7.15 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 patients with mild to moderate Crohn's disease affecting the ileum and/or ascending colon.

1.2 In July 2018, the PBAC recommended the listing of budesonide for this indication based on the mixed comparator of mesalazine and prednisolone. While the PBAC accepted the mixed comparator, it did not accept the proposed weighting of mesalazine ([redacted]%) and prednisolone ([redacted]%) to calculate the price for budesonide and instead considered that a weighting that allows for one-fifth to one quarter of mesalazine is more appropriate.

1.3 The basis of the minor resubmission's request was to update the weighting of the mixed comparator of mesalazine and prednisolone to [redacted]% and [redacted]% respectively, using BEACH and NPS data for pricing purposes.

2 Requested listing

2.1 The resubmission requested the following listing based on advice provided by the PBAC at the July 2018 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.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BUDESONIDE Oral, 3 mg modified release capsule	90	2	$[redacted]*	Entocort® Emerge Health

Category / Program	Section 85 (general schedule)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	N/A
Severity:	Mild to moderate
Condition:	Crohn's disease
PBS Indication:	Mild to moderate Crohn's disease
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒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.
~~**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 *daily* 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.

* Note: If the [redacted]% safety premium is not accepted, then the DPMQ is $[redacted]

Secretariat comments on the restriction

2.3 The treatment criterion "must be treated by a gastroenterologist" was removed from the proposed restriction. This follows the advice from the PBAC in July 2018 to align with the restrictions for mesalazine and prednisolone.

2.4 The Secretariat amended the proposed listing to include nurse practitioners as the submission did not include it in error. The PBAC advised that budesonide is suitable for prescribing by nurse practitioners at its July 2018 meeting and the restriction table

presented in this minor resubmission refers to nurse practitioners in the administrative advice section.

2.5 The Secretariat also removed 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' as the PBAC previously considered that this was not required to administer the listing (paragraph 2.4, item 7.11 budesonide Pubic Summary Document (PSD), July 2018).

2.6 The PBAC is asked to advise, under Section 101 (4AACD) of the National Health Act, if Budenofalk and Entocort should be considered equivalent for the purposes of substitution (i.e. 'a' flagged in the Schedule). The Secretariat noted that Budenofalk and Entocort have different capsule formulations. Entocort is described as a "hard gelatine capsule filled with gastric acid-resistant, prolonged release granules for oral use. The granules are practically insoluble in gastric juice and have prolonged release properties adjusted to release budesonide in the ileum and the ascending colon." (Entocort approved PI, p1). Budenofalk is described as an enteric capsule in the approved Product Information (PI) (p1). The pre-PBAC response stated that Entocort is a unique formulation of budesonide that is distinct from other forms of budesonide available, such that budesonide is released at different pH levels for Entocort (pH 5.5) when compared to the other available brands (Budenofalk pH 6.4; Cortiment pH 7). The pre-PBAC response stated that Entocort should not be considered as substitutable with other brands.

2.7 The Secretariat noted that the requested restriction is simple.

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 and July 2018 meeting.

3.3 The PBAC did not recommend the listing of budesonide at the November 2017 meeting on the basis that mesalazine, as the nominated comparator was

[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.

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 recommended the listing of budesonide at the July 2018 meeting. The sponsor proposed a mixed comparator of mesalazine and prednisolone (with a weighting of [redacted]% and [redacted]% respectively), and while the PBAC accepted the mixed comparator, it did not accept the proposed proportions (paragraph 7.4, budesonide PSD, July 2018).

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

4 Population and disease

4.1 The clinical place of budesonide in mild to moderate CD remains unchanged from the previous submissions. In November 2017, the PBAC accepted that budesonide is likely to be used in first or second line treatment of mild to moderate CD.

5 Comparator

5.1 The previous minor resubmission considered by the PBAC in July 2018 nominated mesalazine and prednisolone as comparators. This was unchanged in the current minor resubmission given that the PBAC accepted the mixed comparator.

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 individuals (2) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with budesonide, such as the reduction of flares, and the lack of side effects such as osteoporosis, insomnia and weight issues when compared to alternative treatments.

6.3 The PBAC noted the consumer comments highlighted the clinical need for treatment options in mild to moderate CD.

Clinical trials

6.4 As a minor submission, no new clinical trials were presented in the resubmission.

Clinical claim

6.5 The minor resubmission claimed that there is clinical evidence to demonstrate that budesonide is superior to mesalazine and non-inferior to prednisolone in terms of

comparative effectiveness, and that budesonide is superior to both mesalazine and prednisolone in terms of comparative safety. The comparative effectiveness claim in the resubmission was changed from the previously accepted claim of non-inferiority.

6.6 In July 2018, 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. A [redacted]% premium on the cost-minimised price of budesonide was requested in the resubmission based on the comparative safety claim.

