

5.01 BUDESONIDE, Tablet (orally disintegrating) 1 mg, Jorveza[®], Dr Falk Pharma Australia.

1 Purpose of submission

- 1.1 The submission requested Authority Required (Streamlined) listing for budesonide 1 mg orally disintegrating tablets (BOT) for the treatment of eosinophilic oesophagitis (EoE). The key components of the clinical issues addressed in the submission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults diagnosed with eosinophilic oesophagitis (EoE)
Intervention	Budesonide 1 mg orally disintegrating tablets (topical corticosteroid)
Comparator	Placebo
Outcomes	<p><u>Induction of remission (EOS-1/BUL-1 trial)</u> Primary: clinicohistologic remission (composite) Secondary: histologic remission; change in peak eosinophil count; resolution of symptoms based on NRS scores for dysphagia and odynodysphagia; EEsAI-PRO score/ VDQ score/ AMS score; modSHS; EoE QoL-A; Safety</p> <p><u>Maintenance of remission (EOS-2/BUL-2 trial)</u> Primary: maintenance of clinicohistologic remission (free of treatment failure [composite]) Secondary: clinical relapse; histologic relapse; change in peak eosinophil count; EEsAI-PRO relapse; deep disease remission; modified EREFS (grading of major features); endoscopist's overall assessment of EoE activity; safety</p>
Clinical claim	In adults diagnosed with EoE: <ul style="list-style-type: none"> • Budesonide is superior in terms of effectiveness compared to placebo • Budesonide is inferior in terms of safety compared to placebo

Source: Table 1-1, p3 of the submission.

Abbreviations: AMS = avoidance, modification and slow eating; BOT/BUL = budesonide orally disintegrating tablet; EEsAI-PRO = Eosinophilic Oesophagitis Activity Index-Patient Reported Outcome; EoE = eosinophilic oesophagitis; EoE-QoL-A = Eosinophilic Oesophagitis Quality of Life Scale for Adults; EOS = eosinophilic oesophagitis study; EREFS = Endoscopic Reference Score; NRS = numerical rating scale; PPI = proton pump inhibitor; PRO = patient reported outcome; modSHS = modified Short Health Scale; STC = swallowed topical corticosteroids; VDQ = Visual Dysphagia Questionnaire.

2 Background

Registration status

- 2.1 BOT was TGA registered on 15 September 2020 for treatment of EoE in adults at a dose of 1 mg BID for 6 weeks, with extension for an additional 6 weeks in patients who are not appropriately responding. The submission stated that the results for use of BOT in the maintenance setting (beyond 12 weeks) are expected to be submitted to the TGA late 2020 for inclusion in the amended Product Information (PI). This TGA application will also include BOT 0.5 mg strength. The submission requested PBS listing

for use in the maintenance setting (beyond 12 weeks) which is beyond the maximum duration of treatment reflected in the current approved PI. The Pre-Sub-Committee Response (PSCR) noted that data from the EOS-2 trial, which included both 1 mg and 0.5 mg BID dosing regimens for maintenance therapy, were not available at the time of the initial regulatory submission.

- 2.2 An application for registration of BOT 0.5 mg was submitted and accepted for evaluation by the TGA (based on the notification letter received through correspondence with sponsor on 5th January 2021). The evaluation plan from the TGA letter indicated that the completion of evaluation phase is expected on 31st August 2021, the ACM outcome is expected on 24th December 2021, and the initial decision by the Delegate (decision letter) is expected on 14th January 2022.
- 2.3 BOT has been registered by the European Medicines Agency (EMA), Switzerland, Canada, and Israel. The indication approved by these regulatory agencies is consistent with the currently approved TGA indication. However, the EMA approved PI indicated that the recommended daily dose for maintenance of remission is BOT 1 mg (as 0.5 mg twice daily) or BOT 2 mg (as 1 mg twice daily) depending on the individual clinical requirement of the patient, with a maintenance dose of BOT 1 mg BID recommended for patients with a long-standing disease history and/or high extent of oesophageal inflammation in their acute disease state. The PSCR stated that when approved, it is expected that the recommended dosing will be in line with the current posology in the European label. The pre-PBAC response stated that BOT 0.5 mg and BOT 1.0 mg have similar safety and efficacy profiles and as such patients with EoE would not be compromised by having only BOT 1.0 mg available if approved for PBS listing.

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

3 Requested listing

- 3.1 The submission proposed two listing options: a simple listing which did not specify the criteria for the initial and continuing treatment periods; and a more complex option comprising evaluation of response to initial treatment, first continuing treatment, and subsequent continuing treatment criteria. The PBAC agreed with the ESC that the proposed 'simple restriction' was inconsistent with the clinical evidence presented and TGA dose recommendation in that it would allow all patients to continue treatment regardless of whether they achieved remission or not. As such, the 'complex restriction' is shown below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed price for maximum quantity	Available brands
BUDESONIDE						
budesonide 1 mg orally disintegrating tablet, 90	NEW	1	90	1	\$ [REDACTED]	Jorveza
Restriction Summary [new] / Treatment of Concept: [new]						
Concept ID	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
	Restriction type: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – Streamlined [new code] <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online) <input type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic upload to Hobart)					
	Episodicity: blank					
	Severity: blank					
	Condition: Eosinophilic oesophagitis					
	Indication: Eosinophilic oesophagitis					
	Treatment Phase: Initial treatment – Induction of remission					
	Clinical criteria:					
	<i>Patient must have a history of symptoms of oesophageal dysfunction.</i>					
	AND					
	Clinical criteria:					
	<i>Patient must have eosinophilic infiltration of the oesophagus, demonstrated by oesophageal biopsy specimens obtained by endoscopy confirming the presence of at least 15 eosinophils in at least one high powered field (corresponding to approximately 60 eosinophils per mm² hpf).</i>					
	Patient must have a diagnosis of eosinophilic oesophagitis based on: (i) clinical presentation (ii) endoscopic examination of the oesophagus and (iii) histologic assessment on oesophageal biopsy confirming presence of at least 15 eosinophils in at least one high powered field (corresponding to approximately 60 eosinophils per mm² hpf) and (iv) a thorough evaluation and exclusion of other potential causes of oesophageal eosinophilia;					
	AND					
	Clinical criteria:					
	Patient must not receive more than 90 days* of treatment under this restriction					
	Treatment criteria:					
	Must be treated by a gastroenterologist.					
	Prescribing criteria:					
	<i>Applications for treatment of this condition must be received within XX weeks of biopsy.</i>					
	Administrative Advice: <i>Symptoms of oesophageal dysfunction include at least one of the following: transient or self-cleared food impaction, chest pain, epigastric discomfort, vomiting/regurgitation.</i>					
	Administrative Advice: Diagnostic sensitivity increases with the number of biopsies and is maximised after taking at least six biopsies (minimum of 2 collected from each of the distal, mid and proximal segments) from both normal and abnormal appearing areas of the oesophagus.					
	Administrative Advice: A histologic assessment on oesophageal biopsy of the patient should be planned to take place within 90 days of the first PBS-subsidised treatment with this drug under this restriction to determine the patient's eligibility for "continuing therapy".					
	Administrative Advice:					
	<i>No increase in the maximum number of repeats may be authorised.</i>					
	Administrative Advice:					
	<i>No increase in the maximum quantity or number of units may be authorised.</i>					

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*Note: The restriction refers to 90 days initial treatment, as opposed to up to 12 weeks as recommended in the TGA approved Production Information for JORVEZA® so as to align with the 90-tablet pack size.

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budesonide 1 mg orally disintegrating tablet, 60	NEW	1	60	5	\$ [REDACTED]	Jorveza
Restriction Summary [new] / Treatment of Concept: [new]						
Concept ID	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
	Restriction type: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – Streamlined [new code] <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online) <input type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic upload to Hobart)					
	Episodicity: blank					
	Severity: blank					
	Condition: Eosinophilic oesophagitis					
	Indication: Eosinophilic oesophagitis					
	Treatment Phase: First continuing treatment – confirmation of remission					
	Clinical criteria:					
	Patient must have previously been issued with an authority prescription for initial treatment with this drug: <i>Patient must have previously received PBS-subsidised initial treatment with this drug for this condition in this treatment cycle.</i>					
	AND					
	Clinical criteria:					
	Patient must have documented evidence of having achieved histologic remission while receiving initial PBS-subsidised treatment with this drug for this condition, defined as a peak eosinophil count of less than 5 eosinophils per high power field (corresponding to less than 16 eosinophils per mm ² high power field on oesophageal biopsy);					
	AND					
	Clinical criteria:					
	Patient must, in the opinion of the treating specialist, have continued to benefit from receiving PBS-subsidised treatment with this drug for this condition.					
	Treatment criteria:					
	Must be treated by a gastroenterologist by another physician in consultation with a gastroenterologist.					
	Administrative Advice: Histologic assessment should be based on the peak eosinophils count derived from the evaluation six oesophageal biopsies (two collected from each of the distal, mid and proximal segments). The histologic assessment should, where possible, be performed by the same physician who confirmed the diagnosis of EoE in the patient. This assessment, which will be used to determine eligibility for continuing treatment, should be submitted within 4 weeks of the date of assessment, and no later than 2 weeks prior to the patient completing their current treatment course, to avoid an interruption to supply. Where a histologic assessment is not undertaken and the results submitted, the patient will be deemed to have failed to respond to treatment with this drug.					
	Administrative Advice:					
	<i>No increase in the maximum number of repeats may be authorised.</i>					
	Administrative Advice:					
	<i>No increase in the maximum quantity or number of units may be authorised.</i>					

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	Episodicity: blank					
	Severity: blank					
	Condition: Eosinophilic oesophagitis					
	Indication: Eosinophilic oesophagitis					
	Treatment Phase: Subsequent continuing treatment – maintenance of remission					
	Clinical criteria:					
	Patient must have previously been issued with an authority prescription for a first continuing treatment with this drug. <i>Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction.</i>					
	OR					
	Clinical criteria:					
	Patient must have previously been issued with an authority prescription for a second or subsequent continuing treatment with this drug.					
	AND					
	Clinical criteria:					
	Patient must, in the opinion of the treating doctor, have continued to benefit from receiving PBS-subsidised treatment with this drug for this condition. <i>Patient must have demonstrated an adequate response to treatment with this drug for this condition in this treatment cycle.</i>					
	Treatment criteria:					
	Must be treated by a gastroenterologist or by another physician in consultation with a gastroenterologist.					
	Administrative Advice:					
	<i>No increase in the maximum number of repeats may be authorised.</i>					
	Administrative Advice:					
	<i>No increase in the maximum quantity or number of units may be authorised.</i>					

- 3.2 The submission sought an Authority Required (Streamlined) listing for BOT for the treatment of EoE. As the complex restriction involves histological assessment to determine eligibility for continuing treatment the PBAC considered an Authority Required (Telephone) listing was appropriate.
- 3.3 The requested listing included an initial 90-day treatment period, where the 90-tablet pack size will be dispensed with one repeat. For patients achieving remission by day

90, the 60-tablet pack size will be subsequently dispensed with five repeats for the first continuing and the second and subsequent continuing treatment restrictions.

- 3.4 The proposed listing for the initial treatment phase was inconsistent with the TGA/PI dose recommendation and clinical evidence in terms of treatment duration and assessment schedule. While treatment duration of BOT (induction setting) reflected in the TGA approved PI and the clinical evidence was 12 weeks with assessment of response needed at 6 weeks, the proposed PBS listing would allow patients up to almost 13 weeks of treatment with no assessment required at 6 weeks.
- 3.5 Furthermore, the requested use of BOT in the maintenance setting (beyond 12 weeks) is beyond the maximum duration of treatment reflected in the current TGA approved PI. The PSCR argued the chronicity and potential for disease progression provides a strong rationale for maintenance therapy of EoE. The PSCR stated that international practice guidelines recommend long-term therapy with STC in patients with EoE. The PSCR noted that without a PBS listing for maintenance therapy it is possible that remitting-relapsing patients would cycle in and out of induction therapy potentially risking disease progression and adverse sequelae. The PSCR acknowledged that, while the current TGA-approved label for BOT is for the treatment of EoE, its use in the maintenance setting is not explicitly addressed. The PSCR argued that the results from the placebo group in the EOS-2 trial suggest that the majority of patients would suffer relapse within 12 months if they did not receive maintenance therapy. The ESC noted that a 0.5 mg BID regimen along with the requested 1 mg BID regimens are used in the EOS-2 trial for maintenance treatment. The ESC noted that a decision regarding TGA approval of the 0.5 mg strength of BOT or the use of either strength of BOT in the maintenance setting was not expected until January 2022.
- 3.6 The proposed listing was for the general EoE population. However, the patient population for which clinical evidence was presented differed from a general EoE population in that:
- All patients in EOS-1 were refractory to previous proton pump inhibitor (PPI) therapy of at least 4 weeks duration. While the submission is seeking a listing for use that does not refer to prior PPI exposure, the submission did not present comparative evidence on the efficacy or safety of using BOT in PPI naïve patients. The PSCR noted that early guidelines had cited the existence of a specific EoE subgroup who were responsive to PPIs (the PPI-REE group) and recommended these patients be identified with a trial of PPI treatment as part of the diagnostic work-up. The PSCR noted that current guidelines removed this procedure as the PPI-REE cohort was clinically, endoscopically and histologically indistinguishable from all other patients with a confirmed EoE diagnosis. The ESC considered that some EoE patients do respond to PPI therapy. However, the ESC noted that including the need to be refractory to PPIs in the restriction would require all patients to use a non-TGA approved and non-PBS subsidised therapy. The PBAC

considered it appropriate to include PPI naïve patients in the proposed PBS population.

