

7.12 TEDUGLUTIDE, Powder for injection 5 mg, Revestive[®], Shire Australia Pty Ltd

1 Purpose of Application

- 1.1 The resubmission requested a Section 100 (Highly Specialised Drugs Program) PBS listing for teduglutide for the treatment of patients with Type III (chronic) intestinal failure associated with short bowel syndrome.
- 1.2 The listing was requested on a cost-effectiveness basis compared to standard care.
- 1.3 Table 1 presents the key components of the clinical issue addressed in the resubmission (changes compared with the July 2018 resubmission are underlined).

Table 1: Key components of the clinical issue addressed in the resubmission

Component	Description
Population	Patients with Type III (chronic) short bowel syndrome with intestinal failure following major surgery and with a history of dependence on parenteral support for at least 12 months. <u>Patients who require parenteral support for at least 3 days per week to meet caloric, fluid or electrolyte needs due to ongoing malabsorption.</u> Patients must be stable on their parenteral support regimen for at least four consecutive weeks before initiating teduglutide treatment.
Intervention	Teduglutide 0.05mg/kg given as a once daily subcutaneous injection, plus standard care.
Comparator	Standard care, consisting of best supportive care focusing on optimisation of remnant intestinal function through a combination of parenteral support, dietary interventions, oral rehydration solutions, anti-diarrhoeal and anti-secretory agents.
Outcomes	Treatment response defined as $\geq 20\%$ reduction from baseline in weekly parenteral support fluid volume; additional days off parenteral support; number of patients weaned off parenteral support.
Clinical claim	Teduglutide plus standard care is superior in terms of effectiveness compared with standard care alone. <u>Teduglutide plus standard care is inferior in terms of safety compared to standard care alone; acknowledging the continuing need for parenteral support for some teduglutide-treated patients, and the short-term duration of the comparative trial of teduglutide versus placebo.</u>

Source: Table 1.1.1, p.15 of the resubmission.

2 Requested listing

Name, restriction, manner of administration, form	Max. Qty (units)	No. of repeats	DPMQ		Proprietary name and manufacturer
			Public	Private	
TEDUGLUTIDE 5 mg lyophilised powder, 0.5 mL water for injection	28	5	\$ [REDACTED] [\$ [REDACTED] SPA]	\$ [REDACTED] [\$ [REDACTED] SPA]	Revestive [®] Shire Australia

\$ SPA = price related to proposed special price arrangement

- 2.1 The resubmission proposed a special pricing arrangement, with an effective price of \$ [REDACTED], which represents a [REDACTED]% discount to the proposed published price and was consistent with the price offered in the July 2018 pre-PBAC response.
- 2.2 The requested PBS listings, as proposed in the resubmission, are outlined below.

Requested PBS Listing – Initial 12 months of treatment (as proposed in the resubmission)

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Severity:	Chronic, Type III
Condition	Short bowel syndrome with intestinal failure
PBS Indication:	Treatment of patients with Short Bowel Syndrome who are dependent on parenteral support The treatment must include initiation, stabilisation and review of therapy as required
Treatment phase:	Initial treatment - new patients
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	The treatment must be under the supervision and direction of a medical specialist with experience in the management of patients with short bowel syndrome. The written authority application must include documentation of the number of days on parenteral support in the 4 weeks preceding application. A maximum of up to 12 months of treatment is allowed under this restriction.
Clinical criteria:	The patient must have short bowel syndrome with intestinal failure following major surgery; AND The patient has a history of dependence on parenteral support for at least 12 months; AND The patient requires parenteral support for at least 3 days per week to meet caloric, fluid, or electrolyte needs due to ongoing malabsorption; AND The patient must be stable on their parenteral support regimen for at least 4 consecutive weeks before initiating teduglutide treatment; AND The patient has no active gastrointestinal malignancy or history of gastrointestinal malignancy within the last five years.
Population criteria:	Adult patient
Administrative advice:	Special Pricing Arrangements apply
Notes:	Initial treatment – Balance of supply provision is requested for patients who cease teduglutide treatment for medical reasons within the initial 12 months of treatment.

- 2.3 The proposed initial treatment restriction requires patients to have a history of dependence on parenteral support for at least 12 months, and a stable parenteral support regimen for at least four consecutive weeks prior to initiating teduglutide. This was consistent with the PBAC’s previous advice of 12 months’ prior parenteral nutrition dependence, which aligned with the inclusion criteria of the key trial (Paragraph 7.5, July 2018 teduglutide Public Summary Document (PSD)).
- 2.4 The proposed restriction requires patients to be on parenteral support at least 3 days per week. This was consistent with the PBAC previous advice that treatment with teduglutide should be limited to patients who require at least three days per week of parenteral support given the lack of clinical evidence in patients with lesser requirements, who are likely to have a lower clinical need (Paragraph 7.4, July 2018 teduglutide PSD). The Secretariat considered that it may be necessary to specify the time period over which a patient must have received at least 3 days per week of parenteral support (i.e. for the four weeks prior to commencing teduglutide) and the Pre-Sub-Committee Response (PSCR) agreed with the proposed amendment.
- 2.5 To help address concerns raised by the evaluation regarding the timing and measurement of parenteral support requirements, the pre-PBAC response proposed that across the initiation and continuation restrictions, a ‘Stable parenteral support

regimen' should be defined as "the same number of days of parenteral support (parenteral nutrition \pm IV fluids) per week for 4 consecutive weeks to meet caloric, fluid or electrolyte needs". This assessment would be required: at initiation to establish that a patient has been stable on at least 3 days per week of parenteral support before commencing treatment; to establish a 'baseline measurement' of parenteral support requirements to compare the 12 month assessment against; and to assess whether a patient has been stable for 6 months (in which case a trial cessation period would be required). However, if a patient experiences any fluctuations in parenteral support requirements in the four consecutive weeks immediately prior to the authority application, this would not accurately reflect a patient's response. Assessment of the mean number of days over the whole treatment period since the previous authority approval may be more appropriate.

