's and Colitis Australia 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 which can cause significant short and long term toxicity (paragraphs 6.2 and 6.3, budesonide PSD, November 2017).

Clinical trials

- 6.4 As a minor submission, no new clinical trials were presented in the resubmission.
- 6.5 The minor resubmission relied on the previously submitted and evaluated trials consisting of: one head-to-head trial comparing budesonide to mesalazine (Thomsen 1998); one trial comparing Budenofalk® to mesalazine (Tromm 2011); three trials comparing budesonide to placebo (Greenberg 1994; Tremaine 2002; Suzuki 2013);

and data additionally extracted from two trials of budesonide versus prednisolone (Rutgeerts 1994; Campieri 1997) during the evaluation.

- 6.6 The basis of the minor resubmission's request was a change to a mixed comparator based on the current Australian clinical guidelines. The PBAC accepted the nomination of a mixed comparator (mesalazine and prednisolone) subject to changes in the proportion of patients in each comparator group presented in the minor resubmission.

Clinical claim

- 6.7 The minor resubmission claimed that there is clinical evidence that budesonide is superior to mesalazine in terms of inducing clinical remission in adult patients with mild to moderate CD affecting the ileum and/ascending colon and there is strong clinical evidence that budesonide is superior to mesalazine in terms of safety.
- 6.8 In November 2017, the PBAC noted that statistically significantly more patients treated with budesonide achieved remission at Week 8 compared to mesalazine in Thomsen 1998. However, the PBAC noted that based on Tromm 2011 no significant differences in remission were seen between budesonide and mesalazine. The lower 95% CI was within the trial's pre-specified non-inferiority margin indicating the two treatments to be non-inferior. Overall, the PBAC considered the claim of superior effectiveness versus mesalazine to be uncertain (paragraph 6.11 and 6.12, budesonide PSD, November 2017). The PBAC considered that on balance the claim of superior safety of budesonide versus mesalazine was supported (paragraph 6.17, budesonide PSD, November 2017).
- 6.9 The minor resubmission claimed that there is some clinical evidence that budesonide is not significantly different from prednisolone in terms of inducing clinical remission in CD and there is strong clinical evidence that budesonide is superior to prednisolone in terms of safety.
- 6.10 In November 2017, the PBAC noted that while there was no statistically significant difference between budesonide and prednisolone in the induction of remission of CD at 8 weeks it did numerically favour prednisolone (paragraph 6.16, budesonide PSD, November 2017). The PBAC considered that in terms of safety, the trial evidence suggests budesonide to be superior to prednisolone, particularly in terms of glucocorticoid associated AEs (paragraph 7.5, budesonide PSD, November 2017).

Economic analysis

- 6.11 In the major submission considered by the PBAC in November 2017, the submission presented a cost-utility analysis against mesalazine. The PBAC was not supportive of the analysis given that it did not consider that mesalazine was the appropriate comparator (paragraph 6.25, budesonide PSD, November 2017).

- 6.12 A cost-minimisation analysis versus prednisolone was conducted during the evaluation of the November 2017 submission. 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 (paragraph 7.6, budesonide PSD, November 2017).
- 6.13 The minor resubmission presented a brief summary of a weighted average approach used to determine the price of budesonide. The resubmission stated the price of budesonide is based on a weighted average cost of mesalazine and prednisolone for 12 weeks. The cost of treatment for 12 weeks for each mesalazine brands in the original submission (Table 1), with the exception of Mesasal®, listed for CD was calculated. The cost of treatment was based on a dose of 4 g/day for the Pentasa® brands of mesalazine and a dose of 4.5 g/day followed by a 3 g/day taper dose (4 weeks) for the Salofalk® brand. The same was done for prednisolone based on a dose of 25 mg/day followed by a 5 mg/day taper dose (4 weeks). A weighted average cost for budesonide was then calculated based on the lowest cost mesalazine and prednisolone brands, with the assumption of a 3 week taper period for budesonide (average of 2 and 4 weeks taper).