Pricing approach – updated weighted average pricing

6.7 The minor resubmission presented an updated weighted average approach to determine the price of budesonide. The minor resubmission nominated mesalazine and prednisolone as a mixed comparator, which was unchanged from the minor resubmission at its July 2018 meeting.

6.8 At its July 2018 meeting, the PBAC did not agree with the calculation of the weighted average price using the nominated mixed comparators, mesalazine and prednisolone. 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 ([redacted]%) and prednisolone ([redacted]%) 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 might be more appropriate, with the corresponding weighting for prednisolone applied accordingly.

6.9 The resubmission disagreed with the PBAC's recommended weighting from July 2018, as this was a non-empirical split. Additionally, use of this split would result in a price that would not be sustainable for the sponsor to list Entocort on the PBS.

6.10 Additional data were provided in the current minor resubmission to justify an updated weighted split between mesalazine and prednisolone. The weighting was based on the same BEACH data (April 2011 to March 2016) as well as additional data from Medicines Insight NPS data (NPS data, 2013 to 2018). The resubmission noted that findings of the NPS data align with the BEACH data and showed that treatment practices have remained largely unchanged. There were no significant differences in the annual proportions of patients with Crohn's Disease prescribed prednisolone/prednisone or mesalazine between 2013 and 2018, suggesting that physician prescribing practices for prednisolone/prednisone and mesalazine have not changed significantly in the last 5 years. The resubmission stated the additional data should alleviate concerns previously raised by the PBAC over the applicability of

BEACH data to current clinical practice. The data were averaged to generate a comparator proportion. The weighting from the updated data was calculated to be [redacted]% for mesalazine and [redacted]% for prednisolone.

6.11 The resubmission stated the price of budesonide is based on a weighted average cost of mesalazine and prednisolone for 12 weeks. This is unchanged from the previous resubmission. The cost of treatment for 12 weeks for each of the mesalazine brands listed for CD (Table 1), with the exception of Mesasal®, 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 cheapest 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 July 2018 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 6.30, budesonide PSD, November 2017). This was unchanged in the March 2019 resubmission. AR = Authority Required, UC = Ulcerative colitis, CD = Crohn disease.

6.12 A [redacted]% weighting was applied to the $608.94 cost for the cheapest mesalazine for 12 weeks and a [redacted]% weighting was applied to the $8.17 cost for the cheapest prednisolone for 12 weeks. This resulted in a cost of $[redacted] for 12 weeks of budesonide use. This is a reduction from $[redacted] for 12 weeks of budesonide use calculated in the July 2018 submission. The PBAC noted the cost of the cheapest mesalazine decreased between submissions from $712.21 to $608.94 as mesalazine underwent a statutory price reduction on 1 June 2018.

6.13 The submission proposed an AEMP for budesonide of $[redacted] (cost-minimised price). The resubmission also sought a [redacted]% premium for the superior safety profile of

budesonide over mesalazine and prednisolone. The [redacted]% premium resulted in an AEMP for budesonide of $[redacted]. The prices were based on BEACH and NPS data, and the least expensive PBS listed form of mesalazine and prednisolone. The PBAC could only recommend listing budesonide at a higher price than the alternative therapy or therapies if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies.

Drug cost/patient/course in submission: $[redacted]

6.14 Based on a [redacted]%:[redacted]% weighted price comparison with both mesalazine and prednisolone for a 12-week course with a 3-week taper period (2.45 packs). This compares with $8.17 per course for prednisolone and $608.94 per course for mesalazine. No weighting was applied for the sulfasalazine substitution that is unchanged from the previous submission.

6.15 The drug-cost/patient/course was underestimated, as it did not consider wastage. When accounting for wastage, based on a [redacted]%:[redacted]% weighting the updated drug-cost/patient/course using 3 packs is $[redacted].

Estimated PBS usage & financial implications

6.16 The minor resubmission used an epidemiological approach to estimate the likely extent of budesonide use and associated financial implications. This was unchanged from the July 2018 minor resubmission.

6.17 As previously noted by the PBAC in July 2018, the listing of budesonide on the PBS is expected to result in decreased utilisation of the therapies currently used to treat CD patients. The BEACH and NPS data used to calculate the weighted price for budesonide was used to determine the split between mesalazine and prednisolone 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 the majority of the savings estimated in the resubmission are a result of replacement of higher-cost mesalazine, the split between mesalazine and prednisolone will have a significant impact on the financial estimates.