- Neither the proposed simple nor complex restrictions specified the diagnostic criteria to apply with respect to the clinical presentation of EoE. Inclusion in EOS-1 had history of clinical symptoms of oesophageal dysfunction for diagnosis of EoE (at least one of the following; transient or self-cleared food impaction, chest pain, epigastric discomfort, vomiting/regurgitation); disease state with score of at least 4 points on a 0–10 numerical rating scale (NRS) for either dysphagia or odynodysphagia, and for Patient's Global Assessment (PatGA). The PSCR argued that NRS for the assessment of EoE symptom severity are not used in routine clinical practice. The PBAC considered the inclusion of a clinical criterion referencing a history of symptoms of oesophageal dysfunction appropriate.
- EOS-1 did not include patients with a peak eosinophil count between 60 eos/mm² hpf (corresponding to 15 eos/hpf)^a and 65 eos/mm² hpf (corresponding to 20 eos/hpf)^b. Such patients would be eligible for treatment under the proposed PBS listing. The ESC agreed with the PSCR that eosinophil counts are commonly ≥ 20 eos/hpf in the oesophagus of EoE patients with active disease.
- Patients in the trials were restricted from the concurrent use of systemic or topical glucocorticosteroids, biologics, or immunosuppressants; or initiating dietary restrictions. This is not reflected in the wording of the proposed prescriber instructions.

3.7 The proposed restriction allows use of BOT in the retreatment setting. However, no evidence was presented to establish whether patients who relapse after an initial response would respond to a subsequent course of treatment (re-treatment).

3.8 The submission stated that there is the possibility that some patients will receive BOT after TGA registration and prior to PBS listing, either as part of a treatment familiarisation program or alternatively through private prescriptions. Such patients would require a grandfathering restriction in order to access continuing treatment with BOT on the PBS. The submission did not provide a grandfathering restriction, nor did it account for the use of BOT in grandfathered patients in the financial estimates.

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

4 Population and disease

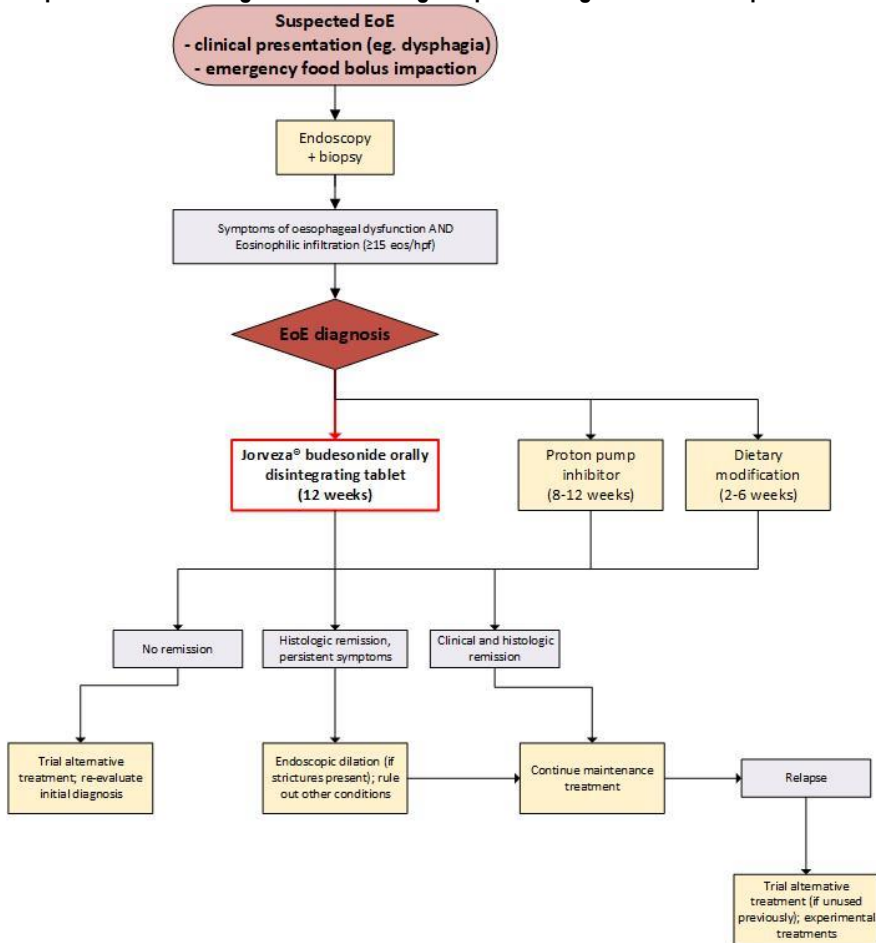
4.1 The PBAC has not previously considered any applications for the listing of drugs for EoE.

^a Eosinophil count of 15 eos/hpf is consistent with AGREE criteria 2018 for diagnosis of EoE.

^b Eosinophil count of 20 eos/hpf is consistent with EOS-1 and EOS-2 trials.

- 4.2 EoE is an immune mediated (atopic), chronic and progressive inflammatory disease, characterised histologically by the accumulation of eosinophils in the oesophageal lining and clinically by symptoms of oesophageal dysfunction.
- 4.3 BOT is a non-halogenated glucocorticosteroid, which achieves an anti-inflammatory effect through its binding to the glucocorticoid receptor. The exact mechanism of action in the treatment of EoE is not fully understood, however it is thought that budesonide may inhibit antigen-stimulated secretion of several pro-inflammatory signal molecules, such as thymic stromal lymphopoietin, interleukin-13 and eotaxin-3 in the oesophageal epithelium.
- 4.4 Under the current treatment algorithm presented by the submission, adult patients diagnosed with EoE will be offered either PPI, swallowed topical corticosteroids (STC), or dietary modification as a first line therapy; the choice of treatment strategy being based on clinician guidance and patient preference. The proposed treatment algorithm (Figure 1) positions BOT as the only approved first line alternate therapy to PPI or diet modification. This acknowledges that, in practice, BOT would be anticipated to replace PPIs or diet modification.

Figure 1: Proposed treatment algorithm indicating the positioning of JORVEZA® post-PBS listing



Source: Figure 1-9, p39 of the submission.

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Notes: Histologic remission is defined as an eosinophil count of less than 5 eos/hpf (corresponding to less than 16 eos/mm² hpf). For Dietary modification, endoscopies are performed every 2-6 weeks after reintroduction of each food.

- 4.5 The submission noted that while BOT would be the only treatment option specifically indicated for EoE, the off-label use of PPI therapy may remain a preferred first line treatment option for some patients based on local clinicians' advice; for example, in those with co-existing gastro-oesophageal reflux disease (GORD). However, it is acknowledged that the overall proportion of patients currently receiving PPIs first line might reduce over time with the availability of BOT. While this may be reasonable, the use of PPI may still remain a desired initial treatment for some patients with EoE (PPI-responsive). Current clinical guidelines from the Royal Australian College of General Practice (RACGP 2015^c) note that PPIs and STCs may be used for EoE treatment in patients who do not respond to dietary measures alone. In particular, STCs, namely fluticasone and budesonide "slurry", are currently regarded as the initial therapy of choice. Although there are no direct comparative data available, both agents are regarded as efficacious. Furthermore, the updated European guidelines 2017^d and AGREE criteria 2018^e suggest that PPIs should be considered as a potential early or initial treatment, while STCs or dietary elimination may also be considered.
- 4.6 The submission has not proposed that use of BOT be restricted to the second-line, post-PPI setting.
- 4.7 As there is no PBS listed treatment currently for adults with EoE, BOT will not substitute directly for any other PBS-listed medicines. However, it is quite possible that BOT will replace off label use of other PBS listed drugs such as PPIs and STCs.

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

5 Comparator

- 5.1 The submission nominated placebo as a proxy for standard of care (SOC) as the main comparator.
- 5.2 The submission acknowledged that PPIs and STC therapy (represented by the compounded budesonide slurry; or by swallowed fluticasone propionate, in either liquid form for nebulising or as powder) are currently used in the treatment of patients with EoE. However, the submission justified exclusion of these therapies as comparators on the basis that: the use of these treatments in EoE is off-label and the

^c Yaxley & Chakravarty. Eosinophilic oesophagitis – a guide for primary care. The Royal Australian College of General practitioners 2015; 44(10):723-7.

^d Lucendo AJ, Molina-Infante J, Arias Á, von Arnim U, Bredenoord AJ, Bussmann C, Amil Dias J, Bove M, González-Cervera J, Larsson H, Miehlke S. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European gastroenterology journal. 2017 Apr;5(3):335-58.

^e Dellon, E. S., Liacouras, C. A., Molina-Infante, J. et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology. 2018; 155(4), 1022-1033.

quality of the data supporting their use are generally poor; and the cost-effectiveness of these medications in the treatment of EoE has not been evaluated by the PBAC. The exclusion of these therapies on this basis may be reasonable. In addition, patients in the pivotal trial presented had been previously treated with PPIs, reducing the relevance of PPIs as a main comparator in the post-PPI setting.

- 5.3 The submission justified exclusion of dietary modification as a comparator to BOT on the basis that dietary modification is not a preferred treatment approach for many patients because of the requirement for repeat endoscopies and biopsies after each food reintroduction, the difficulty in sustaining a restricted diet, requiring access to a specialist dietician, and the out-of-pocket expense relating to use of food alternatives. Although this seemed reasonable the PBAC noted that the RACGP 2015 guidelines recommend dietary modification as first-line treatment for EoE in children and adults.
- 5.4 While there is no clinical evidence presented comparing BOT with PPIs or STCs, information was presented in the economic analysis section of the submission which provided a comparison of the anticipated daily cost of treatment of the three therapies in the EoE setting.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease and how the drug would be used in practice. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (5) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the limitations associated with the off-label treatment options currently available for EoE. These include the medication costs, compounding issues and the confusion that can arise when medicines indicated for asthma (and intended to be inhaled) are used for EoE (and need to be swallowed). The comments also describe the pain and anxiety associated with the symptoms of oesophageal dysfunction for both children and adults and the desire for EoE specific treatment options.

Clinical trials

- 6.3 The submission was based on two head-to-head randomised trials comparing BOT to placebo:

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- EOS-1 for the induction setting: randomised (2:1), double-blind (DB), placebo-controlled (PC), parallel group (PG), multicentre (MC) phase III study comparing BOT 1 mg BID vs. placebo for 6-weeks, with an additional 6 week open-label induction (OLI) phase with BOT 1 mg BID.
- EOS-2 for the maintenance setting: randomised (1:1:1), DB, PC, comparative, MC, phase III study comparing BOT 1 mg BID, BOT 0.5 mg BID, with placebo for 48 weeks.