- 2.6 The proposed restrictions stated that 'Treatment must be under the supervision and direction of a medical specialist with experience in the management of patients with short bowel syndrome'. The PBAC considered that the restriction should instead specify that a gastroenterologist must treat the patient.
- 2.7 The resubmission's proposed restriction was for use in adult patients, consistent with the TGA registered indication. However, the PBAC considered that it would be appropriate for the restriction not to specify any age criteria, noting that teduglutide has been studied in paediatric patients and shown to be well tolerated (Carter et al 2017).
- 2.8 The initial treatment restriction proposed five repeats, providing a patient with 6 months of initial treatment. At the PBAC clinician consultation meeting in September 2018, clinicians advised that 12 months represent a reasonable time-point for assessing response to teduglutide treatment, and noted that some potential benefits could be missed if shorter periods (e.g. six months) are used to assess response. The PBAC agreed that a 12-month time-point for assessing initial treatment response was reasonable, and therefore considered that 11 repeats in the initial treatment phase was appropriate.
- 2.9 The proposed initial treatment restriction also included a balance of supply provision, which would enable patients who temporarily cease teduglutide treatment within the initial 12 months of treatment for medical reasons to recommence treatment. For example, the Product Information states that patients may discontinue teduglutide treatment due to dehydration, or temporarily discontinue treatment due to intestinal obstruction and lactation. Additionally, a balance of supply restriction will facilitate review and monitoring of a patient within the initial treatment period if a clinician wishes to prescribe less than the allowable 12 months of initial therapy.

Requested PBS Listing – Continuing treatment (12 month review for treatment response “continuation criteria”)

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Treatment phase:	Continuing treatment - responders.
Restriction:	Authority Required (In Writing)
Treatment criteria:	Treatment must be under the supervision and direction of a medical specialist with experience in the management of patients with short bowel syndrome. The written authority application must include documentation of treatment response to be eligible for continuing treatment. Treatment response is defined as a reduction in parenteral support frequency of at least one day per week from baseline, where baseline is measured immediately prior to initiating treatment with teduglutide. Patients who discontinue teduglutide must be monitored in accordance with an individualised monitoring program.
Clinical criteria:	The patient must have previously received PBS-subsidised treatment with teduglutide for the treatment of short bowel syndrome with intestinal failure.
Population criteria	Adult patient

Treatment response

- 2.10 The proposed continuing treatment restriction requires demonstration of a reduction in parenteral support frequency of at least one day per week from baseline, where baseline is measured immediately prior to initiating treatment with teduglutide. The proposed treatment response criteria were appropriately changed from “a reduction of at least a 20% in weekly parenteral support volume” to address the PBAC’s previous concerns that it would be more appropriate for the continuation criteria to be based on days reduction in parenteral support requirements (rather than volume reduction) as consumer comments indicated that this was the most patient-relevant outcome (Paragraph 7.8, July 2018 teduglutide PSD).
- 2.11 The evaluation considered that the proposed restriction provided limited guidance on the timing of assessment, and the required duration of the treatment response. Under the proposed restriction, patients could qualify for continuing treatment following an improvement of one day per week in parenteral support at any time during the initial 12 months of treatment. The PSCR stated that the continuation criteria was intended to be based on assessments made at particular points in time: at baseline, at 12 months of treatment, and at 6-monthly intervals thereafter; and was not intended to consider fluctuations during the intervening period. The PSCR proposed that, if required, the number of days per week of parenteral support at each assessment point could be based on the mean number of days per week over the preceding 4 weeks of treatment. The pre-PBAC response also proposed standardised wording for outlining a 4-week assessment period in the initiation and continuation criteria (e.g. for the continuation criteria, the pre-PBAC response proposed that the patient must have achieved and maintained a ‘treatment response’ for 4 consecutive weeks preceding the application for continuing treatment). The PBAC considered that in order to reflect the intended assessment intervals, it would be more appropriate to have separate first continuing and subsequent continuing restrictions, as well as calculating an average

number of days of parenteral support over the preceding treatment period as outlined in Paragraph 2.5 above, would help to mitigate some of the evaluation’s concerns regarding the timing and assessment of patient response.

Requested PBS Listing – trial treatment cessation

Treatment phase:	Continuing treatment - trial treatment cessation.
Restriction:	Authority Required (In Writing)
Treatment criteria:	Treatment must be under the supervision and direction of a medical specialist with experience in the management of patients with short bowel syndrome. Treatment must be ceased when there has been a stable frequency of days per week of parenteral support in the preceding 6 months of continuing treatment. Patients are exempt from treatment cessation under this criterion if the patient has weaned off parenteral support completely. Patients who discontinue teduglutide must be monitored in accordance with an individualised monitoring program.
Clinical criteria:	The patient must have previously received PBS-subsidised treatment with teduglutide for the treatment of short bowel syndrome with intestinal failure.