6.18 The 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 when using the cost-minimised price. When using the cost-effective price (price with the [redacted]% premium for safety) 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 was estimated. This is summarised in Table 2 below as well as the expected patient numbers.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
CD patients per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate of uptake	20%	25%	30%	32%	34%	35%
Total patients treated with budesonide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts for budesonide[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-minimised price ($[redacted] DPMQ)[2]						
Total budesonide cost to the PBS from listing	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total decrease in cost to the PBS from substitution	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost-effective price ($[redacted] DPMQ)[3]						
Total budesonide cost to the PBS from listing	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total decrease in cost to the PBS from substitution	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

[1] assumes 3 episodes per year with 2.3 scripts per episode (7 scripts per year).
[2] Cost-minimised price= price without a [redacted]% premium for the safety benefit of price of budesonide over prednisolone and mesalazine
[3] Cost-effective price= cost-minimised price with a [redacted]% premium for the safety benefit of price of budesonide over prednisolone and mesalazine
DPMQ: Dispensed Price for Maximum Quantity, CD = Crohn's disease
Source: Table 20 p49, Table 24 p50, Table 34 p59 and Table 35 p59 of the resubmission.

6.19 The net effect on the PBS/RPBS is highly dependent on the proportion of medicines substituted by budesonide upon listing. In July 2018, the PBAC considered that there were significant uncertainties in the financial estimates presented that may lessen or reverse the overall estimated cost savings. At that time, the PBAC considered the budget impact for the proposed listing was highly uncertain and therefore recommended a risk sharing arrangement 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 (paragraph 7.9, item 7.11 budesonide PSD, July 2018). No risk sharing arrangement was proposed in

the minor resubmission. The PBAC remained of the view that a risk sharing arrangement may be appropriate.

6.20 As a minor submission, the financial estimates have not been independently evaluated.

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

7 PBAC Outcome

7.1 The PBAC reaffirmed its previous recommendation to list budesonide (Entocort) for treatment of mild to moderate CD affecting the ileum and/or ascending colon on a cost minimisation basis against a weighted mixed comparator of mesalazine and prednisolone.

7.2 The PBAC noted the consumer comments from two individuals that highlighted the clinical need for treatment options in mild to moderate CD.

7.3 The PBAC recalled that in its consideration of budesonide in July 2018 it had considered that a comparison against mesalazine and prednisolone was appropriate; however, did not agree that the calculation of the weighted price presented in the submission was appropriate.

7.4 The PBAC maintained its views that 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, as was presented in the July 2018 minor resubmission.

7.5 The PBAC noted that the equi-effective doses which were recommended at the July 2018 meeting remained the same: 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 current minor resubmission presented an updated comparator weighting of [redacted]%:[redacted]% (mesalazine:prednisolone). The weighting was based on the same BEACH data presented in July 2018 as well as additional data from Medicines Insight NPS data. The PBAC considered the inclusion of the additional NPS data did not reduce the uncertainty around the true proportion of patients in whom prednisolone is not an alternative therapy and maintained its view that while contemporary Australian guidelines acknowledge a role for mesalazine in CD, it is a limited role. Therefore, the PBAC was of the view that the price of Entocort should continue to be based on a weighting of [redacted]%:[redacted]% (mesalazine:prednisolone) as recommended in July 2018.

7.7 The current minor resubmission estimated a net save to the PBS/RPBS with the listing of Entocort. The PBAC maintained that there were significant uncertainties in the financial estimates presented that may lessen or reverse the overall estimated cost savings, should there be a higher use of budesonide or lower levels of mesalazine substitution than predicted in the minor resubmission. Therefore, the PBAC was of the

same view as in July 2018, that a risk sharing agreement is required to manage these uncertainties, set at the level of the projected financial estimates of budesonide.

7.8 The PBAC maintained its recommendation 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.

7.9 The PBAC advised the Minister that it considered under Section 101 (4AACD) of the *National Health Act*, that Budenofalk and Entocort brands of budesonide could be considered equivalent for the purposes of substitution by the pharmacist at the point of dispensing (i.e. 'a' flagged in the Schedule), as the active ingredient is designed to work locally in the small intestine and colon so the formulation differences are not expected to result in differences in outcomes.

7.10 The PBAC maintained its advice that budesonide is suitable for prescribing by nurse practitioners.

7.11 The PBAC maintained its recommendation that the Early Supply Rule should not apply.

7.12 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	№.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:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	N/A
Severity:	Mild to moderate
Condition:	Crohn's disease
PBS Indication:	Mild to moderate Crohn's disease
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒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

The Sponsor acknowledges that the PBAC accepts that the Entocort brand of budesonide offers a significant safety advantage over prednisolone and mesalazine in Crohn's disease. It is also important that the committee agreed to a weighted comparator approach against the two alternate treatments. If the Committee had

maintained their view of selecting the cheapest alternate comparator, no listing would be possible and patients would be denied access to subsidised budesonide. The Sponsor and the PBAC, however, continue to disagree on the value of alternate sources of evidence to inform the weighting calculation.