Table 1: Current PBS listings of mesalazine and prednisolone for use in CD

PBS Code	Brand name	Strength and form	Restriction level
1611T	Mesasal (mesalazine) ^a	250 mg modified release tablet	AR (Streamlined) UC and CD
2214M	Pentasa (mesalazine)	500 mg modified release tablet	AR (Streamlined) UC and CD
2234N	Pentasa (mesalazine)	1 g modified release granules	AR (Streamlined) UC and CD
2287J	Pentasa (mesalazine)	2 g modified release granules	AR (Streamlined) UC and CD
3413P	Pentasa (mesalazine)	1 g modified release tablet	AR (Streamlined) UC and CD
8731M	Salofalk (mesalazine)	500 mg enteric tablet	AR (Streamlined) UC and CD
1916W	Panafcortelone/Solone (prednisolone)	25 mg tablet	Unrestricted
1917X	Panafcortelone/Solone (prednisolone)	5 mg tablet	Unrestricted
3152X	Panafcortelone/Predsolone (prednisolone)	1 mg tablet	Unrestricted

^a Mesasal was included in the November 2017 submission but excluded from the minor resubmission based on feedback that it is unlikely to be substituted with budesonide as the PI does not recommend doses above 1.5 g/day (paragraph 6.34, budesonide PSD, November 2017).

AR = Authority Required, UC = Ulcerative colitis, CD = Crohn disease.

- 6.14 The PBAC noted that, as indicated in Table 1, the PBS listings for mesalazine in CD are confounded by the dual indication under the same PBS item code for both UC and CD. This potentially makes the calculation of the proportion of mesalazine

prescribed for CD difficult to verify as it is dependent upon correct selection of the streamlined authority code at the time of prescribing and dispensing. The PBAC also noted that current PBS listings for prednisolone are unrestricted so no information on the condition for which the drug is prescribed is available. Therefore the PBS data are not informative for assessing the proportional of use of prednisolone and mesalazine for CD.

- 6.15 A [REDACTED]% weighting was applied to the \$712.21 cost for the least expensive mesalazine for 12 weeks and a [REDACTED]% weighting was applied to the \$8.17 cost for the lowest cost prednisolone for 12 weeks. This results in a cost of \$[REDACTED] for 12 weeks of budesonide use. The PBAC noted that no weighting was applied for sulfasalazine substitution.
- 6.16 The weighting applied was based on BEACH data from April 2011 to March 2016 for patients with CD. The submission pooled data for both prednisolone and prednisone (a precursor drug of prednisolone) in the calculation of the split between mesalazine ([REDACTED]%) and prednisolone ([REDACTED]%) use in CD. As noted in paragraph 4.2, evidence on the lack of efficacy of 5-ASAs in CD has emerged in recent years (Lim 2016 Cochrane Review). BEACH data from the most recent year may therefore be more appropriate than data collected over 5 years from 2011. However, the BEACH data was limited to a total of 77 data points for these medicines over the 5 year period. The limited data available and concerns regarding applicability to current practice may reduce the reliability of any proportionality for the purposes of determining an appropriate price for budesonide, derived from it.
- 6.17 The pre-PBAC response argued that the split between mesalazine and prednisolone was best determined using BEACH data which collects prescribing data by CD and UC separately. In addition, the pre-PBAC response argued that use of BEACH data is appropriate as in the treatment of CD, prescribing is led by specialists and so prescribing in general practice should be consistent with this.
- 6.18 The PBAC remained concerned that, due to the limitations of the BEACH data presented, the weighting of comparators determined was unlikely to reflect the true proportion of patients in whom prednisolone is not an alternative therapy. While contemporary Australian guidelines acknowledge a role for mesalazine in CD, the PBAC considered it was a limited role. Hence, the PBAC did not accept the 59.7% weighting applied for mesalazine and the [REDACTED]% weighting applied for prednisolone. The PBAC considered that, unless more robust current data becomes available, a weighting that allows for one-fifth to one quarter, but closer to one-fifth, of use in which mesalazine is the alternative therapy may be more appropriate, with the corresponding weighting for prednisolone applied accordingly.