Trial cessation of treatment

- 2.12 In its previous consideration, the PBAC advised that a stopping rule would be appropriate (i.e. where patients who have improved are required to cease teduglutide) to ensure that patients do not continue on treatment that may be unnecessary. In providing this advice, the PBAC noted that other factors such as endogenous intestinal adaptation and intestinal rehabilitation programs may contribute to clinical improvements and that small studies have shown that when teduglutide is ceased, parenteral support requirements have remained lower than they were at baseline (Paragraph 7.7, July 2018 PSD). To address this, the resubmission proposed a ‘trial of treatment cessation’ restriction.
- 2.13 Under the proposed restriction, patients would be exempt from the requirement to undergo a trial treatment cessation if they have completely weaned off parenteral support. The PBAC considered this was appropriate and noted that it aligned with advice from clinicians at the PBAC clinician consultation meeting in September 2018, wherein clinicians advised that there should be no requirement to stop teduglutide in patients who wean off parenteral support completely (i.e. patients who completely wean off parenteral support should receive ongoing teduglutide treatment). The clinicians considered that it may be difficult to recommence parenteral support in these patients if their condition worsens after ceasing teduglutide, and clinicians considered that the psychological harm of recommencement of parenteral support would be detrimental to many patients.
- 2.14 Under the proposed restriction, a patient would be required to undertake a trial of treatment cessation once they have a stable frequency of days per week of parenteral support in the preceding 6 months to reflect a lack of continued improvement despite ongoing treatment. The resubmission proposed that this 6-month period for measuring a stable parenteral support regimen should commence after the initial 12-month treatment period. The PBAC considered this was reasonable, and noted that

this would align with the period between the recommended first and subsequent continuing restrictions.

- 2.15 The PBAC noted that, under the proposed restriction, patients who are continuing to improve would not be required to undergo a trial of treatment cessation. The PBAC considered this was appropriate (i.e. patients who have had a reduction in the number of days per week of parenteral support since the last assessment would be eligible for continuing access to teduglutide).
- 2.16 The PBAC noted that, under the proposed restriction, patients whose parenteral support requirements are increasing (at least one day per week increase in parenteral support over a consecutive 4 week period) would not be considered ‘stable’ and would not be required to undergo a trial cessation period under the proposed restriction. The PBAC considered that patients whose parenteral support requirements increase while on teduglutide under either of the continuing restrictions should be considered a treatment failure and should be required to permanently cease teduglutide therapy. This is proposed in the context of such patients having previously experienced a response (improvement of one day per week since baseline) which is no longer maintained despite ongoing treatment.

Requested PBS Listing – Recommencement of treatment after trial treatment cessation

Treatment phase:	Recommencement of treatment after trial treatment cessation.
Restriction:	Authority Required (In Writing)
Treatment criteria:	The treatment must be under the supervision and direction of a medical specialist with experience in the management of patients with short bowel syndrome. The patient may recommence treatment with teduglutide at any point during a trial treatment cessation where an increase in parenteral support frequency of ≥ 1 day per week from the pre-cessation level can be demonstrated. The written authority application must include documentation of an increase in parenteral support frequency of ≥ 1 day per week from pre-cessation level to meet caloric, fluid or electrolyte needs.
Clinical criteria:	The patient must have previously received PBS-subsidised treatment with teduglutide for the treatment of short bowel syndrome with intestinal failure; AND The patient must have demonstrated treatment response to previous PBS-subsidised teduglutide for the treatment of short bowel syndrome with intestinal failure.

- 2.17 Under the ‘recommencement of treatment after trial treatment cessation’ restriction, patients may recommence treatment with teduglutide at any point during a trial of treatment cessation, where an increase in parenteral support frequency of at least 1 day per week from the pre-cessation level can be demonstrated. However, at the PBAC clinician consultation meeting in September 2018, clinicians advised that recommencement of teduglutide should be based on clinician judgement as there are no simple objective measures for assessing deterioration, and waiting for clinical signs of deterioration may unnecessarily delay treatment. Though not intended as a prescriptive list, the clinicians outlined that the parameters for justification of recommencement may include:

- an increase in parenteral support requirements by one or more days;
- changes in renal function or urinary sodium levels; or

- changes in body weight.
- 2.18 The PBAC agreed with the clinician consultation meeting and considered that recommencement of teduglutide should be based on clinician judgement, as there are no simple objective measures for assessing deterioration.
- 2.19 The evaluation noted that the proposed restriction provided limited guidance on the timing of assessment, and the required duration of the increase in parenteral support frequency. At the PBAC clinician consultation meeting in September 2018, clinicians advised that there should be no time limit on accessing this “recommencement pathway” (eg patients should be able to recommence teduglutide even if it is years after they ceased therapy). The pre-PBAC response stated “a 12-month time limit for recommencement of treatment after a ‘trial cessation’ was considered reasonable”. However, the PBAC agreed with the advice from the clinician consultation meeting and considered that there should be no time limit on accessing the recommencement restriction.
- 2.20 The resubmission also requested grandfathering provisions for teduglutide-treated patients who would have met the proposed PBS criteria. The resubmission stated this restriction is intended to provide access for nine patients (estimated at the time of resubmission) who are expected to be initiated on teduglutide through a patient familiarisation program by the time of PBS listing. The resubmission stated that the eligibility criteria for the familiarisation program align with the proposed PBS restriction.