6.4 Details of the trials presented in the submission are provided in Table 2. There were no other potentially relevant trials identified during the evaluation.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Included in further review in main body of the submission		
EOS-1 (NCT02434029)	<p>Double-blind, randomized, placebo-controlled, phase III trial on the efficacy and tolerability of a 6-week treatment with budesonide effervescent tablets vs. placebo for induction of clinicopathological remission in adult patients with active eosinophilic esophagitis Lucendo AJ, Miehke S, Schlag C et al. Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for Eosinophilic Esophagitis in a Randomized Placebo-Controlled Trial.</p> <p>Lucendo, A., et al. Budesonide orodispersible tablets are highly effective for treatment of active eosinophilic esophagitis: Results from a randomized, double-blind, placebo-controlled, pivotal multicenter trial (EOS-1).</p> <p>Lucendo, A., et al. Prolongation of eosinophilic esophagitis treatment with budesonide orodispersible tablets for incomplete responder is effective and safe: results from a 6-weeks open-label treatment phase of the pivotal trial EOS-1.</p> <p>Lucendo, A., et al. Budesonide orodispersible tablets can effectively induce complete remission of endoscopic and histologic mucosal abnormalities and can induce deep disease remission in active eosinophilic esophagitis: results from a post-hoc analysis of the randomized, double-blind, placebo-controlled EOS-1 trial.</p> <p>Miehke, S., et al. A randomized, double-blind, placebo-controlled, pivotal multicenter trial with budesonide orodispersible tablets for treatment of active eosinophilic esophagitis (EOS-1).</p> <p>Miehke, S., et al. Predictive factors for early vs delayed response to budesonide orodispersible tablets in eosinophilic esophagitis: Results from the pivotal trial EOS-1.</p> <p>Miehke, S., et al. A novel budesonide orodispersible tablet with a special esophageal-targeting can induce complete clinical, endoscopic and histologic remission in active Eosinophilic Esophagitis: Results from a post-hoc analysis of the randomized, double-blind, placebo-controlled EOS-1 trial.</p> <p>Straumann A, Lucendo AJ, Greinwald R. Efficacy and safety of budesonide orodispersible tablets in active eosinophilic oesophagitis: Results from a randomised, double-blind, placebo-controlled, pivotal, European multicentre trial (EOS-1)"Annual Meeting Swiss Society of Gastroenterology, SGG-SSG, Swiss Society of Visceral Surgery, SGVC-SSCV, Swiss Association for the Study of the Liver, SASL and Swiss Society of Endoscopy Nurses and Associates, SVEP-ASPE.</p>	<p>February 2017</p> <p><i>Gastroenterology</i> 2019a Jul;157(1):74-86.e15.</p> <p><i>Gastroenterology</i> 2017d;152(5): S207</p> <p><i>Gastroenterology</i> 2018a;154(6): S-75.</p> <p><i>Gastroenterology</i> 2019b;156(6); S-715-S-716.</p> <p><i>Allergy: European Journal of Allergy and Clinical Immunology</i> 2017;72: 78-79.</p> <p><i>Allergy: European Journal of Allergy and Clinical Immunology</i> 2018;73: 37.</p> <p><i>United European Gastroenterology Journal</i> 2019;7(8): 423.</p> <p><i>Swiss Medical Weekly</i> 2017a;147Suppl 225.</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	<p>Straumann, A., et al. Efficacy and safety of budesonide orodispersible tablets in active eosinophilic oesophagitis: Results from a randomised, double-blind, placebo-controlled, pivotal, European multicentre trial (EOS-1).</p> <p>Straumann, A., et al. Efficacy and safety of budesonide orodispersible tablets in active eosinophilic oesophagitis: Results from a randomised, double-blind, placebo-controlled, Pivotal, European multicentre trial (EOS-1).</p>	<p><i>Swiss Medical Weekly</i> 2017;147: 10S.</p> <p><i>United European Gastroenterology Journal</i> 2017b;5(5): A146-A147.</p>
EOS-2 (NCT02493335)	<p>Double- blind, randomized, placebo-controlled, phase III study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinicopathological remission in adult patients with eosinophilic esophagitis.</p> <p>Straumann A, Lucendo AJ, Miehke S et al.. Budesonide Orodispersible Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With Eosinophilic Esophagitis.</p> <p>Lucendo, A., et al. Budesonide orodispersible tablets are highly effective to maintain clinic-histological remission in adult patients with eosinophilic esophagitis: results from the 48-weeks, double-blind, placebo-controlled, pivotal EOS-2 trial.</p> <p>Lucendo, A. J., et al. A novel oral budesonide formulation is highly effective for induction of remission in patients with active eosinophilic esophagitis : Results from the 6-weeks open-label treatment phase of EOS-2 trial.</p> <p>Schlag, C., et al. Budesonide orodispersible tablets are superior to maintain and even further improve quality of life in adult patients with eosinophilic esophagitis: Results from the 48-weeks, double-blind, placebo-controlled pivotal EOS-2 trial.</p> <p>Schlag, C., et al. Efficacy of budesonide orodispersible tablet for induction of remission in patients with active eosinophilic esophagitis: results from the 6-weeks open-label treatment phase of EOS-2 trial.</p>	<p>May 2019</p> <p><i>Gastroenterology</i> 2020 Jul 25:S0016-5085(20)35002-2.</p> <p><i>Gastroenterology</i> 2019c:156(6): S-1509.</p> <p><i>United European Gastroenterology Journal</i> 2019d:7(8): 54.</p> <p><i>United European Gastroenterology Journal</i> 2019a:7(8): 705.</p> <p><i>Gastroenterology</i> 2019b:156(6): S-715.</p>

Source: Table 2-5, pp58-59 of the submission

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

Table 3: Key features of the included evidence

Trial	Intervention arm	No. randomised	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
BOT vs. placebo							
EOS-1 ^a	BOT 1 mg BID	59	6-week R, DB, PC, PG, Phase 3 study	Low	Adults aged 18-75 years with clinicohistologically active EoE refractory to treatment with standard dosages of PPI used for a 4-week period.	Primary: clinicohistologic remission (composite) Secondary: histologic remission; change in peak eosinophil count; resolution of symptoms based on NRS scores for dysphagia and odynodysphagia; EEsAI-PRO score/ VDQ score/ AMS score; modSHS; EoE QoL-A; Safety	Remission rates
	Placebo	29					
EOS-2	BOT 1 mg BID	68	48-week R, DB, PC, Phase 3 study	Low	Adults, 18 to 75 years of age, with confirmed clinicohistological diagnosis of EoE who are in clinicohistological remission of EoE and have a documented trial with PPI therapy.	Primary: maintenance of clinicohistologic remission (free of treatment failure [composite]) Secondary: clinical relapse; histologic relapse; change in peak eosinophil count; EEsAI-PRO relapse; deep disease remission; modified EREFS (grading of major features); endoscopist's overall assessment of EoE activity; safety	Remission rates
	BOT 0.5 mg BID	68					
	Placebo	68					

Source: Table 1-1, p3, Table 2-6, pp64-65, and Table 2-9, p72 of the submission. Page 67 of the submission.

Abbreviations: AMS = avoidance, modification and slow eating; BOT = budesonide orally disintegrating tablet; BID = twice daily; DB = double-blind; EEsAI-PRO = Eosinophilic Esophagitis Activity Index-Patient Reported Outcome; EoE = eosinophilic esophagitis; EoE-QoL-A = Eosinophilic Esophagitis Quality of Life Scale for Adults; EOS = Eosinophilic Oesophagitis Study; EREFS = Endoscopic Reference Score; mg = milligram; modSHS = modified Short Health Scale; NRS = numerical rating scale; OLI = open label induction; PPI = proton pump inhibitor; PRO = Patient Reported Outcome; PC = placebo-controlled; PG = parallel group; R = randomised; STC = swallowed topical corticosteroids; VDQ = Visual Dysphagia Questionnaire.

Notes: a. 51 (58.0%) patients in EOS-1 trial (23 [39.0%] patients initially randomised to BOT and 28 [96.9%] patients initially randomised to placebo) who were not in clinicohistological remission at completion of the DB treatment phase (week 6), or who were prematurely withdrawn due to lack of efficacy after at least 4 weeks of treatment were invited to enter an OLI phase of the trial in which all received BOT 1.0 mg BID.

- 6.6 As noted, the submission is seeking listing of BOT 1 mg only, however, the EOS-2 trial included BOT 0.5 mg. However, BOT 0.5 mg is not yet TGA registered, thus listing of that strength was not requested by the submission.
- 6.7 Patients in EOS-1 (23 [39.0%] from BOT and 28 [96.9%] from placebo) who were not in clinicohistological remission at completion of the DB treatment phase (week 6), or who were prematurely withdrawn due to lack of efficacy after at least 4 weeks of treatment, were invited to enter a further OLI phase of the trial in which all received BOT 1.0 mg BID. The risk of bias in the OLI phase of EOS-1 may be high due to this phase being non comparative (single arm).
- 6.8 The primary endpoint in both trials comprised both objective and subjective measures. The dysphagia NRS, odynodysphagia NRS, and Patient's Global Assessment

(PatGA) were used to measure the clinical remission co-primary endpoint. These instruments may be subject to bias due to the subjective nature of their assessment.

- 6.9 Across trials, almost all study patients had current dysphagia symptoms at baseline, with approximately 15% of patients previously undergoing oesophageal dilation. Approximately 50-60% of patients had experienced odynodysphagia, with majority experiencing food impaction symptoms.
- 6.10 The proportion of patients who discontinued treatment in both trials was lower for BOT compared with placebo, being 5.1% vs. 13.8% for BOT and placebo respectively in EOS-1, and 13.2% vs. 66.2% for BOT (0.5, 1 mg) and placebo respectively in EOS-2. However, the submission noted that the only reason for discontinuation in EOS-1 was the lack of efficacy. High discontinuation rate due to lack of efficacy in the placebo arm is consistent with the natural course of the disease when left untreated.

Comparative effectiveness

EOS-1 (induction of remission)

- 6.11 The primary outcome in EOS-1 was clinicohistologic remission at week 6 defined as:
- Histological remission: peak of <16 eos/mm² hpf (< 5 eos/hpf) at week 6/EOT; and
 - Clinical remission: symptom severity of ≤ 2 points on (0-10 point) NRS for both dysphagia AND odynodysphagia on each day in the week prior to week 6 (EOT).
- 6.12 The secondary outcomes in EOS-1 were histological remission; change in the peak eos/mm² hpf; resolution of clinical symptoms based on NRS scores for dysphagia and odynodysphagia; clinical remission based on EEsAI-PRO score; improvement in VDQ/AMS score; change in Short Health Survey score (modSHS); change in adult Eosinophilic Esophagitis quality of life (EoE-QoL-A) questionnaire. Key results for the primary and secondary endpoints are presented in Table 4 and Table 5.

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Table 4: Results for key endpoints in EOS-1 induction of remission study

Outcome measure	BOT 1 mg BID N=59	Placebo N=29	Treatment difference	RR (95%CI) ^c	RD (95%CI) ^c
Primary endpoint					
Clinicohistologic remission ^a at 6 weeks (LOCF; FAS-DB): n/N (%)	34/59 (57.6%)	0/29 (0.0%)	57.63% (95% RCI: 38.22%, 71.97%); p<0.0001^b	34.50 (2.19, 543.57)	0.58 (0.44, 0.71)
Cumulative clinicohistologic remission after 6 weeks DB treatment + additional 6 weeks OLI treatment for those not in clinicohistologic remission at the end of DB phase: n/N (%)	50/59 (84.7%)	N/A ^d	N/A ^d	N/A ^d	N/A ^d
A-priori ordered key secondary endpoints					
Histologic remission at 6 weeks (LOCF, FAS-DB): n/N (%)	55/59 (93.2%)	0/29 (0.0%)	93.22% (95% RCI:0 86.81%, 99.64%); p<0.0001	55.50 (3.55, 867.78)	0.93 (0.85, 1.01)
Change in the peak eos/mm ² hpf from baseline to week 6 (LOCF; FAS-DB): Mean (SD)	-225.5 [^] (150.37)	-4.3 (135.64)	-221.3 (95% CI: -287.0, -155.6); p<0.0001	N/A ^d	N/A ^d
Resolution of symptoms on each day in the week prior to week 6 based on the NRS score of <2 for dysphagia and odynodysphagia (LOCF; FAS-DB): n (%)	35/59 (59.3%)	4/29 (13.8%)	45.53% (95% CI: 27.79%, 63.27%); p<0.0001	4.30 (1.89, 28.74)	0.49 (0.28, 0.63)
Clinical remission, as defined as a EEsAI-PRO score of ≤20 at week 6 (LOCF; FAS-DB): n (%)	30/59 (50.8%)	2/29 (6.9%)	43.95% (95% RCI: 8.03%, 59.69%); p<0.0001	7.37 (1.89, 28.74)	0.44 (0.28, 0.60)

Source: Table 2-1, p50, Table 2-18, p106, Table 2-19, p109, Table 2-21, p112, Table 2-22, p114, Table 2-23, p115, and Table 2-24, p115 of the submission.

Abbreviations: BID = twice daily; BOT = budesonide orally disintegrating tablets; CI = confidence interval; DB = double-blind treatment phase; EEsAI-PRO = eosinophilic oesophagitis activity index- patient reported outcome; eos = eosinophils; FAS = full analysis set; hpf = high power field; LOCF = last observation carried forward; NRS = numerical rating scale; n = number of participants with event; N = total participants in group; N/A = not applicable; OLI = open label induction treatment; RCI = repeated confidence interval; RD = risk difference; RR = relative risk.

Notes: **Bold** indicates statistically significant results.

[^] error identified during the evaluation (should be -225.5 instead of 225.5).

a. Defined as histological remission, i.e., peak of <16 eos/mm² hpf at week 6 (LOCF), AND resolution of symptoms (i.e., no or only minimal problems) defined as a severity of ≤2 points on 0 to 10-point (0-10) NRS for dysphagia AND a severity of ≤2 points on 0-10 NRS for pain during swallowing on each day in the week prior to week 6 (LOCF).

b. One-sided p-value from Fisher's exact test.

c. Calculated post-hoc for the submission using Review Manager 5.4.

d. Not presented by the submission.

6.13 The percentage of patients in clinicohistologic remission at 6 weeks was 57.6% (34/59) in the BOT 1 mg BID group and 0.0% (0/29) in the placebo group (difference=57.63%; 95% RCI: 38.22%, 71.97%, p<0.0001).

6.14 The submission stated that the overall cumulative percentage of patients in clinicohistologic remission, after a total treatment period of up to 12 weeks with BOT

1 mg BID, increased to 84.7% (50 of the 59 patients randomised to BOT). The calculated cumulative percentage should be interpreted with caution due to the different treatment duration between the two groups of patients (6 weeks versus 12 weeks), and the lack of a control group in the OLI phase of EOS-1.

6.15 Results of the secondary endpoints histological remission, clinical remission, and mean change in peak eos/mm² hpf from baseline, at 6 weeks showed a statistically significant treatment effect in favour of BOT 1 mg compared to placebo. The change in both VDQ and the AMS score at week 6 showed no statistically significant treatment effect between groups.

Table 5: Change from baseline to week 6 in the Adult Eosinophilic Esophagitis Quality of Life Questionnaire (LOCF; FAS-DB)

Outcome	BOT 1 mg BID		Placebo		MD (95% CI)	p-value ^a
	N	Mean change (SD)	N	Mean change (SD)		
30 items	57	0.47 (0.56)	29	0.24 (0.47)	0.23 (-0.01, 0.47)	NS
24 items	57	0.48 (0.56)	29	0.24 (0.47)	0.24 (-0.00, 0.48)	NS
Eating/diet impact (10 items)	57	0.65 (0.88)	29	0.15 (0.60)	0.50 (0.13, 0.86)	<0.05
Eating/diet impact (4 items)	57	0.69 (0.87 ^a)	29	0.20 (0.64)	0.50 (0.13, 0.86)	<0.05
Social impact	57	0.46 (0.73)	29	0.30 (0.74)	0.16 (-0.17, 0.49)	NS
Emotional impact	57	0.44 (0.60)	29	0.24 (0.51)	0.20 (-0.06, 0.46)	NS
Disease anxiety	57	0.31 (0.53)	29	0.15 (0.49)	0.16 (-0.08, 0.39)	NS
Swallowing anxiety	57	0.60 (0.78)	29	0.40 (0.72)	0.19 (-0.15, 0.54)	NS

Source: Table 2-26, p116 of the submission.