Drug cost/patient/course: \$[REDACTED]

- 6.19 This is based on a [REDACTED]%:[REDACTED]% weighted price comparison with both mesalazine and prednisolone for a 12-week course with a 3-week taper period. This compares

with \$8.17 per course for prednisolone and \$712.21 per course for mesalazine. The PBAC noted that the drug cost/patient/course would need to be updated once a new AEMP has been negotiated.

Estimated PBS usage & financial implications

6.20 The minor resubmission again used an epidemiological approach to estimate the likely extent of budesonide use and associated financial implications. Table 2 summarises the data sources used in the resubmission’s estimates and indicates whether the source is (un)changed from the November 2017 submission.

Table 2: Steps and assumptions used to determine the costs of budesonide

Step	Estimate	Value	Source/Assumption	Source (un)changed from November 2017/Comments
1	19,529,153 adults in Australia in 2018, increasing to 21,139,340 in 2023	-	ABS catalogue no. 3222.0 – Population Projections, Australia – Series B	Source unchanged The evaluation of the November 2017 submission stated the source was reasonable.
2	Adults in Australia already diagnosed with Crohn’s disease	38,531 in 2018	Prevalence from Studd et al. (2016) of 197.3 in 100,000	Sources unchanged The evaluation of the November 2017 submission stated that 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, particularly as there are significant cost offsets claimed against mesalazine.
3	New cases/year of Crohn’s disease in Australia	3,125 in 2018	Incidence from Vegh et al. (2014) of 16 in 100,000	
4	Total patients with Crohn’s disease in Australia	41,656 in 2018	Total of diagnosed patients and new cases	-
5	Deaths/year for patients with Crohn’s disease in Australia	666 in 2018	Mortality rate for Crohn’s disease from Loftus (2006) of 1.6%	Source unchanged
6	Total patients surviving with Crohn’s disease in Australia	40,989 in 2018	Total patients minus deaths	-

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7	Eligible population in Australia	18,199 in 2018	44% eligible based on mild to moderate CD, eligible for first/ second-line treatment criteria	<p>Source unchanged (remains based on clinician survey) but the proportion has increased from 20% to 44% as the November 2017 submission assumed budesonide would be used second line only</p> <p>The evaluation of the November 2017 submission stated the submission claimed that this was derived from the clinician survey, this was not able to be verified, the survey did not ask for an answer to this issue.</p>
8	Treated population in Australia	3,640 in 2018	<p>Assumptions on uptake rate for budesonide</p> <p>– 20%–35% in Years 1–6 of PBS listing</p>	<p>Source unchanged (remains an assumption by the sponsor) but the uptake rate for budesonide in the November 2017 submission was 20%–50% in Years 1–6 of PBS listing.</p> <p>The evaluation of the November 2017 submission stated that the assumption of a 20%–50% uptake in Years 1–6 may be an underestimate. Clinicians surveyed by the sponsor indicated use of budesonide on the PBS may be higher. From approximately 10–20% presently on private prescription rising up to 80% of their patients after PBS listing.</p>
9	Total budesonide packs per year	25,479 in 2018	<p>Budesonide dosage of 9 mg/day for 8 weeks followed by an average dose of 4.5 mg/day for 4 weeks based on PI (due to dose tapering);</p> <p>Assumed each CD patient will have 3 episodes per year (adjusted from clinical survey results) requiring 2.3 packs per episode (7 packs per year)</p>	<p>Source unchanged</p> <p>The evaluation of the November 2017 submission stated that the clinician surveys indicated an average of 2 flare ups per year per patient is likely. However, the submission then added one extra episode to the analysis, and justified this on the basis that some of the specialists answering the survey more commonly treated their patients with biologics or immunosuppressants, which are more effective than mesalazine at preventing flares. This may not be appropriate given immunosuppressants and biologic therapies are reserved for patients with more severe CD and are not usually administered in 1st or 2nd line treatment for mild and moderate CD.</p>