Requested PBS Listing – Grandfathered patients

Treatment phase:	Initial or continuing treatment - grandfathered patients
Restriction:	Authority Required (In Writing)
Treatment criteria:	<p>Must be treated under the supervision and direction of a medical specialist with experience in the management of patients with short bowel syndrome</p> <p>The written authority application must include:</p> <ol style="list-style-type: none"> 1. Documentation to demonstrate the patient would have met the clinical criteria for initial PBS-subsidised teduglutide treatment, at the time they first initiated teduglutide treatment, including: <ol style="list-style-type: none"> a. The patient must have SBS-IF following major surgery; AND b. The patient had a history of dependence on parenteral support for at least 12 months; AND c. The patient required parenteral support for at least 3 days per week to meet caloric, fluid, or electrolyte needs due to ongoing malabsorption; AND d. The patient must have been stable on their parenteral support regimen for at least 4 consecutive weeks before initiating teduglutide treatment; AND e. The patient had no active gastrointestinal malignancy or history of gastrointestinal malignancy within the last five years 2. Documentation of teduglutide treatment start date and any balance of supply request to a maximum of 12 months initial supply. 3. Documentation of response to teduglutide treatment (if relevant). Treatment response is defined as a reduction in parenteral support frequency of at least one day per week from baseline, where baseline is measured immediately prior to initiating treatment with teduglutide. <p>Patient may qualify for PBS-subsidised treatment under this restriction once only</p>
Clinical criteria:	The patient must be receiving treatment with teduglutide for short bowel syndrome with intestinal failure at the time of application.

- 2.21 There is a risk of use outside of the PBS restriction for other conditions associated with intestinal failure (intestinal fistula, intestinal dysmotility, mechanical obstruction, extensive small bowel mucosal disease), Type II intestinal failure, patients who do not have at least 12 months of prior parenteral support dependence, or in patients who are on parenteral support fewer than 3 days per week. However, the written authority proposed in the resubmission, and as requested by the PBAC in its previous consideration, is likely to mitigate some of the risk of use outside of the proposed restriction. Further, the PBAC previously considered that that use of teduglutide outside the restriction may be constrained by the limited number of clinicians experienced in the treatment of this condition (Paragraph 2.20, July 2018 PSD).
- 2.22 There may be ongoing use of teduglutide despite not having achieved the required improvements specified in the proposed continuation criteria and stopping rule. The PBAC considered that the risk sharing arrangement proposed in the pre-PBAC response had adequately addressed this concern (refer to Paragraph 6.64).
- 2.23 While the ESC acknowledged that the proposed PBS restriction had tried to incorporate comments from the clinician consultation and the previous PBAC Minutes, the ESC was concerned that the restriction may create the situation whereby it is possible to manipulate clinical management to satisfy PBS criteria (around initiation, continuation, cessation and re-commencement), which may not be in the best interests of the patient. The PBAC noted that key aspects of the revised restriction were developed in consultation with clinicians experienced in the management of

patients with this condition, and considered that it was important that the restrictions should not impede good clinical practice with respect to management of parenteral support.

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

3 Background

Registration status

- 3.1 Teduglutide was granted orphan drug status by the TGA on 16 December 2015.
- 3.2 Teduglutide was registered on the ARTG on 19 May 2017 for the treatment of adult patients with short bowel syndrome who are dependent on parenteral support. Patients should be stable on their parenteral support regimen for at least to 4 weeks prior to initiating teduglutide.
- 3.3 The ESC noted that the TGA indication is significantly broader than the proposed PBS restriction.

Previous PBAC consideration

- 3.4 Major submissions for teduglutide for the treatment of patients with Type III (chronic) intestinal failure associated with short bowel syndrome were considered at the November 2017 and July 2018 PBAC meetings.
- 3.5 Table 2 presents a summary of the outstanding matters of concern from the July 2018 PBAC meeting.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern (July 2018 teduglutide PSD)	How the resubmission proposed to address it
Clinical place in therapy	Initiation should be limited to patients who require ≥ 3 days/week of parenteral support at baseline (Para 7.3-7.4).	Addressed.
Requested PBS listing	Continuation criteria should be based on days reduction in parenteral support requirements (rather than volume reduction) (Para 7.8).	Addressed: Continuation criteria require patients to demonstrate a reduction of at ≥ 1 day per week in parenteral support during the first 12 months.
	A stopping rule would be appropriate (i.e. where patients who have improved are required to cease teduglutide) (Para 7.7).	Addressed: Patients who remain on PS must undertake a trial of treatment cessation after 6 months of stable parenteral support.
Clinical effectiveness	There was a lack of long-term comparative clinical evidence to define the magnitude of the treatment effect associated with teduglutide (Para 7.9).	Not addressed. No new relevant randomised controlled trials were identified.
Safety	Claim of non-inferior safety of teduglutide over standard care not adequately justified (Para 7.10).	Addressed: Revised to claim of inferior safety of teduglutide over standard care.
Cost effectiveness	Placebo response should be included in the economic model (Para 7.12).	Addressed.
	Carer disutilities should be included in a supplementary analysis rather than in the base case economic evaluation (Para 7.12).	Addressed.
	Inappropriate to include the anniversary price reductions in the base case (Para 7.12).	Addressed:
	It may be clinically plausible to assume that reductions in parenteral support volume plateau after a certain period of treatment (Para 7.12).	Not addressed: Transition probabilities beyond 120 weeks in the teduglutide arm were derived by extrapolating data from Week 108 to 120.
	Economic model and financial estimates should be updated to incorporate the impact of the stopping rule and continuation criteria (Para 7.14).	Addressed.
	A substantial price reduction was required to achieve a cost-effective listing (Para 7.16).	Not addressed: Proposed price unchanged from the July 2018 pre-PBAC response.
Financial impacts	Financial estimates should be updated to reflect the requirement for patients to be on ≥ 3 days per week of parenteral support at baseline (Para 7.15).	Addressed.