Abbreviations: BID = twice daily; BOT = budesonide orally disintegrating tablet; CI = confidence interval; DB = double-blind; FAS = full analysis set; LOCF = last observation carried forward; MD = mean difference; NS = not significant; PBO = placebo; SD = standard deviation; SHS = short health survey.

Notes: ^aTypographical error was identified and corrected during evaluation (corrections were obtained from EOS-1 CSR, p878). **Bold** indicates statistically significant results.

a. p-value estimated based on confidence intervals as exact p-value was not reported.

6.16 The mean absolute change in the EoE-QoL-A questionnaire overall score (30 items) was greater for the BOT 1 mg (0.47) versus the placebo group (0.24), indicating greater improvement in QoL from baseline for the patients in the BOT 1 mg group, albeit this difference was not statistically significant. There were, however, statistically significant differences in favour of BOT for the eating/diet impact (in both 10, and 4 items). The absolute change in Short Health Survey (modSHS) mean scores from baseline to week 6 were greater in the BOT 1 mg group, versus the placebo group.

EOS-2 (maintenance of remission)

6.17 Maintenance of clinicohistologic remission was defined as absence of the following criteria at any time during the 48-week DB treatment phase:

- Clinical relapse, i.e., symptom score of ≥4 points for dysphagia or odynodysphagia, respectively, (based on 7-day recall, using 0-10 point NRS)
- Histological relapse, i.e., a peak of ≥48 eos/mm² hpf at week 48/EOT

- Experiencing a food impaction requiring endoscopic intervention at any time
- Need for an endoscopic dilation at any time
- Premature withdrawal for any reason

- 6.18 The key results for primary and secondary endpoints are presented in Table 6 and Table 7. The percentage of study subjects maintaining clinicohistologic remission after 48 weeks in the FAS-DB treatment phase was 75.0% (51/68) in the BOT 1 mg BID group, 73.5% (50/68) in the BOT 0.5 mg BID group and 4.4% (3/68) in the placebo group. The submission stated that the one-sided p-value resulting from the normal approximation test was <0.001, indicating a statistically significant treatment effect in favour of both BOT regimens; BOT 1 mg BID versus placebo (difference: 70.60%; 97.5% CI: 57.56%, 83.61%); BOT 0.5 mg BID versus placebo (difference: 69.1%; 95% CI: 55.89%, 82.34%). This was reasonable. As noted, a statistically significant treatment effect in favour of BOT 0.5 mg was also observed in EOS-2, indicating superiority of this strength against placebo in the maintenance setting (48 weeks).
- 6.19 Results from the secondary endpoints of histological relapse, clinical relapse, mean change in the peak eos/mm² hpf, clinical remission, deep disease remission, at 48 weeks showed a statistically significant treatment effect in favour of both BOT regimens (0.5 and 1 mg) versus placebo.

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Table 6: Results for key endpoints in the EOS-2 maintenance of remission study

Outcome measure	BOT 1 mg BID N=68	BOT 0.5 mg BID N=68	Placebo N=68	Treatment difference (from placebo)		RR (95%CI) ^a		RD (95%CI) ^a	
				BOT 1 mg BID	BOT 0.5 mg BID	BOT 1 mg BID	BOT 0.5 mg BID	BOT 1 mg BID	BOT 0.5 mg BID
Primary endpoint									
Maintaining clinicohistologic remission at 48 weeks/EOT (FAS-DB): n/N (%)	51/68 (75.0%)	50/68 (73.5%)	3/68 (4.4%)	70.60% (97.5% CI: 57.56%, 83.61%); p<0.0001	69.12% (97.5% CI: 55.89%, 82.34%); p<0.0001	17.00 (5.58, 51.83)	16.67 (5.46, 50.85)	0.71 (0.59, 0.82)	0.69 (0.58, 0.81)
A-priori ordered key secondary endpoints									
Histological relapse at 48 weeks/EOT (FAS-DB)	7/68 (10.3%)	9/68 (13.2%)	61/68 (89.7%)	-79.41% (97.5% CI: -91.09%, -67.73%); p<0.0001	76.47% (97.5% CI: -88.84%, -64.10%); p<0.0001	0.11 (0.06, 0.23)	0.15 (0.08, 0.27)	-0.79 (-0.90, -0.69)	-0.76 (-0.87, -0.66)
Change in the peak eos/mm ² hpf from baseline to week 48/EOT (FAS-DB): Mean (SD)	21 (63.9) [n=65]	38 (112.5) [n=66]	262 (216.7*) [n=65*]	-241.0 (95% CI: -295.84, -186.16); p<0.0001	-224.0 (95% CI: -283.17, -164.83); p<0.0001	NR	NR	NR	NR
Clinical relapse, food impaction which needed endoscopic intervention, or endoscopic dilation at 48 weeks/EOT (FAS-DB)	5/68 (7.4%)	7/68 (10.3%)	41/68 (60.3%)	-52.94% (97.5%CI: -68.01%, -37.87%); p<0.0001	-50.0% (97.5% CI: -65.66%, -34.34%)* p<0.0001	0.12 (0.05, 0.29)	0.17 (0.08, 0.35)	-0.53 (-0.66, -0.40)	-0.50 (-0.64, -0.36)
Clinical remission defined as total weekly score of EEsAI-PRO score of ≤20 at 48 weeks/EOT: n/N (%)	50/68 (73.5%)	49/68 (72.1%)	14/68 (20.6%)	52.9% (97.5% CI: 36.7%, 69.2%); p<0.0001	51.5% (97.5% CI: 35.1%, 67.9%); p<0.0001	3.57 (2.19, 5.82)	3.50 (2.14, 5.71)	0.53 (0.39, 0.67)	0.51 (0.37, 0.66)
Deep disease remission at 48 weeks/EOT: n/N (%)	36/68 (52.9%)	27/68 (39.7%)	0/68 (0%)	52.9% (97.5% CI: 39.4%, 66.5%); p<0.0001	39.7% (97.5% CI: 26.4%, 53.0%); p<0.0001	73.00 (4.57, 1165.80)	55.00 (3.42, 883.82)	0.53 (0.41, 0.65)	0.40 (0.28, 0.51)

Source: Table 2-2, p51, Table 2-27, p117, Table 2-28, p119, Table 2-29, p121, Table 2-30, p122, Table 2-31, p124, Table 2-32, p125 of the submission.

Abbreviations: BID = twice daily; BOT = budesonide orally disintegrating tablets; CI = confidence interval; DB = double-blind treatment phase; EEsAI-PRO = eosinophilic oesophagitis activity index- patient reported outcome; eos = eosinophils; EOT = end of treatment; FAS = full analysis set; hpf = high power field; NR = not reported; RD = risk difference; RR = relative risk.

Notes: *Typographical error identified and corrected during evaluation (corrections were obtained from EOS-2 CSR, p678). *Confidence interval values obtained from EOS-2 CRS, pp614-615 (these values were presented in the submission as “not reported”). **Bold** indicates statistically significant results.

a. Calculated post-hoc for the submission using Review Manager 5.4.

6.20 The overall EoE-QoL-A score and the scores of each of the six domains decreased, indicating deterioration of QoL from baseline to end of treatment. In contrast, the overall EoE-QoL-A score and scores of each of the six domains improved in the two

BOT groups. The differences between absolute changes from the baseline revealed statistically significant differences in favour of both BOT versus placebo.

Table 7: Change from baseline in the Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) Questionnaire

Treatment arm	Intervention		Placebo		MD (95% CI)	p-value ^a
	N	Mean change (SD)	N	Mean change (SD)		
Change from Baseline to EOT in the EoE-QoL-A Questionnaire (week 48/EOT; FAS-DB treatment phase)						
30 items						
BOT 1 mg BID	63	0.26 (0.50)	61	-0.24 (0.62)	0.50 (0.30, 0.70)	<0.0001^b
BOT 0.5 mg BID	62	0.23 (0.44)	61	-	0.46 (0.27, 0.65)	<0.0001
24 items						
BOT 1 mg BID	63	0.26 (0.51)	61	-0.26 (0.62)	0.52 (0.32, 0.72)	<0.0001^b
BOT 0.5 mg BID	62	0.23 (0.45)	61	-	0.49 (0.30, 0.68)	<0.0001^b

Source: Table 2-35, p130 of the submission.

Abbreviations: BID = twice daily; BOT = budesonide orally disintegrating tablet; CI = confidence interval; DB = double-blind; EOT = end of treatment; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life; FAS = full analysis set; LOCF = last observation carried forward; MD = mean difference; NR = not reported; PBO = placebo; SD = standard deviation; SHS = Short Health Survey.

Notes: **Bold** indicates statistically significant results.

a. one-sided normal approximation test.

b. One-sided p-value from Fisher's exact test.

c. Calculated post-hoc for the submission using Review Manager 5.4.

Comparative harms

EOS-1 (induction of remission)

- 6.21 The summary of key adverse events (AE) data for BOT from EOS-1 is presented in Table 8. The submission noted that there were no SAEs, AEs leading to discontinuation, or deaths reported during the study. The submission stated that overall, the frequency of TEAEs was low in both treatment groups but was higher for BOT noting the vast majority of AEs were of mild or moderate severity. This seems reasonable and was consistent with the clinical claim of BOT inferiority in terms of safety compared to placebo.
- 6.22 The most frequently reported TEAE during the 6-week DB phase was suspected local fungal infection, documented in 14/59 (23.7%) of patients receiving BOT 1 mg (none for placebo). The difference between the treatment groups was statistically significant in terms of the risk difference; RD = 0.24 (95% CI: 0.12, 0.35).

Table 8: Summary of key adverse events^a in EOS-1

Trial ID	BOT 1 mg BID n = 59		Placebo n = 29		Post-hoc analyses of treatment difference (BOT vs. PBO) RR <1 or RD < 0 favours BOT	
	No. of events	No. of patients n/N (%)	No. of events	No. of patients n/N (%)	RR (95% CI) ^b	RD (95% CI) ^b
EOS-1						
Any TEAE	62	37/59 (62.7)	19	12/29 (41.4)	1.52 (0.94, 2.44)	0.21 (-0.00, 0.43)
Severe AE	0	0		1/29 (3.4)	0.17 (0.01, 3.97)	-0.03 (-0.12, 0.05)
Oesophageal food impaction	0	0	1	1/29 (3.4)	0.17 (0.01, 3.97)	-0.03 (-0.12, 0.05)
Study drug related TEAE	27	23/59 (39.0)	1	1/29 (3.4)	11.31 (1.60, 79.63)	0.36 (0.21, 0.50)
Serious AE	0	0	0	0	NA	0.00 (-0.05, 0.05)
TEAE leading to withdrawal from study	0	0	1	1/29 (3.4)	0.17 (0.01, 3.97)	-0.03 (-0.12, 0.05)

Source: Table 2-36, p132 of the submission.

Abbreviations: AE = adverse event; BID = twice daily; BOT = budesonide orally disintegrating tablet; CI = confidence interval; DB = double-blind; NA = not applicable; n = number of participants reporting data; N = total participants in group; PBO = placebo; RD = risk difference; RR = relative risk.

Notes: **Bold** indicates statistically significant results.

a. Definitions: Treatment emergent AE defined as any event with an onset occurring after first administration of the intervention or, if pre-existing, worsening after first administration of the intervention, and occurring within the period of treatment with the intervention.

A study drug related TEAE was defined as an AE that was certainly, probably/likely, or possibly caused by the administration of IMP according to the assessment of the investigator.

Serious AE defined as any untoward medical occurrence that at any dose: results in death, is life threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

b. Calculated post-hoc for the submission using Review Manager 5.4.

EOS-2 (maintenance of remission)

- 6.23 A summary of the key AE data for BOT from EOS-2 is presented in Table 9.
- 6.24 There were 34 events of study drug related TEAE reported in a total of 22 patients (32.4%) in both BOT groups (0.5 mg and 1 mg) versus 3 events in a total of three patients (4.4%) in the placebo group. The submission stated that there were no SAEs reported in the placebo group, 1 (1.5%) in the BOT 1 mg BID group and 4 (4.4%) in the BOT 0.5 mg BID group. In post-hoc analyses, the difference in frequency of study drug related TEAE between BOT treatment group and the placebo group was statistically significant in favour of placebo. The safety profile of BOT was consistent with the clinical claim that BOT is inferior to placebo in terms of safety after 48 weeks. Safety of BOT beyond 12 weeks (induction) has not been assessed by the TGA.
- 6.25 The submission stated that there was a higher incidence of TEAEs leading to discontinuation in the placebo group (60.3%) and this was statistically significant versus both the BOT 1 mg BID group (11.8%) and the BOT 0.5 mg BID group (10.3%). The major reason for discontinuation was 'condition aggravated', occurring in 60.3% of the placebo group, versus 7.4% and 10.3% in the BOT 1 mg BID and the BOT 0.5 mg groups, respectively. This is consistent with the natural history of the disease when left untreated.