10	Mesalazine and prednisolone doses	mesalazine – Pentasa – 4g a day episodic dose, 4g a day taper dose (4 weeks) mesalazine – Salofalk - 4.5g a day episodic dose, 3g a day taper dose (4 weeks) prednisolone - 25mg a day episodic dose, 5mg a day taper dose (4 weeks)	Product information stated as the source in the minor resubmission.	Source changed The mesalazine dose (4 g/day) used in the November 2017 submission was based on the Thomsen 1998 trial.
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Source: Table 19 p49, Table 26 p58, Table 27 p59, Table 28 p59 and Table 30 p 60 of the minor resubmission. Table 4.2.1 of the Commentary on the budesonide November 2017 PBAC submission

- 6.21 The eligible population was increased in the minor resubmission by including both first and second line therapy for mild and moderate CD. This increased the eligible percentage of total CD patients from 20% to 44%. The PBAC considered at November 2017 meeting that budesonide is likely to be used in first or second line treatment of mild to moderate CD (paragraph 7.2, budesonide PSD, November 2017). The November 2017 submission and the resubmission state that the proportion of CD patients eligible for budesonide (i.e. 20% and 44% respectively) is based on expert surveys of gastroenterologists. Five gastroenterologists were surveyed for the November 2017 submission. As noted in the evaluation of the November 2017 submission the claim that information was derived from the clinician survey was not able to be verified as the survey did not ask for an answer to this issue. The same survey information was used to inform the resubmission and hence the reliability of the eligibility rate is uncertain given the lack of data to substantiate the figure provided. The PBAC considered the increase in the eligible population to account for both first and second line therapy was likely to be appropriate.
- 6.22 The minor resubmission also reduced the uptake rate used in the financial estimates from a maximum of 50% in year 6 in the major submission to 35% in year 6, however the text of the resubmission still states that an uptake rate of 50% in year 6 was used. The evaluation of the November 2017 submission considered the uptake rate likely underestimated (Table 2). No justification for the decrease in uptake rates was provided in the resubmission. The PBAC considered the uptake rate presented in the minor resubmission was likely to be underestimated.
- 6.23 The minor resubmission stated that there are an estimated 500 patients who access budesonide on the private market each year. It is unclear whether the 20% uptake rate in Year 1 takes into consideration patients currently accessing budesonide on the private market.
- 6.24 The minor resubmission used the approach outlined in Step 9 of Table 2 to estimate the number of packs of budesonide that will be dispensed. Step 9 assumes that

patients will experience 3 episodes per year that require treatment. This was based on the responses of the gastroenterologists surveyed that indicated that patients treated with mesalazine typically had between 0 and 2 episodes per year. The resubmission added “1 extra” episode to the model as it was assumed that the gastroenterologists surveyed would use biologics in some cases and that it was “expected that biologics and other immunosuppressants are more effective than mesalazine or prednisolone at achieving remission”. As stated in the evaluation of the November 2017 submission, this may not be appropriate given immunosuppressants and biologic therapies are reserved for patients with more severe CD and are not usually administered in first or second line treatment for mild and moderate CD. Hence, the reliability of this assumption was uncertain and would be expected to have a substantial effect on the financial implications. The PBAC considered that the number of episodes experienced by patients per year that require treatment was likely to be overestimated.

- 6.25 The minor resubmission proposed a DPMQ for budesonide of \$ [REDACTED]. The resubmission stated that the proportion of patients in each beneficiary type of mesalazine and prednisolone was used to estimate the proportions for budesonide based on PBS data from 2016. It is unclear whether the proportions from both mesalazine and prednisolone were used to disaggregate the estimates by beneficiary type in the calculations undertaken.
- 6.26 The listing of budesonide on the PBS is expected to result in decreased utilisation of the therapies currently used to treat CD patients. The minor resubmission has updated the approach taken to estimate the changes in use and financial impact of other medicines by including prednisolone as well as mesalazine in the estimates. The November 2017 submission included mesalazine only. The resubmission estimated the percentage market share of each mesalazine and prednisolone formulation / brand, based on 2017 PBS data for the two medicines. The BEACH data used to calculate the weighted price for budesonide (see paragraph 6.16) was used to determine the split between mesalazine ([REDACTED]%) and prednisolone ([REDACTED]%) use in CD. As indicated in Table 1, the PBS listings for mesalazine in CD are confounded by use for UC and CD under the same item code and the PBS listings for prednisolone are unrestricted so no information on the condition for which the drug is prescribed is available. As noted previously (see paragraph 6.16) the reliability of using BEACH data to determine an appropriate split between mesalazine and prednisolone use in CD is uncertain due to concerns around the limited number of data points available and applicability to current practice. As the majority of the savings estimated in the resubmission are from the replacement of higher-cost mesalazine the split between mesalazine and prednisolone will have a significant impact on the financial estimates. As outlined in paragraph 6.18, the PBAC did not accept the 59.7% weighting applied for mesalazine and the [REDACTED]% weighting applied for prednisolone and instead considered a reduced weighting applied for mesalazine may be more