Source: Pages 14-15 and Table 3.12.1, p.135 of the resubmission.

Abbreviations: PNDU, Parenteral Nutrition Down Under; PSD, Public Summary Document; QALY, quality adjusted life years.

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

4 Population and disease

- 4.1 Short bowel syndrome is a malabsorption disorder caused by inadequate anatomical or functional length of small intestine following extensive surgical resection. Intestinal failure occurs when there is a reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, and intravenous supplementation is required to maintain health and/or growth.
- 4.2 The population of patients with short bowel syndrome is highly heterogeneous due to differences in remnant bowel anatomy, comorbidities and clinical management requirements. Symptoms vary depending on the length and function of the remaining bowel, but may include diarrhoea, nutrient deficiencies, electrolyte disturbances, dehydration, malnutrition, and weight loss.

- 4.3 In general, patients are managed by multidisciplinary teams in large treatment centres with home parenteral nutrition management expertise. Management involves a combination of enteral feeding, parenteral support (parenteral nutrition and intravenous hydration), dietary interventions, oral rehydration solutions, pharmacological treatments (anti-diarrhoeal and anti-secretory agents), and surgical interventions.
- 4.4 Intestinal failure associated with short bowel syndrome may be reversible due to intestinal adaptation, and intestinal rehabilitation programs. Type III intestinal failure is a chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years. The submission positioned teduglutide as a treatment option for patients with Type III (chronic) short bowel syndrome receiving home parenteral nutrition.

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

5 Comparator

- 5.1 The nominated main comparator of standard care (comprising enteral feeding, parenteral nutrition, dietary interventions, oral rehydration solutions, and anti-diarrhoeal/anti-secretory agents) was unchanged from the July 2018 resubmission. The PBAC has previously accepted standard care as the appropriate comparator (Paragraph 5.1, July 2018 teduglutide PSD).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (6) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with teduglutide including the reduced need for parenteral support, which leads to an improvement in quality of life for patients, carers and the whole family, an ability to participate in social events, and the reduction of complications associated with parenteral support. The comments also described benefits such as improved sleep quality, improved energy levels, improved ability to tolerate eating food and increased urine output.
- 6.3 The PBAC noted input received from Parenteral Nutrition Down Under Inc. (PNDU) in support of subsidising teduglutide through the PBS. The PNDU outlined the lack of alternative treatments available, and the restrictive impact of parenteral nutrition on patients' and their carers' lives due to the time commitments and clinical requirements of daily infusions.

Clinical trials

- 6.4 The resubmission was based on one head-to-head randomised trial (STEPS) and associated extension studies (STEPS-2, STEPS-3). Supportive evidence from an additional randomised trial (Study 004) and its associated extension study (Study 005) was also included. These trials were previously considered as part of the November 2017 and July 2018 submissions. No additional relevant randomised controlled trials were identified in the updated literature search. The resubmission also presented results from three additional observational studies examining the effectiveness of teduglutide in patients treated in routine clinical settings.
- 6.5 Details of the randomised trials are provided in the table below (unchanged from July 2018 resubmission).

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
CL0600-020 (STEPS)	A 24-week study of the efficacy and safety of teduglutide in subjects with parenteral nutrition-dependent short bowel syndrome. A randomized, double-blind, placebo-controlled, parallel-group study.	Clinical Study Report, 12 July 2011.
	A 24-week study of the efficacy and safety of teduglutide in subjects with parenteral nutrition-dependent short bowel syndrome. A randomized, double-blind, placebo-controlled, parallel-group study. Analysis of SBS-QoL™.	Clinical Study Report, 6 May 2011.
	Jeppesen PB, Pertkiewicz M, Messing B et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure.	<i>Gastroenterology</i> 2012; 143(6):1473-1481.e1473.
	Jeppesen PB, Pertkiewicz M, Forbes A et al. Quality of life in patients with short bowel syndrome treated with the new glucagon-like peptide-2 analogue teduglutide - analyses from a randomised, placebo-controlled study.	<i>Clinical Nutrition</i> 2013; 32(5):13-721.
	Chen K, Xie, J, Tang, W et al. Identifying a subpopulation with higher likelihood of early response to treatment in a heterogeneous rare disease: a post hoc analysis of response to teduglutide for short bowel.	<i>Therapeutics and Clinical Risk Management</i> 2018; 14:1267-1277.
	Jeppesen P, Gabe S, Seidner D et al. Factors associated with response to teduglutide in patients with short bowel syndrome and intestinal failure.	<i>Gastroenterology</i> (2018); 154:874-885.
CL0600-021 (STEPS extension study: STEPS-2)	A long-term, open-label study with teduglutide for subjects with parenteral nutrition dependent short bowel syndrome.	Clinical Study Report, 1 August 2013.
	Schwartz LK, O'Keefe SJD, Fujioka K et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome.	<i>Clinical and Translational Gastroenterology</i> 2016; 7:1-9. e142.
TED-C11-001 (STEPS-2 extension study: STEPS-3)	A one-year, open-label study with teduglutide for subjects with Parenteral nutrition-dependent short bowel syndrome who completed Study CL0600-021.	Clinical Study Report, 18 August 2014.
	Iyer K, Fujioka K, Boullata JI et al. Long-term safety and efficacy with teduglutide treatment in patients with intestinal failure associated with short bowel syndrome (SBS-IF): The STEPS-3 study.	<i>Clinical Nutrition</i> 2014; 33:S167-S168.
	Seidner D, Fujioka K, Boullata J et al. Reduction of parenteral nutrition and hydration support and safety with long term teduglutide treatment in patients with short bowel syndrome-associated intestinal failure: STEPS-3 Study.	<i>Nutr Clin Pract</i> 2018; 33:520-527.
Supplementary randomised trials		
CL0600-004	A study of the efficacy and safety of teduglutide in subjects with parenteral nutrition-dependent short bowel syndrome.	Clinical Study Report, 22 July 2010.
	Jeppesen PB, Gilroy R, Pertkiewicz M et al. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome.	<i>Gut</i> 2011; 60(7):902-914.
CL0600-005	A study of the safety and efficacy of teduglutide in subjects with Parenteral nutrition-dependent short bowel syndrome who Completed protocol CL0600-004.	Clinical Study Report, 22 July 2010.
	O'Keefe SJD, Jeppesen PB, Gilroy R et al. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure.	<i>Clinical Gastroenterology and Hepatology</i> 2013; 11(7):815-823.