Table 9: Summary of key adverse events^a in EOS-2

Trial ID	BOT 0.5 mg BID n = 68		BOT 1 mg BID n = 68		Placebo n = 68		Post-hoc analyses of treatment difference (BOT vs. PBO) RR < 1 or RD < 0 favours BOT			
	No. of events	No. of patients n/N (%)	No. of events	No. of patients n/N (%)	No. of events	No. of patients n/N (%)	Relative risk (95% CI) ^b		Risk difference (95% CI) ^b	
							BOT 0.5 mg	BOT 1 mg	BOT 0.5 mg	BOT 1 mg
EOS-2										
Any TEAE	258	57/68 (83.8)	226	59/68 (86.8)	161	61/68 (89.7)	0.93 (0.82, 1.07)	0.97 (0.86, 1.09)	-0.06 (-0.17, 0.05)	-0.03 (-0.14, 0.08)
Study drug related TEAE	34	22/68 (32.4)	34	22/68 (32.4)	3	3/68 (4.4)	7.33 (2.30, 23.36) p=0.0007	7.33 (2.30, 23.36) p=0.0007	0.28 (0.16, 0.40) p<0.0001	0.28 (0.16, 0.40) p<0.0001
Serious AEs	4	3/68 (4.4)	1	1/68 (1.5)	0	0/68 (0)	7.00 (0.37, 132.99)	3.00 (0.12, 72.37)	0.04 (-0.01, 0.10)	0.01 (-0.03, 0.05)
TEAE leading to withdrawal from study	7	7/68 (10.3)	9	8/68 (11.8)	42	41/68 (60.3)	0.17 (0.08, 0.34) p<0.0001	0.19 (0.10, 0.37) p<0.0001	-0.51 (-0.65, -0.38) p<0.0001	-0.50 (-0.64, -0.36) p<0.0001

Source: Table 2-38, p136 and Table 2-39, pp136-137 of the submission.

Abbreviations: ADR = adverse drug reaction; AE = adverse event; BID = twice daily; BOT = budesonide orally disintegrating tablet; CI = confidence interval; DB = double-blind; NR = not reported; PBO = placebo; SAF = safety analysis set; WDAE = adverse event where measures include that DB IMP was withdrawn.

Notes: **Bold** indicates statistically significant results.

a. Definitions: Treatment emergent AE defined as any event with an onset occurring after first administration of the intervention or, if pre-existing, worsening after first administration of the intervention, and occurring within the period of treatment with the intervention.

Study drug related TEAS (ADR) is defined as an AE with causality = certain, probably/likely or possible. Causality assessment for suspected ADR was done according to the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring (See CSR p. 98).

Serious AE defined as any untoward medical occurrence that at any dose: results in death, is life threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or meets the definition of other medical important conditions (see CSR p.96).

b. Calculated post-hoc for the submission using Review Manager 5.4.

Benefits/harms

6.26 A summary of comparative benefits and harms for BOT 1 mg BID and placebo is presented in Table 10.

Table 10: Summary of comparative benefits and harms for BOT 1 mg BID and PBO

Trial	BOT n/N	PBO n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				BOT	PBO	
Benefits						
Clinicohistologic remission at 6 weeks						
EOS-1 (induction)	34/59	0/29	34.50 (2.19, 543.57)	57.6	0	0.58 (0.44, 0.71)
Maintaining clinicohistologic remission at 48 weeks						
EOS-2 (maintenance)	51/68	3/68	17.00 (5.58, 51.83)	75.0	4.4	0.71 (0.59, 0.82)
Harms						
Study drug related TEAE						
EOS-1 (induction)	23/59	1/29	11.31 (1.60, 79.63)	39.0	3.4	0.36 (0.21, 0.50)
EOS-2 (maintenance)	22/68	3/68	7.33 (2.30, 23.36) p=0.0007	32.4	4.4	0.28 (0.16, 0.40) p<0.0001
TEAE leading to withdrawal from study						
EOS-1 (induction)	0	1/29	0.17 (0.01, 3.97)	0	3.4	-0.03 (-0.12, 0.05)
EOS-2 (maintenance)	8/68	41/68	0.19 (0.10, 0.37) p<0.0001	11.8	60.3	-0.50 (-0.64, -0.36) p<0.0001
Suspected local fungal infection						
EOS-1 (induction)	14/59	0	14.50 (0.90, 234.88)	23.7	0	0.24 (0.12, 0.35) p<0.0001
EOS-2 (maintenance)	10/68	0	21.00 (1.26, 351.38) p=0.03	14.7	0	0.15 (0.06, 0.23) p=0.01
Oesophageal candidiasis						
EOS-1 (induction)	10/59	0	10.50 (0.64, 173.18)	16.9	0	0.17 (0.06, 0.28) p=0.04
EOS-2 (maintenance)	3/68	0	7.0 (0.37, 132.99)	4.4	0	0.04 (-0.01, 0.10)

Source: Table 2-1, p50, Table 2-2, p51, Table 2-36, p132, Table 2-37, p134, Table 2-38, p136, Table 2-39, pp136-137, Table 2-40, pp138-139, and Table 2-41, pp139-141 of the submission.

Abbreviations: HR = hazard ratio; PBO = placebo; BOT = budesonide orally disintegrating tablet; RD = risk difference; RR = risk ratio; TEAE = treatment emergent adverse event.

Notes: **Bold** indicates statistically significant results.

* Maximum duration of follow-up: EOS-1 = 6 weeks; EOS-2 = 48 weeks.

6.27 On the basis of direct evidence presented by the submission, for every 100 patients treated with BOT 1 mg BID in comparison with placebo:

- Approximately 57.6 additional patients would have been in clinicohistologic remission (an absence of symptoms and without cellular evidence of disease) at 6 weeks.
- Approximately 70.6 additional patients would maintain clinicohistologic remission (an absence of symptoms and without cellular evidence of disease) at 48 weeks.

- Approximately 35.6 additional patients would experience a study drug related TEAE after 12 weeks of therapy.
- Approximately 28 additional patients would experience a study drug related TEAE once continuing therapy beyond 12 weeks.
- Approximately 23.7 additional patients would experience suspected local fungal infection (including oral, oesophageal, and oropharyngeal infections) during the first 12 weeks, of which 16.9 additional patients would experience oesophageal candidiasis (a fungal infection in the throat).
- Approximately 14.7 additional patients would experience suspected local fungal infection (including oral, oesophageal, and oropharyngeal infections) during the 48 weeks of maintenance treatment, of which 4.4 additional patients would experience oesophageal candidiasis (a fungal infection in the throat).

Clinical claim

- 6.28 The submission described BOT 1 mg BID as superior in terms of effectiveness compared to placebo. Overall, the clinical claim of superiority compared to placebo at either 6 or 48 weeks was well supported by the evidence. The ESC agreed with the evaluation that the clinical claim of superiority was well supported by the evidence. However, the ESC considered a key issue was that the use of BOT in the maintenance setting (beyond the 12 weeks of induction phase) was not consistent with the current TGA approved PI.
- 6.29 The applicability of the clinical effectiveness claim to the proposed use on the PBS remains uncertain largely due to the trial excluding patients who were PPI-naïve and those with baseline EoE disease activity that would be included in the proposed PBS listing. The PSCR argued that the eligibility criteria in the BOT studies reflected early guidelines, which have since been updated to remove the requirement for a PPI trial as part of the diagnostic work-up for EoE patients. The ESC noted that the requirement to be refractory to PPI treatment in the proposed restriction would require all patients to be treated with a non-TGA approved and non-PBS subsidised treatment prior to being eligible for BOT. The PBAC considered it appropriate to include PPI naïve patients in the proposed PBS population.
- 6.30 Evidence for supplementary treatment with BOT 1 mg BID for an additional 6 weeks (for a total of 12 weeks) for patients who had not responded to the treatment during the first 6 weeks was non-comparative. Thus, the claim of BOT superiority relies on acceptance of the premise that no patients in the placebo group would have achieved spontaneous resolution of EoE with a further six weeks of follow-up. This may be reasonable given the natural history of EoE (Dellon 2018^f). The ESC agreed with the

^f Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. *Gastroenterology*. 2018;154(2):319-332.

PSCR that given the natural history of EoE spontaneous resolution on placebo was unlikely.

- 6.31 The submission described BOT as inferior in terms of safety compared to placebo. The ESC considered this claim was adequately supported.
- 6.32 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.33 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.34 The submission presented a stepped economic evaluation based on the direct RCTs (EOS-1 and EOS-2), including a modelled cost-utility analysis (CUA) comparing BOT 1 mg BID (induction and maintenance therapy) with SOC (i.e. no active treatment). The key components of the economic evaluation are described in Table 11.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	BOT vs SOC
Time horizon	5 years in the model base case vs. 60 weeks (12 weeks induction + 48 weeks maintenance) in the key trials (EOS-1 and EOS-2)
Outcomes	% patients with clinicohistologic remission, quality-adjusted life-years (QALYs)
Methods used to generate results	Markov model
Health states ^a	<p>Seven health states (plus death)</p> <ul style="list-style-type: none"> • Induction • Clinicohistologic remission (BOT and SOC^b) • Histologic remission only (BOT and SOC) • No remission (i.e. neither clinicohistologic or histologic) • All-cause death
Cycle length	3 months
Transition probabilities	<p><u>Based on EOS-1</u></p> <ul style="list-style-type: none"> • Probability of clinicohistologic remission with induction therapy • Probability of histologic remission only with induction therapy • Probability of achieving clinical remission during maintenance treatment (from histologic remission) <p><u>Based on EOS-2</u></p> <ul style="list-style-type: none"> • Probability of losing clinicohistologic remission during maintenance treatment • Probability of losing histologic remission during maintenance treatment (from histologic remission) <p><u>Based on Australian life tables</u></p> <ul style="list-style-type: none"> • Probability of all-cause mortality
Extrapolation method	The submission assumed the probability of losing histologic remission within each treatment cycle remained constant over the 5-year time horizon. 74% of incremental QALYs (and 59% of incremental costs) occurred in the extrapolated period. ^c
Health related quality of life	Survey of Australian adults EoE patients (n=68) using EQ-5D-5L questionnaire in two different contexts (symptomatic EoE and non-symptomatic EoE). The utility value applied were: Clinicohistologic remission health state = 0.780; No remission and histologic remission only health state = 0.609.
Resource utilisation	PBS: cost of drugs; MBS: physician consults; Hospital services: endoscopy (treatment evaluation), endoscopy (dilation), food bolus impactions requiring endoscopic removal. The approach in the model was to include health care use that reflected local practice even if not observed in the clinical trials, such as dilation and endoscopic removal of food due to impaction.

Source: compiled during the evaluation based on data from the submission and Table 3-1, p167 of the submission.

Abbreviations: BOT = budesonide orally disintegrating tablets; EoE = eosinophilic oesophagitis; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; QALY = quality-adjusted life-year; SOC = standard of care.

^a The health state of clinicohistologic remission refers to a health state where the patient has neither symptoms (clinical) nor evidence of EoE on endoscopy (histologic; i.e. <5 eos/hpf; equivalent to <16 eos/mm²hpf). Histologic remission only refers to a health state where the patient has no evidence of EoE on endoscopy, but symptoms have remained.

^b The term standard of care (SOC) was used to mean “no active treatment”, or placebo.

^c Calculated during the evaluation by subtracting incremental QALYs and costs in Step 4 from Step 5, then dividing it by the incremental QALYs and costs in Step 5 (Table 3-20, p220 of the submission).

6.35 The submission included an additional BOT treatment algorithm in the model to assess the cost-effectiveness of a single cycle of induction therapy (single induction followed by SOC maintenance). In this algorithm, the model excluded the event cost associated with one post-induction therapy endoscopy (to assess treatment response) from the BOT arm. This may not be reasonable as clinicians may use endoscopy to assess histological response upon treatment completion due to the poor correlation between symptoms and histological severity (RACGP 2015). Further, the model does not allow for the repeated use of BOT induction therapy and this is not aligned with the proposed restriction which allows the use of BOT in a retreatment setting. The

PSCR stated that the economic model did not explicitly allow for repeated cycles of BOT induction therapy upon relapse, given the presumption that patients attaining histological/clinicohistologic remission would undergo maintenance therapy with BOT. The ESC considered the model and its inputs was designed to consider BOT as induction and maintenance therapy, and is not well suited to considering BOT as induction therapy only.