appropriate. The PBAC noted the uncertainty around the proportional split based on the BEACH data was not explored in a sensitivity analysis in the resubmission.

6.27 The minor resubmission estimated a net save to the PBS/RPBS of less than \$10 million in Year 6 of listing, with a total net save to the PBS/RPBS of less than \$10 million over the first 6 years of listing. This is summarised in Table 3 below as well as the expected patient numbers.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
CD patients per year	██████	██████	██████	██████	██████	██████
% of population with mild to moderate CD eligible for first/second line treatment	44%	44%	44%	44%	44%	44%
Population eligible for mesalazine, prednisolone or budesonide	██████	██████	██████	██████	██████	██████
Rate of uptake	20%	25%	30%	32%	34%	35%
Total patients treated with budesonide	██████	██████	██████	██████	██████	██████
Number of scripts for budesonide ¹	██████	██████	██████	██████	██████	██████
Total budesonide cost to the PBS from listing	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Total decrease in cost to the PBS from substitution	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Net cost to PBS/RPBS	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████

¹ assumes 3 episodes per year with 2.3 scripts per episode (7 scripts per year).

Source: Table 27 p59, Table 30 p 60 and Table 38 p 69 of the minor resubmission.

The redacted table shows that at Year 6 the estimated number of patients was less than 10,000.

6.28 The PBAC considered the net effect on the PBS/RPBS is highly dependent on the proportion of medicines substituted by budesonide upon listing. The PBAC considered the proportion of mesalazine substitution very likely to be overestimated and noted that a higher proportion of prednisolone substitution would lessen or reverse the estimated overall cost saving from listing of budesonide. Hence, the PBAC considered the budget impact for the proposed listing remains highly uncertain and advised that a risk sharing arrangement may be appropriate.

6.29 As a minor submission, the financial estimates have not been independently evaluated. The PBAC noted that the financial implications need to be recalculated to take into account the outcome of its considerations.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of budesonide for treatment of mild to moderate CD affecting the ileum and/or the ascending colon. The PBAC recommended the listing on cost minimisation basis against a weighted mixed comparator of mesalazine and prednisolone. In making this recommendation, the PBAC noted the clinical need for additional treatment options in patients with mild to moderate CD.
- 7.2 The PBAC welcomed the input from individuals, health care professionals and organisations across the minor resubmission and the November 2017 submission. The PBAC noted the input provided described the clinical need for treatment options in mild to moderate CD with reduced short and long term AEs.
- 7.3 The PBAC recalled that in its consideration of budesonide in November 2017 it had considered that a comparison against mesalazine was not appropriate — noting that prednisolone was a more appropriate comparator. The PBAC maintained the view that a comparison wholly against mesalazine was not appropriate. However, the PBAC acknowledged that contemporary Australian guidelines continue to indicate a limited role for 5-ASAs such as mesalazine in CD. Moreover, the PBAC considered that there was a subset of patients who would be treated with mesalazine instead of prednisolone as the AE profile of the latter would prohibit a trial or ongoing use in clinical practice. The PBAC therefore accepted the nomination of a mixed comparator (mesalazine and prednisolone).
- 7.4 The PBAC did not agree that the calculation of the weighted price presented in the minor resubmission was appropriate. The proposed proportion of comparators was derived from BEACH data. The PBAC considered that, as the BEACH data were collected over a 5 year period from 2011 with a limited number of data points available, the weighting of mesalazine (59.7%) and prednisolone (40.3%) determined was uncertain and unlikely to reflect the true proportion of patients in whom prednisolone is not an alternative therapy. While contemporary Australian guidelines acknowledge a role for mesalazine in CD, the PBAC considered it was a limited role. The PBAC considered that, unless more robust current data becomes available, a weighting that allows for one-fifth to one quarter, but closer to one-fifth, of use in which mesalazine is the alternative therapy may be more appropriate, with the corresponding weighting for prednisolone applied accordingly. The PBAC noted that the AEMP would need to be updated to reflect the new weighted proportions of comparators negotiated between the sponsor and the Commonwealth.
- 7.5 The PBAC noted that the equi-effective doses were nominated as: budesonide 9 mg/day for 9 weeks followed by 4.5 mg/day for 3 weeks; Pentasa® brands of mesalazine 4 g/day for 12 weeks; Salofalk® brands of mesalazine 4.5 g/day for 8 weeks followed by a 3 g/day for 4 weeks; and prednisolone 25 mg/day for 8 weeks followed by 5 mg/day for 4 weeks.
- 7.6 The PBAC considered that, consistent with the restrictions of mesalazine and