Source: Table 2.2.2, p.50 of the resubmission.

6.6 The key features of the randomised trials are summarised in Table 4 (unchanged from July 2018 resubmission).

Table 4: Key features of the randomised trials, teduglutide vs. placebo

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
STEPS	86	Randomised, double-blind, placebo-controlled multi-centre trial 24 weeks + extension	Low	Adults with short bowel syndrome dependent on PS for at least 12 months	Reduction in weekly PS volume of $\geq 20\%$; Reduction of ≥ 1 day in weekly PS days; Patients weaned off PS	Reduction in PS days per week
Study 004	84	Randomised, double-blind, placebo-controlled multi-centre trial 24 weeks + extension	Low	Adults with short bowel syndrome dependent on PS for at least 12 months	Graded response score; Reduction in weekly PS volume of $\geq 20\%$; Reduction of ≥ 1 day in weekly PS days; Patients weaned off PS.	Not used

Source: Table 2.4.1, pp.59-61 and Table 2.4.8, pp68-70 of the resubmission; Table 2.2.1, p.7 and Table 2.2.3, pp16-18 of Attachment S2A2 of the resubmission.

Abbreviations: PS, parenteral support.

6.7 Following completion of STEPS, patients could opt to continue into a two-year, open-label extension study (STEPS-2). The study also included 12 previously untreated patients who were screened, optimised, and stabilised (but not randomised) for the STEPS trial. All patients in STEPS-2 (N = 88) received teduglutide. Patients who received teduglutide in STEPS received up to 30 months of teduglutide treatment; patients who received placebo (and previously untreated patients) in STEPS received up to 24 months of teduglutide treatment.

6.8 The ESC noted that the mean age of patients in the STEPS trial was 50 years at baseline, and considered that it was not clear if this reflects the Australian population.

Comparative effectiveness

6.9 The results presented for comparative effectiveness in the resubmission were unchanged from the July 2018 resubmission.

6.10 Table 5 presents the results for the proportion of patients achieving at least a 20% reduction in weekly parenteral support volume at Week 20, which was maintained to Week 24 (primary outcome of the STEPS).

Table 5: Responder rates for at least a 20% reduction in weekly parenteral support volume

Study	Teduglutide 0.05 mg/kg n (%)	Placebo n (%)	Difference, % (95% CI)	p-value
STEPS (24 weeks)	27/43 (62.8)	13/43 (30.2)	32.6% (11%, 51%)	p = 0.002
Study 004 (24 weeks)	16/35 (45.7)	1/16 (6.3)	39.5% (13%, 58%)	p = 0.009

Confidence intervals calculated during the evaluation using StatsDirect software.

Source: Table 2.5.1, p.72 of the resubmission; Table 2.3.1, p.20 of Attachment S2A2 of the resubmission.

Abbreviations: CI, confidence interval.

6.11 In STEPS, responder rates were 62.8% and 30.2% for the teduglutide and placebo groups respectively (for at least a 20% reduction in weekly parenteral support volume). Treatment with teduglutide was associated with a statistically significantly higher proportion of responders compared to placebo. The high proportion of patients with at least a 20% reduction in weekly parenteral support volume in the placebo arm

suggests that other factors may contribute to improvements in parenteral support volume (Paragraph 6.13, July 2018 teduglutide PSD).

6.12 In STEPS-2, responder rates at Week 104 were 55% (prior placebo-treated patients), 67% (previously untreated patients) and 93% (prior teduglutide-treated patients). The results indicate that additional patients achieved a response beyond 24 weeks of treatment in the STEPS trial. However, the magnitude of the treatment effect attributable to teduglutide was uncertain as there was no control arm in the extension study (Paragraph 6.14, July 2018 teduglutide PSD).