- 6.36 The submission also presented supplementary comparative cost analyses of BOT versus off-label STC, off-label PPI and dietary management.
- 6.37 While the use of BOT in the induction and maintenance therapy model was consistent with the proposed clinical management algorithm and proposed PBS listing, there were inconsistencies with the clinical evidence. In EOS-1 (induction study), the majority of patients received 6 weeks of induction treatment while the model assumed all patients allocated to BOT received 12 weeks of induction treatment. In EOS-2 (maintenance study), patients had to be in clinicohistologic remission to be eligible for enrolment while the model allowed patients in the histologic remission only health state (i.e. not clinicohistologic remission) to receive maintenance treatment.
- 6.38 To estimate the proportion of patients in clinicohistologic remission who transition to active disease (no remission) during maintenance treatment, the model applied the probability of losing histologic remission instead of the probability of losing clinicohistologic remission during maintenance treatment. The submission's approach implicitly assumed that clinicohistologic patients who experienced clinical relapse (but maintained histologic remission) would continue maintenance treatment, whereas in EOS-2, clinical relapse was one of the criteria for treatment failure. The model inappropriately allowed symptomatic patients (i.e. without clinical remission) to remain in the clinicohistologic health state and accrue the health benefits of a non-symptomatic health state; the model does not allow patients to transition from clinicohistologic to histologic remission only. For BOT, a probability of 14.7% (converted to 4.2% per cycle) was applied in the model based on the proportion of patients who did not maintain histological remission after 48 weeks in EOS-2. In EOS-2, 25% of patients in the BOT arm failed to maintain clinicohistologic remission after 48 weeks of treatment. The PSCR stated that 51 of 68 (75%) of the patients in the BOT 1 mg BID treatment arm of EOS-2 were free of treatment failure. The PSCR argued that it was not necessarily the case that 25% of patients lost clinicohistologic remission as the definition of treatment failure comprised several discrete events, including patient choice/discontinuations. The ESC considered that varying the probability of losing remission with BOT had a minor effect on the ICER (see Table 16).
- 6.39 In the model, patients who were on maintenance treatment in the histologic remission only health state were allowed to transition to a clinicohistologic remission health state. For BOT, a probability of 76.2% was applied in the model based on the assumed proportion of histologic only remitters at Week 6 in EOS-1 who achieved clinicohistologic remission at Week 12 after receiving an additional 6 weeks of

- induction treatment. This was not appropriate as the model applied a probability derived from an induction study to a maintenance treatment health state.
- 6.40 For extrapolation, the model assumed the probability of losing histologic remission within each treatment cycle remained constant over the 5-year time horizon. While a 5-year time horizon may be reasonable, no evidence was presented to support the constant histologic remission rate beyond the trial duration. The PSCR argued that a time horizon of 5 years was consistent with published economic evaluations in EoE. The ESC considered that it remained uncertain what the rate of remission would be, however noted that this only had a minor effect on the ICER (see Table 16).
- 6.41 Due to the inconsistency between the structure of the model and the clinical evidence, the transition probabilities applied in the model did not reflect the flow of patients as observed in the clinical trials. Accordingly, the transitions applied in the model do not reflect the clinical evidence (mostly favouring BOT) but are consistent with the proposed PBS listing.
- 6.42 The utility values applied in the economic model were based on an Australian patient survey (n=68) conducted by the Sponsor in August/September 2020 (the survey collected information on diagnostic history, symptomatic burden, treatment patterns, and resource utilisation as well). This was a vignette-based survey that relied on respondents completing the EQ-5D-5L as if they were in a state of symptomatic EoE or, separately, non-symptomatic EoE. The vignettes did not describe the treatment required to achieve the non-symptomatic state.
- 6.43 The results of the survey should be interpreted with caution due to the high risk of confounding from recall bias, noting that six respondents stated their EoE symptoms were never well controlled. Further, the applicability of the survey may be compromised by the gender distribution (31% males), current treatment (12% STC) and respondents' past experience of symptomatic versus non-symptomatic EoE. The proportion of male patients was reported to be 81% in an Australian prospective observational study by Philpott (2016).
- 6.44 In addressing the gender applicability issue, the submission re-calculated the aggregate EQ-5D scores by weighting mean scores for males and females according to the gender distribution in EOS-1 (83% males). For EoE symptoms not under control, a higher mean score was observed in male respondents (0.6304) compared with female respondents (0.5068). For EoE symptoms under control, a higher mean score was observed in female respondents (0.8079) compared with male respondents (0.7742). As such, the direction of bias is unclear based on the submission's approach in weighting the mean scores according to gender distribution. The utility values derived from the EoE survey were considerably lower than the values reported in published literature for both health states. The PSCR acknowledged the potential weaknesses of the survey but argued the survey generated utility values were internally consistent and able to be applied to the health states of the model. In addition, the PSCR noted that the no alternative published data sources were identified by the evaluation. The

ESC noted that there was an overall lack of high quality evidence around appropriate utility values for the population. The ESC also noted that the model was sensitive to the utility values selected, and concluded that this was the area of most meaningful uncertainty in the model without a clear favoured resolution. The pre-PBAC response argued that by conducting the Australian patient survey the submission attempted to address the lack of EoE specific utility values in the published literature as opposed to relying on proxies or assumptions.

- 6.45 For dilation resource use, the model applied the utilisation rate reported in Runge (2017) in 30% of patients derived from the patient survey. By applying the rates to 30% of patients in the model, the utilisation of dilation was likely to be underestimated because the dilation rates (mean number of dilations per patient) reported in Runge (2017) had implicitly accounted for patients who did not require dilation (48% in responders and 25% in non-responders). For endoscopic removal of impacted food, the model applied the utilisation rate reported in Kuchen (2014) in all patients. This was not consistent with EOS-2, whereby no patients required dilation, and only 1.5% of placebo patients required endoscopic removal of food due to impaction.
- 6.46 The disaggregated outcomes for the comparison of BOT with SOC are presented in Table 12. The model resulted in an incremental benefit of 0.4770 QALYs which was driven by the QALY gain in the clinicohistologic remission health state. The incremental benefit was attributed to the longer time BOT patients spend in the clinicohistologic remission health state (higher utility value) compared with SOC patients.

Table 12: Disaggregated summary of health outcomes included in the economic evaluation

Outcome	BOT	SOC	Incremental outcome
LY			
Induction	0.1250	0.1250	0
CH remission	3.1051	0	3.1051
H remission only	0.0274	0	0.0274
No remission	1.7280	4.8605	-3.1325
Overall total	4.9855	4.9855	0
QALY			
Induction	0.0761	0.0761	0
CH remission	2.1760	0	2.1760
H remission only	0.0164	0	0.0164
No remission	0.9030	2.6184	-1.7154
Overall total	3.1716	2.6945	0.4770

Source: compiled during the evaluation from TreeAge and Figure 3-13, p218 of the submission; Table 3-20, p220 of the submission.

Abbreviations: BOT = budesonide orally disintegrating tablet; LY = life-year; QALY = quality-adjusted life-year; SOC = standard of care

- 6.47 The disaggregated costs for the comparison of BOT with SOC are presented in Table 13. The application of dilation costs based on the published literature and patient survey resulted in a 23.6% reduction of total incremental costs, favouring BOT.

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Table 13: Health care resource items: disaggregated summary of cost impacts

Resource item	BOT	SOC	Incremental cost	% of total incremental cost
Pharmaceutical products				
Induction drug costs	\$ [REDACTED]	\$0.00	\$ [REDACTED]	9.4%
Maintenance drug costs	\$ [REDACTED]	\$0.00	\$ [REDACTED]	106.5%
Total	\$ [REDACTED]	\$0.00	\$ [REDACTED]	115.9%
Medical services				
Physician consultation costs	\$541.56	\$541.56	\$0.00	0%
Endoscopy costs (treatment evaluation)	\$1,234.93	\$0.00	\$1,234.93	9.3%
Dilation costs (endoscopy)	\$4,496.47	\$7,636.66	-\$3,140.19	-23.6%
Impaction costs (requiring endoscopy)	\$187.00	\$396.62	-\$209.61	-1.6%
Total	\$6,459.96	\$8,574.84	-\$2,114.88	-15.9%
Overall total	\$ [REDACTED]	\$8,574.84	\$ [REDACTED]	100%

Source: Table 3-21 of the submission.

Abbreviations: BOT = budesonide orally disintegrating tablet; SOC = standard of care

6.48 A summary of the key drivers of the model is presented in Table 14. The model results were most sensitive to the utility estimates, with the ICER increasing from \$25,000 to < \$35,000/QALY in the base case to \$75,000 to < \$95,000/QALY when the utility estimates from Goodwin 2020 were applied. The utility values (EQ-5D-3L) from a conference abstract produced by Goodwin 2020 were derived from an RCT conducted in an EoE-specific population comparing budesonide (oral suspension) with placebo. By using the utility estimates from Goodwin 2020, disutility due to adverse events from BOT could be considered implicitly accounted for, whereas the Australian EoE survey has not accounted for this effect. However, the ESC noted that this was not necessarily a high-quality source of evidence, being from a conference abstract with little details of methodology and population. The PBAC acknowledged ESC's concerns regarding the use of utility values from a conference abstract. However, the PBAC noted Goodwin 2020 was a phase 3 RCT involving 318 patients randomised to receive budesonide for EoE with health states captured using a validated multi-attribute utility instrument. Of the published and nonpublished sources identified the PBAC considered that Goodwin 2020 was the preferred source of utility values based on evidence hierarchy considerations outlined in the PBAC Guidelines Version 5.0.

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Table 14: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$ [redacted] /QALY gained
Utilities	Survey of Australian population of adults EoE patients (CH remission = 0.780, H remission only and no remission = 0.609)	High, favours BOT. Use of utilities from Goodwin 2020 (0.971, 0.907) increased the ICER to \$ [redacted] /QALY gained.
Time horizon	5 years extrapolated from 60 weeks data (12 weeks induction + 48 weeks maintenance) of the key trials (EOS-1 and EOS-2)	Moderate, favours BOT. A time horizon of 1 year increased the ICER to \$ [redacted] /QALY gained.
Dilation costs	Rate reported in Runge (2017) applied to 30% of patients derived from the patient survey	Moderate; bias unclear. Removing dilation costs increased the ICER to \$ [redacted] /QALY gained but applying them to all patients decreased it to \$ [redacted] /QALY.
Extrapolation	Probability of losing remission with BOT each cycle (14.7%; converted to 4.2% per cycle).	Moderate, favours BOT. ICER varies from \$ [redacted] /QALY (25%; 7.5% per cycle) to \$ [redacted] /QALY (first year 14.7%, subsequent years same as SOC)

Source: constructed during the evaluation

Abbreviations: BOT = budesonide orally disintegrating tablet; EoE = eosinophilic oesophagitis; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$55,000 to < \$75,000

³ \$35,000 to < \$45,000

⁴ \$5,000 to < \$15,000

6.49 The results of the stepped economic evaluation are presented in Table 15. Transforming the health outcomes to QALYs (in Step 3) resulted in an ICER of \$35,000 to < \$45,000/QALY. The difference in QALYs between the two arms was driven by the utility values as the total LYs in both arms were the same. The QALY gain was due to more patients in the BOT arm spending their time in clinicohistologic remission compared with patients in the SOC arm (0%).

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Table 15: Results of the stepped economic evaluation

Step and component	BOT	SOC	Increment
Step 1a: Trial-based, induction, 12 weeks, drug costs only, H remission			
Costs	\$█	\$0	\$█ ¹
H remission	0.9322	0	0.9322
Incremental cost/extra H remission gained			\$█ ¹
Step 1b: Trial-based, induction, 12 weeks, drug costs only, CH remission			
Costs	\$█	\$0	\$█ ¹
CH remission	0.8475	0	0.8475
Incremental cost/extra CH remission gained			\$█ ¹
Step 2: Modelled, induction and maintenance, 12 months, drug costs only, CH remission			
Costs	\$█	\$0	\$█ ²
CH remission	0.8173	0	0.8173
Incremental cost/extra CH remission gained			\$6,154
Step 3: Transform to QALYs			
Costs	\$█	\$0	\$█ ²
QALY	0.7180 [^]	0.5941 [^]	0.1239 [^]
Incremental cost/extra QALY gained			\$█ ^{^,3}
Step 4: Include non-drug costs			
Costs	\$█ [^]	\$█ [^]	\$█ [^]
QALY	0.7180 [^]	0.5941 [^]	0.1239 [^]
Incremental cost/extra QALY gained			\$█ ^{^3}
Step 5: Extrapolate to 5 years			
Costs	\$█	\$8,575	\$█ ²
QALY	3.1716	2.6945	0.4770
Incremental cost/extra QALY gained			\$█ ⁴

Source: Table 3-20, p220 of the submission.

Abbreviations: BOT = budesonide orally disintegrating tablet; CH = clinicohistologic; H = histologic; QALY = quality-adjusted life-year; SOC = standard of care

Notes: [^] Corrected error identified during the evaluation (Attachment 6 Excel, "Stepped_EE sheet", cells D11, E11, G10-11, H10-11). Cells reference to _stage = 4 (15 months) when it should have been _stage = 3 (12 months).

The redacted values correspond to the following ranges:

¹ \$0 to < \$5,000

² \$5,000 to < \$15,000

³ \$35,000 to < \$45,000

⁴ \$25,000 to < \$35,000

6.50 The results of key univariate and multivariate sensitivity analyses are summarised in Table 16. The model was robust to the additional parameter variations tested for: the probability of clinicohistologic or histologic remission only with BOT induction; probability of losing remission while on BOT maintenance; utilisation of food impactions requiring endoscopy; and the exclusion of histologic remission only health state.