prednisolone, the prescribing of budesonide should not be limited to gastroenterologists.

- 7.7 The PBAC considered that on balance the evidence presented in the minor resubmission supported a clinical claim that budesonide was non-inferior in terms of comparative effectiveness and superior in terms of comparative safety to both mesalazine and prednisolone. Although treatment with budesonide would be substantially more costly than treatment with prednisolone, the PBAC was satisfied that budesonide would provide a significant reduction of toxicity over prednisolone.
- 7.8 The PBAC noted that the minor resubmission did not present an economic analysis and considered that the justification provided for the approach taken was poor. However, the PBAC accepted an overall cost minimisation approach was appropriate subject to the changes in the proportion of patients in each comparator group as outlined in paragraph 7.4.
- 7.9 The minor resubmission estimated a net save to the PBS/RPBS with the listing of budesonide. However, the PBAC considered that there were significant uncertainties in the financial estimates presented that may lessen or reverse the overall estimated cost savings. The PBAC considered the budget impact for the proposed listing was highly uncertain and therefore recommended a risk sharing agreement between the sponsor and the Commonwealth be entered into to reduce the financial impact of higher use of budesonide or lower levels of mesalazine substitution than predicted.
- 7.10 The PBAC advised that budesonide is suitable for prescribing by nurse practitioners.
- 7.11 The PBAC recommended that the Early Supply Rule should not apply.
- 7.12 The PBAC recommended that budesonide be included as one of the prior systemic therapies that need to be failed prior to qualifying for subsidy of a biological medicine for severe CD. The PBAC noted that the flow-on restriction changes need to be developed for this including the appropriate dose and duration of treatment with budesonide.
- 7.13 The submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
BUDESONIDE Oral, 3 mg modified release capsule	90	2	Entocort®	Emerge Health

Category/Program	Section 85 (general schedule)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Mild to moderate
Condition:	Crohn disease
PBS Indication:	Mild to moderate Crohn disease
Restriction:	<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
Clinical criteria:	The condition must affect the ileum, OR The condition must affect the ascending colon, OR The condition must affect the ileum and ascending colon.
Prescriber Instructions	The total duration of therapy should be no more than 12 weeks in any single course.
Administrative Advice	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.

9 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.

10 Sponsor's Comment

Emerge Health provided evidence from the BEACH survey showing the use of prednisolone and mesalazine in Crohn's disease and is prepared to list at prices based on this split. The PBAC assumed an alternate, very different, split which indicated a price more than 50% below the lowest price for Entocort internationally. This assumed split was generated by the PBAC Committee. Emerge Health is unable to supply Entocort at this far reduced price. Emerge Health is considering options for an additional submission.