6.13 Table 6 presents the results for the proportion of patients achieving at least a 1-day reduction in days per week on parenteral support across the placebo-controlled trials.

Table 6: Responder rates for at least a 1-day reduction in days per week on parenteral support

Extension study	Teduglutide (0.05 mg/kg) n (%)	Placebo n (%)	Difference, % (95% CI)	p-value
STEPS (24 weeks)	21/39 (53.8)	9/39 (23.1)	30.7% (9%, 50%)	p = 0.005
Study 004 (24 weeks)	11/35 (31.4)	4/16 (25.0)	6.4% (-22%, 30%)	p = 0.749

Confidence intervals calculated during the evaluation using StatsDirect software.

Source: Table 2.5.2, p.76 of the resubmission; Table 2.3.5, p.22 of Attachment S2A2 of the resubmission.

Abbreviations: CI, confidence interval.

6.14 In STEPS, the proportion of patients who achieved at least a 1-day reduction in days per week on parenteral support were 53.8% and 23.1% at Week 24 for the teduglutide and placebo groups, respectively. Treatment with teduglutide was associated with a statistically significantly higher proportion of ‘responders’ compared to placebo. The difference in responder rates between teduglutide and placebo in Study 004 was not statistically significant. Relatively high proportions of responders in the placebo group for patients achieving a reduction of a least 1 day per week also suggests that other factors may play a role in parenteral support reductions (Paragraph 6.16, July 2018 teduglutide PSD).

6.15 Results across the extension studies indicate that additional patients achieved a response (1-day reduction in days per week on parenteral support) with teduglutide treatment beyond 24 weeks treatment in the STEPS trial.

6.16 Table 7 presents the results for the number of patients who completely weaned off parenteral support across the placebo-controlled trials.

Table 7: Proportion of patients who completely weaned off parenteral support

Study	Teduglutide (0.05 mg/kg) n (%)	Placebo n (%)	Difference, % (95% CI)
STEPS (24 weeks)	0/43 (0.0)	0/43 (0.0)	0% (-8%, 8%)
Study 004 (24 weeks)	2/35 (5.7)	0/16 (0.0)	5.7% (-14%, 19%)

Confidence intervals calculated during the evaluation using StatsDirect software.

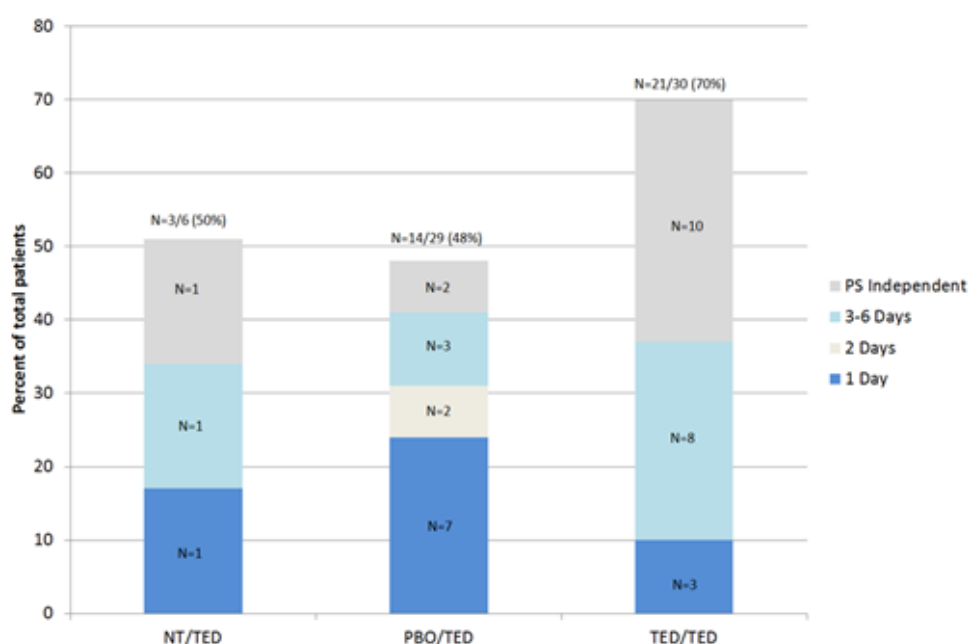
Source: Section 2.5.1.2.3, p.78 of the resubmission; p.62 of the Study 004 clinical study report.

Abbreviations: CI, confidence interval.

6.17 No patients were completely weaned off parenteral support in the teduglutide or placebo groups in the STEPS trial. Two patients treated with teduglutide 0.05 mg/kg were completely weaned in Study 004.

- 6.18 In STEPS-2, the proportions of patients who completely weaned off parenteral support whilst treated with teduglutide were 5.1% (placebo-treated patients in STEPS), 8.3% (patients not treated in STEPS), and 27% (teduglutide-treated patients in STEPS).
- 6.19 The resubmission also presented an analysis of additional days per week off parenteral support among patients in STEPS-2 who had completed ≥ 24 months of teduglutide treatment. The number and percentage of patients who achieved additional 1-, 2-, 3-6 and 7-day reductions in parenteral support per week are shown in Figure 1. Among the patients who completed treatment with teduglutide for 30 consecutive months (the “TED/TED only” group), 33% (10/30) were able to discontinue parenteral support completely. The ESC considered that discontinuation of parenteral support would represent a meaningful clinical benefit for these patients, but acknowledged these data did not include a comparison against standard care alone (which it considered to be particularly important as other factors may contribute to clinical improvements such as endogenous intestinal adaptation and intestinal rehabilitation programs).