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Table 16: Results of sensitivity analyses

Variable	Base-case	Sensitivity analysis	Incremental costs	Incremental QALYs	ICER	% change from base case
Base-Case	-	-	\$ [REDACTED]	0.4770	\$ [REDACTED] ¹	-
Efficacy inputs						
Probability H remission only becomes CH	76% per cycle (16/21)	Removed (0%)	\$ [REDACTED]	0.4379	\$ [REDACTED] ¹	11%
		Halved (38%)	\$ [REDACTED]	0.4730	\$ [REDACTED] ¹	1%
Probability of losing remission with BOT each cycle (after year 1)	4.2% each cycle	Removed	\$ [REDACTED]	0.5698	\$ [REDACTED] ¹	-3%
		Decreased 50%*	\$ [REDACTED] [^]	0.5271 [^]	\$ [REDACTED] ^{^,1}	-2%
		Increased 50%*	\$ [REDACTED] [^]	0.4353 [^]	\$ [REDACTED] ^{^,1}	2%
		Doubled*	\$ [REDACTED] [^]	0.4005 [^]	\$ [REDACTED] ^{^,1}	4%
		Same as SOC*	\$ [REDACTED]	0.1987	\$ [REDACTED] ²	28%
Probability of losing remission with BOT each cycle during maintenance treatment	Year 1: 4.2% per cycle; Sub Years: 4.2% per cycle	Year 1: 7.5% per cycle ¹ ; Sub Years: 7.5% per cycle*	\$ [REDACTED]	0.3726	\$ [REDACTED] ¹	6%
		Year 1: 7.5% per cycle ¹ ; Sub Years: Doubled*	\$ [REDACTED]	0.2931	\$ [REDACTED] ¹	12%
Resource utilisation and cost inputs						
Dilation costs (endoscopy)	\$1,938.60	Double	\$ [REDACTED]	0.4770	\$ [REDACTED] ³	-24%
		Increased 50%	\$ [REDACTED]	0.4770	\$ [REDACTED] ³	-12%
		Decreased 50%	\$ [REDACTED]	0.4770	\$ [REDACTED] ¹	12%
		Removed	\$ [REDACTED]	0.4770	\$ [REDACTED] ¹	24%
Dilation utilisation	Applied to 30% of patients	Removed 30%*	\$ [REDACTED]	0.4770	\$ [REDACTED] ⁴	-55%
Utility inputs						
Utility estimates	0.609 ^a and 0.780 ^a (EoE survey sex adjusted)	0.70 and 0.95 (Cotton 2015)	\$ [REDACTED]	0.6974	\$ [REDACTED] ³	-32%
		0.89 and 0.93 (Cotton 2017)	\$ [REDACTED]	0.1116	\$ [REDACTED] ⁵	327%
		0.94 and 1.00 (Miller 2011)	\$ [REDACTED]	0.1674	\$ [REDACTED] ⁶	185%
		0.543 and 0.798 (EoE survey crude)	\$ [REDACTED]	0.7114	\$ [REDACTED] ³	-33%
		0.907 and 0.971 (Goodwin 2020)	\$ [REDACTED]	0.1785	\$ [REDACTED] ⁷	167%
Other inputs						
Model duration	5 years	1 year	\$ [REDACTED]	0.1239	\$ [REDACTED] ²	56%
		2 years*	\$ [REDACTED]	0.2434	\$ [REDACTED] ¹	19%
		3 years*	\$ [REDACTED]	0.3391	\$ [REDACTED] ¹	8%
		4 years*	\$ [REDACTED]	0.4157	\$ [REDACTED] ¹	3%
		10 years	\$ [REDACTED]	0.6422	\$ [REDACTED] ¹	-5%
Multivariate analysis						
Multivariate analysis	Sensitivity analysis: Probability H remission only becomes CH (removed), Probability losing remission with BOT each cycle during maintenance (7.5% Year 1 and Sub Years), Food impaction removal utilisation (CH: 0.007 per cycle; No remission and H only: 0.017 per cycle), Utility estimates (Goodwin 2020), Adverse events costs (included), Probability of BOT discontinuation (3.3% per cycle)*		\$ [REDACTED]	0.1101	\$ [REDACTED] ⁶	209%

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Variable	Base-case	Sensitivity analysis	Incremental costs	Incremental QALYs	ICER	% change from base case
Multivariate (row 17) + remove dilation and impaction		Sensitivity analysis: As above plus remove dilation and impaction costs*	\$ [REDACTED]	0.1101	\$ [REDACTED] ⁸	275%

Source: Table 3-24, pp223-224 of the submission.

Abbreviations: BOT = budesonide orally disintegrating tablets; CH = clinicohistologic; EoE = eosinophilic oesophagitis; H = histologic; HS = health state; ICER = incremental cost-effectiveness ratio; LCL = lower confidence level; QALY = quality adjusted life year; Sub = subsequent; UCL = upper confidence level; Var = variable

Notes: *Sensitivity analyses conducted during the evaluation using TreeAge. Per cycle rates generated using the ProbToProb function, where applicable.

[^] Corrected error in the root definition for "p_Rem_CH_loseCH" - _stage<5 (applied over 4 cycles in Year 1) instead of _stage<=5 (applied over 5 cycles in Year 1).

^a Typographical error identified during the evaluation; corrected based on values included in TreeAge and Attachment 7

¹ Based on the percentage of patients who failed to maintain clinicohistologic remission after 48 weeks of treatment in EOS-2 (25%; 17/68)

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$35,000 to < \$45,000

³ \$15,000 to < \$25,000

⁴ \$5,000 to < \$15,000

⁵ \$115,000 to < \$135,000

⁶ \$75,000 to < \$95,000

⁷ \$55,000 to < \$75,000

⁸ \$95,000 to < \$115,000

6.51 When considering BOT as induction therapy only, the ICER decreased to \$5,000 to < \$15,000/QALY over a 5-year time horizon. The model results for BOT induction only were most sensitive to the utility estimates and endoscopy costs for treatment evaluation. As previously noted, the model excluded the cost of endoscopy for treatment evaluation in the BOT induction only algorithm (including this cost increased the ICER from \$5,000 to < \$15,000/QALY to \$25,000 to < \$35,000/QALY). The PSCR stated exclusion of endoscopy costs from the BOT induction only scenario was considered reasonable given that undergoing an endoscopy for treatment evaluation, in the context of having no effective PBS listed drug for maintenance therapy, would not provide any utility in decisions regarding subsequent maintenance treatment. As a result, it would not be considered a cost-effective use of endoscopy resources. The PSCR acknowledged that it is feasible that BOT as induction therapy only would be associated with higher costs (and disruptions to QoL) related to endoscopies, due to not only the requirement for this procedure for treatment evaluation, but also to determine whether the patient meets the proposed eligibility criteria for each BOT induction cycle. The PSCR stated this is a particularly important consideration given that the vast majority of subjects in the placebo arm of the EOS-2 trial relapsed within 12 months. The ESC reiterated its concerns that the model is not well suited to considering BOT as induction therapy only (see paragraph 6.35). The pre-PBAC response argued that the economic model is adequate to evaluate the cost-effectiveness of a single induction cycle of BOT.

Drug cost/patient/year

6.52 The drug cost per patient per year is presented in Table 17. The estimates applied in the financial model were consistent with those applied in the economic model. Both the economic and financial models assumed full compliance (100%) for BOT treatment. Treatment compliance of BOT 1 mg BID reported in the clinical evidence was 98% for induction treatment (EOS-1) and 94.7% for maintenance treatment (EOS-2).

Table 17: Drug cost per patient for BOT

		BOT Trial dose and duration	BOT Model	BOT Financial estimates
A	Mean dose (daily)	1 mg twice daily (2 mg daily)	1 mg twice daily (2 mg daily)	1 mg twice daily (2 mg daily)
B	Cost/pack BOT 1 mg tablet, 60's (DPMQ) ^a	\$██████	\$██████	\$██████
C	Cost/mg (= B/60)	\$██████	\$██████	\$██████
D	Treatment compliance	94.7%	100%	100%
E	Cost/patient/year (chronic) (= A*C*D*365)	\$██████ ^b	\$██████ ^c	\$██████ ^c

Source: p148 of EOS-2 trial report; p219 of the submission; TreeAge; sheet 3a and 3b of the utilisation-and-cost-model workbook.

Abbreviations: BOT = budesonide orally disintegrating tablets; DPMQ = dispensed price for maximum quantity

Notes: Calculated based on cost of BOT maintenance treatment

a Pricing according to the pack of 60 tablets has been applied to reflect the ongoing, steady state, nature of treatment.

b Treatment compliance applied based on BOT 1 mg BID arm of EOS-2 (i.e. \$██████ / 60 * 2 * 365 * 94.7%).

c Assumed full treatment compliance (100%; i.e. \$██████ / 60 * 2 * 365). The submission estimated the cost/patient/year to be \$██████ (at full compliance). The minor difference was due to rounding.

Estimated PBS usage & financial implications

6.53 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the expected use and associated financial implications of BOT 1 mg BID (induction and maintenance therapy). The key inputs used by the submission to inform the financial estimates are summarised in Table 18.

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Table 18: Key inputs for financial estimates

Data	Value	Source	Comment
Prevalent patients	Yr 1: [redacted] ¹ Yr 2: [redacted] ¹ Yr 3: [redacted] ¹ Yr 4: [redacted] ¹ Yr 5: [redacted] ¹ Yr 6: [redacted] ¹	ABS population - 3222.0 Series B (as provided in the Utilisation and Cost Model Workbook). Prevalence rate (42.2 per 100,000) informed by Navarro 2019 (systematic review).	Uncertain pooled prevalence rate (likely overestimated)
Uptake rate	Yr 1-6: 10%	Assumption	Likely underestimated
Treatment response at 90 days (~13 weeks)	93.22% (=55/59)	EOS-1 trial; 55 out of 59 patients respond at 6 weeks. Taken as a response observed on the PBS after 90 days (this was 13 weeks in the cost-effectiveness model; approximation)	Reasonable
Treatment discontinuation (any cause) at the end of Year 1 (over 275 days or ~39 weeks after the response evaluation)	12.18%	EOS-2 trial; a probability of discontinuation 14.71% over 48 weeks (10 out of 68 patients receiving BOT 1 mg BID), translating to an annualised probability of 15.83%.	Likely underestimated
Annualised treatment discontinuation (any cause) each year in Year 2+	15.83%		
BOT – initiation treatment (i.e. induction)	\$ [redacted]	Requested price (DPMQ) for pack of 45 tablets, BOT 1 mg	-
BOT – continuation treatment (i.e. maintenance)	\$ [redacted]	Requested price (DPMQ) for pack of 30 tablets, BOT 1 mg	-
Endoscopy (treatment evaluation)	\$1,242.81	NHCDC Round 22 (2017-2018) Non-admitted care Tier 2 "1006 Endoscopy - Gastrointestinal"	Appropriate
Dilation (endoscopy)	\$1,938.60	AR-DRG v10 "G47C Gastroscopy, MINC"	Appropriate
Food bolus impactions requiring endoscopic removal	\$1,344.60	Emergency care URG v.1.45; URG 11	Appropriate

Source: Table 4-1, Table 4-2 and Table 4-4 of the submission.

Abbreviations: AR-DRG = Australian refined diagnosis-related groups; BOT = budesonide orally disintegrating tablet; DPMQ = dispensed price for maximum quantity; EoE = eosinophilic oesophagitis; NHCDC = National Hospital Cost Data Collection; URG = urgency related group

Note: No MBS items nor drug cost-offsets were applied in the financial estimates

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

6.54 The submission relied on a recent systematic review by Navarro (2019) to determine the number of prevalent patients eligible for BOT treatment. The pooled prevalence rate (42.2; 95% CI, 31.1-55) was uncertain (likely overestimated) due to methodological issues identified in two of the nine pooled adult studies. It appears that two of the studies (Molina-Infante 2018b and Arias 2019) accumulated annual incident cases over time to derive the annual prevalence rates, resulting in an overestimation of the prevalence during the study period. The percentage of patient contributions from these studies to the overall pooled results was not reported. Based on the uncertainty in patient numbers, the sponsor indicated a willingness to discuss a risk-sharing arrangement.

- 6.55 The submission stated that the uptake rate of BOT was expected to be gradual and modest (10% of newly initiating patients each year over the six-year forward estimates). No justification was provided for this assumption. This may be underestimated as BOT would be the first TGA-registered treatment for EoE listed on the PBS, if recommended. The uptake rate was applied to the estimated prevalent pool of patients each year without adjusting for patients who had commenced BOT treatment in previous years (i.e. replacement approach). The pre-PBAC response argued that while BOT would be the first TGA registered treatment, many prevalent patients are being successfully managed on unregistered treatments and would therefore be reluctant to switch in the short term. The PBAC noted the comments from consumers highlighting the compounding issues and the confusion that can arise when medicines indicated for asthma are used for EoE. As such, the PBAC considered it highly likely that patients would switch from unregistered treatments to BOT.
- 6.56 To estimate the number of patients receiving maintenance treatment, the submission applied the probability of treatment response at 90 days based on the percentage of BOT patients in histologic remission at Week 6 in EOS-1 (93.2%; 55/59). This was a combination of the probabilities of clinicohistologic (84.7%) and histologic remission only (8.5%) in EOS-1, as applied in the economic model. While this reflects the intended use on the PBS, eligibility for maintenance therapy in the EOS-2 study was determined by clinicohistologic remission only.
- 6.57 The submission applied the same assumption regarding treatment discontinuation (any cause) during maintenance treatment as applied in the economic model (14.71%). This probability is likely an underestimate as it has not taken into account other causes of treatment discontinuation such as clinical relapse or withdrawal due to adverse events. In EOS-2, treatment failure (i.e. treatment discontinuation) was 25% in the BOT arm.
- 6.58 Overall, the estimated number of patients was uncertain. While the uptake rate was likely an underestimate, the prevalence rate and the probability of patients continuing maintenance treatment were likely an overestimate.
- 6.59 The submission stated that there are no substitution-related cost-offsets to the PBS since BOT represents the first TGA-registered treatment for EoE in Australia. This was reasonable as it is unclear what proportion of off-label PPIs and STCs are being dispensed for EoE under the PBS.
- 6.60 The estimated use and financial implications of BOT are presented in Table 19. The total cost to the PBS/RPBS of listing BOT was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing.

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Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use (number of patients treated)						
Initiators	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Continuers	■ ^{a,3}	■ ^{b,3}	■ ³	■ ³	■ ³	■ ³
Estimated financial implications of BOT						
Cost to PBS/RPBS less copayments	\$■ ⁹	\$■ ⁹	\$■ ¹⁰	\$■ ¹⁰	\$■ ¹⁰	\$■ ¹⁰
Net cost to PBS/RPBS	\$■ ⁹	\$■ ⁹	\$■ ¹⁰	\$■ ¹⁰	\$■ ¹⁰	\$■ ¹⁰
Net cost of other resource use ²	\$■ ⁹	-\$■ ^{c,9}	-\$■ ^{c,9}	-\$■ ^{c,9}	-\$■ ^{c,9}	-\$■ ^{c,9}
Net cost to PBS/RPBS/ other resource use	\$■ ^{c,9}	\$■ ^{c,9}	\$■ ^{c,9}	■ ^{c,10}	■ ^{c,10}	■ ^{c,10}

Source: compiled during the evaluation from sheet 3a, 5, Dr Falk BIM of the utilisation-and-cost-model workbook; Table 4-7, Table 4-8 and Table 4-10 of the submission.

Abbreviations: BOT = budesonide orally disintegrating tablet

Notes: a ■³ x 93.22% (= Year 1 initiators who successfully respond at 90 days)

b ■³ initiating and responding at 90 days in Year 2 PLUS ■³ patients continuing on from Year 1

c Corrected errors identified during the evaluation. The model inappropriately applied the same number of patients from Year 1 to estimate utilisation in subsequent years. The number of patients receiving BOT in subsequent years (after factoring in treatment persistence/discontinuation) should have been used instead. Further, cells F160-J160 and cells F169-J169 in Dr Falk BIM sheet did not account for patients initiating in Year 1.

1 Estimated by applying the number of scripts required per initiator (with continuation rate and treatment persistence incorporated) to the number of initiators (Initiation: 2; Continuation, first: 5.59; Continuation, subsequent: Yr 1: 2.95, Yr 2: 9.96, Yr 3: 8.38, Yr 4: 7.06; Yr 5: 5.94; Yr 6: 5.00)

2 Consist of endoscopy + biopsy procedures for response assessment and efficacy monitoring, oesophageal dilation for symptomatic relief and endoscopic removal of food impaction.

The redacted values correspond to the following ranges:

³ 500 to < 5,000

⁴ 5,000 to < 10,000

⁵ 10,000 to < 20,000

⁶ 20,000 to < 30,000

⁷ 30,000 to < 40,000

⁸ 40,000 to < 50,000

⁹ \$0 to < \$10 million

¹⁰ \$10 million to < \$20 million

6.61 The extent of other resource costs (i.e. endoscopy + biopsy procedures for response assessment and efficacy monitoring, oesophageal dilation for symptomatic relief and endoscopic removal of food impaction) was calculated based on the estimates from the economic model and thus reflect the same concerns regarding how the estimates were formed.

6.62 The results of the sensitivity analyses conducted during the evaluation are presented in Table 20. The estimates were most sensitive to changes in the assumed uptake rate (varied from 10% to 15%), resulting in an increase in the estimated net cost to the

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PBS/RPBS (\$0 to < \$10 million in Year 1 increasing to \$20 million to < \$30 million in Year 6).

Table 20: Results of the sensitivity analyses conducted during the evaluation

Year	2021	2022	2023	2024	2025	2026
Net cost to PBS/RPBS						
Base case	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²
Prevalence rate ¹ – 31.8 per 100,000	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²
Prevalence rate ¹ – 55 per 100,000	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ³
Uptake rate ² – 15%	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ³	\$ [redacted] ³
Treatment response ³ – 84.7%	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²
Treatment discontinuation ⁴ – 25%	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²

Source: Sensitivity analyses calculated during the evaluation using sheet Dr Falk BIM of the utilisation-and-cost-model workbook

Notes: 1 Modified cell C20 in Dr Falk BIM sheet of JORVEZA for EoE_Section4_BIM

2 Modified cells D24 (15%) and I24 (90%) using Goal Seek function (resulting in 15% annually; cells D25 to I25) in Dr Falk BIM sheet of JORVEZA for EoE_Section4_BIM

3 Modified cell C30 in Dr Falk BIM sheet of JORVEZA for EoE_Section4_BIM

4 Modified cell D32 in Dr Falk BIM sheet of JORVEZA for EoE_Section4_BIM

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² \$10 million to < \$20 million

³ \$20 million to < \$30 million

6.63 DUSC considered the estimates presented in the submission to be underestimated. The main issues were:

- The uptake is likely to be underestimated as it is the first TGA registered treatment for EoE. The financial estimates are most sensitive to the uptake rates as patients are compounded year on year as patients continue treatment in subsequent years.
- The prevalence of the disease is uncertain due to the range of study locations and settings included in the systematic review, it is unclear how the prevalence rate would apply in Australia. The increase in prevalence rate is due to the change in diagnostic criteria and increased awareness of EoE over time.
- No stopping rule or the potential for treatment breaks were included in the restriction, despite European therapeutic guidelines stating EoE may only occur seasonally.
- It is difficult to estimate usage when the bulk of potential treatment is currently off-label.
- There is a potential for use of this treatment in children.

Quality Use of Medicines

- 6.64 No quality use of medicines (QUM) information was provided in the submission. The submission considered that the current off-label use of PPIs and STC therapies in the Australian EoE treatment setting represents a significant QUM issue, given that quality clinical trial evidence is lacking to support dose optimisation, efficacy and safety. However, the submission did not propose any educational activities for healthcare professionals or monitoring to ensure that QUM is being achieved with the availability of BOT.
- 6.65 DUSC considered the following were QUM issues:
- As no stopping criteria was provided in the restriction, there are concerns with the safety due to the long term steroid usage and potential for damage to the oesophageal lining. There is a potential for sublingual administration.
 - The submission did not provide advice regarding the use of concomitant treatments such as PPIs or other treatments such as systemic or topical glucocorticosteroids, biologics, or immunosuppressants, despite all patients in trials restricted from the concurrent use of these treatments.

Financial Management – Risk Sharing Arrangements

- 6.66 No risk-sharing arrangements were proposed in the submission. However, the sponsor indicated a willingness to discuss a risk-sharing arrangement to address any uncertainties to the PBS budget.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend budesonide orally disintegrating tablets (BOT) for the treatment of eosinophilic oesophagitis (EoE). The PBAC considered the clinical claim of superiority of BOT compared to placebo for both induction and maintenance therapy to be well supported by the evidence. However, the PBAC considered PBS listing for use in the maintenance therapy setting is beyond the maximum duration of treatment reflected in the current approved product information (PI). The PBAC considered the cost-effectiveness of induction therapy alone to be uncertain and the incremental cost-effectiveness ratio (ICER) for both induction and maintenance therapy to be high and uncertain at the proposed price.
- 7.2 The PBAC noted the input from individuals, health care professionals and organisations which highlighted the high clinical need for EoE specific treatment options.
- 7.3 The PBAC considered placebo as a proxy for standard of care (SOC) an acceptable comparator.

- 7.4 The PBAC noted the claim of superior comparative effectiveness compared to placebo was based on the EOS-1 and EOS-2 trials for induction of remission and maintenance therapy respectively. In terms of induction of remission, the PBAC noted that the percentage of patients in clinicohistologic remission at 6 weeks was 57.6% (34/59) in the BOT arm and 0.0% (0/29) in the placebo arm of EOS-1 (difference=57.63%; 95% RCI: 38.22%, 71.97%, $p < 0.0001$). Acknowledging the open-label nature of treatment between 6 and 12 weeks for patients who had not adequately responded, the PBAC noted the percentage of patients in clinicohistologic remission in the BOT arm increased to 84.7% (50/59)(see paragraph 6.14). With respect to maintenance therapy the PBAC noted the percentage of patients maintaining clinicohistologic remission after 48 weeks in EOS-2 was 75.0% (51/68) in the BOT 1 mg BID group and 4.4% (3/68) in the placebo group. The PBAC agreed with the ESC that the claim of superiority at both 6 weeks and 48 weeks was well supported by the evidence.
- 7.5 The PBAC noted that in EOS-1 there were no adverse events leading to discontinuation but the frequency of treatment related adverse events (TEAE) was higher for BOT with the vast majority of mild or moderate severity. In the EOS-2 trial the difference in frequency of study drug related TEAEs between the BOT treatment group and the placebo group was statistically in favour of placebo. However, 60.3% (41/68) of patients in the placebo group experienced a TEAE leading to withdrawal from the study with 'condition aggravated' the major reason for discontinuation. The PBAC considered the claim of inferior safety compared to placebo was reasonable.
- 7.6 While the clinical claims were considered reasonable, the PBAC agreed with ESC that a key issue was that the use of BOT in the maintenance setting (beyond the 12 weeks of induction phase) was not consistent with the current TGA approved PI dose recommendation. The PBAC noted that TGA evaluation of the use of BOT in the maintenance setting is currently underway with the initial decision by the Delegate expected in January 2022. The Pre-Sub-Committee response (PSCR) argued that the chronicity and potential for disease progression provides a strong rationale for maintenance therapy of EoE. The PBAC acknowledged the rationale for maintenance therapy of EoE but advised that TGA approval is required.
- 7.7 The PBAC noted the TGA application under evaluation also included a BOT 0.5 mg strength. The PBAC considered that a clinical claim of superior efficacy and inferior safety compared to placebo was reasonable for BOT 0.5 mg based on the EOS-2 trial. The PBAC noted the PSCR anticipated the recommended daily dose for maintenance of remission would be in line with the current posology in the European label (see paragraph 2.3). The PBAC noted the European label included the BOT 0.5 mg strength as the standard regimen with the BOT 1 mg strength recommended for patients with a long-standing disease history and/or high extent of oesophageal inflammation in their acute disease state. The PBAC considered that, if registered by the TGA, it would be appropriate for patients to have access to BOT 0.5 mg for maintenance therapy in addition to BOT 1 mg.

- 7.8 The submission presented a cost-utility analysis based on the EOS-1 and EOS-2 trials, comparing BOT 1 mg BID (induction and maintenance therapy) with SOC. An additional BOT treatment algorithm was included in the model to assess the cost-effectiveness of induction therapy. The PBAC noted the BOT treatment algorithm was modelled on a single induction cycle followed by SOC maintenance over a 5-year time horizon. The PBAC noted the high rate of relapse reported in the placebo arm of the 48 week EOS-2 trial (see paragraph 7.4) and considered the BOT treatment algorithm did not align with the proposed restriction, which allowed the use of BOT in a retreatment setting. In addition, the PBAC considered the BOT treatment algorithm inappropriately excluded the cost of endoscopy for treatment evaluation. The PBAC noted the model and its inputs was designed to consider BOT as induction and maintenance therapy, and agreed with the ESC that it was not well suited to considering BOT as induction therapy only. As such, the PBAC considered the cost-effectiveness of BOT induction therapy alone was uncertain.
- 7.9 The PBAC noted that when considering BOT for induction and maintenance therapy, the ICER was highly sensitive to the choice of utility values. The utility estimates applied in the base case were derived from an Australian EoE patient survey, which the PBAC considered would be subject to a high risk of confounding from recall bias given that patients used a hypothetical recalled health state instead of their own current health state. Acknowledging the limitations of Goodwin 2020, the PBAC considered it provided appropriate utility values for the model inputs and noted this increased the base case ICER from \$25,000 to < \$35,000/QALY to \$55,000 to < \$75,000 /QALY. The PBAC advised that with the respecified utility value model inputs, a price reduction would be required to achieve a cost-effective ICER. The PBAC considered a cost-effective ICER in this instance would be approximately \$30,000/QALY to \$50,000/QALY.
- 7.10 The PBAC noted the approach taken to estimate the expected use and associated financial implications of BOT included both induction and maintenance therapy. DUSC considered the financial estimates to be underestimated with the prevalence of EoE and the uptake rate key areas of uncertainty. The PBAC noted DUSC's advice that the prevalence of EoE had increased due to the change in diagnostic criteria and increased awareness of the condition over time. In addition, the PBAC agreed with DUSC that the uptake rate was likely underestimated as it is the first TGA registered treatment for EoE. The PBAC noted that the sensitivity analyses undertaken indicated the estimates were most sensitive to changes in the assumed uptake rate. The PBAC agreed with DUSC the financial estimates were likely underestimated. The PBAC noted than any underestimation of the number of treated patients would be conservative in the context of a risk sharing arrangement with a [REDACTED] % rebate above the caps.
- 7.11 The PBAC considered the outstanding issues may be addressed in a simple resubmission for BOT if the following changes were made, without any additional amendments to the economic evaluation or financial implications:

- TGA approval of BOT for maintenance therapy of EoE;
- Inclusion of BOT 0.5 mg for maintenance therapy of EoE in the resubmission;
- A price reduction to achieve an ICER of approximately \$30,000/QALY to \$50,000/QALY based on the scenario outlined in paragraph 7.9;
- Recalculation of the financial implications using the revised BOT price;
- A risk sharing arrangement based on submission predicated use to reduce any residual uncertainty regarding the number of patients treated.

7.12 The PBAC considered an early re-entry pathway would be acceptable if the resubmission addressed each of the points in the above paragraph with no further adjustment. The resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If any of these terms are not acceptable to the sponsor, a standard re-entry pathway is available.

7.13 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 through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The Sponsor is disappointed that Jorveza[®] did not receive a positive recommendation at this time but will work to clarify the issues raised with the intention to re-submit a revised application later in 2021. During the submission review, input from individuals, patient advocacy groups, health care professionals and medical & scientific organisations highlighted the high clinical need for disease-specific treatment options for a patient cohort with a chronic progressive inflammatory disease which has a profound impact on their quality of life.