Figure 2: Additional days per week off parenteral support from baseline, including complete independence (7 days), with long-term teduglutide treatment



Source: Figure ES2, p 7 of the resubmission

NT = not treated; PBO = placebo; PS = parenteral support; TED = teduglutide

Note: 'NT/TED' and 'PBO/TED' = ≥ 24 months of teduglutide; 'TED/TED' = ≥ 30 months of teduglutide

- 6.20 Iyer et al (2016) conducted a post hoc analysis of patients treated with teduglutide 0.05 mg/kg who achieved complete parenteral support independence across the teduglutide studies. Length of treatment with teduglutide at the time of weaning ranged from 12 to 130 weeks. Duration of parenteral support dependency prior to commencing teduglutide ranged from 1 year to 16 years. No patients requiring

parenteral support on 7 days per week at baseline were completely weaned across the available teduglutide studies.

- 6.21 In STEPS, quality of life was assessed using a short bowel syndrome-specific quality of life instrument (SBS-QoL). There were no statistically significant differences between teduglutide and placebo for the SBS-QoL sum score or subscales. The PBAC previously considered that the design and size of the trial may in part explain the lack of significant difference in this outcome, and also noted that some subgroup analyses were suggestive of quality of life benefit (Paragraph 7.7, November 2017 teduglutide PSD).

Comparative harms

- 6.22 In the 24-week placebo-controlled trials (STEPS and Study 004), teduglutide was associated with numerically higher treatment-related adverse events (primarily abdominal distension, abdominal pain, nausea, vomiting, flatulence, peripheral oedema, and stoma complications). There was a lack of comparative safety data beyond 24 weeks (Paragraph 6.28, July 2018 teduglutide PSD).
- 6.23 The ESC noted the increase in treatment-related adverse events with teduglutide over the 24-week placebo controlled period of STEPS. The ESC noted that if teduglutide resulted in a higher proportion of patients being able to completely wean off parenteral support, potential serious long-term complications associated with parenteral support infusions may be avoided.
- 6.24 In STEPS-2, treatment-related serious adverse events included gastrointestinal disorders (abdominal pain, Crohn's disease, intestinal obstruction), injection site haematoma, hepatobiliary disorders (cholecystitis, portal hypertension), gastrointestinal stoma complications, increased bilirubin, vascular disorders (hypertension), and metastatic neoplasm.
- 6.25 The resubmission provided additional safety data, including the most recent Periodic Safety Update Report (PSUR, covering the period from [REDACTED] to [REDACTED]) and updated safety results from an international patient registry study (TED-R13-002).
- 6.26 Based on an expanded assessment of harms, important identified risks associated with teduglutide were unchanged from the previous submission and included biliary adverse events (cholecystitis); pancreatic adverse events (chronic and acute pancreatitis, pancreatic duct stenosis, pancreatic infection and increased blood amylase and lipase); cardiovascular adverse events associated with fluid overload; gastrointestinal stenosis and obstruction; gastrointestinal stoma complications; growth of pre-existing polyps of the colon; benign neoplasia of the gastrointestinal tract including the hepatobiliary system; tumour promoting ability; occurrence of anti-teduglutide antibodies, cross reactivity with GLP-2, and occurrence of anti-E.coli protein (ECP) antibodies (and associated clinical immunogenicity reactions); and anxiety.

Benefits and harms

6.27 A summary of the comparative benefits and harms for teduglutide versus placebo is presented in Table 8 (unchanged from the July 2018 resubmission).

Table 8: Summary of comparative benefits and harms across the 24-week placebo-controlled trials

Benefits					
Responder rates for at least a 20% reduction in weekly parenteral support volume					
Trial	Teduglutide	Placebo	Events/100 patients		RD (95% CI)
			Teduglutide	Placebo	
STEPS	27/43	13/43	62.8	30.2	0.33 (0.11, 0.51)
Study 004	16/35	1/16	45.7	6.3	0.39 (0.13, 0.58)
Responder rates for at least a 1-day reduction in days per week on parenteral support					
Trial	Teduglutide	Placebo	Events/100 patients		RD (95% CI)
			Teduglutide	Placebo	
STEPS	21/39	9/39	53.8	23.1	0.31 (0.09, 0.50)
Study 004	11/35	4/16	31.4	25.0	0.06 (-0.22, 0.30)
Harms					
	Teduglutide ¹	Placebo	Events/100 patients		RD (95% CI)
			Teduglutide	Placebo	
Gastrointestinal disorders					
STEPS	27/42	21/43	64.3	48.8	0.15 (-0.05, 0.36))
Study 004	■	■	■	■	■
Intestinal stoma complication					
STEPS	10/42	3/43	23.8	7.0	0.17 (0.02, 0.32)
Study 004	■	■	■	■	■

Confidence intervals calculated during the evaluation using StatsDirect/Revman software.

Source: Table 2.5.1, p.72; Table 2.5.2, p.76; Table 2.5.10, p.87 of the resubmission. Table 2.3.1, p.20; Table 2.3.5, p.22; Table 2.3.11, p.33 of Attachment S2A2 of the resubmission.

¹ Teduglutide 0.05 mg/kg arm of Study 004.

6.28 On the basis of direct evidence presented in the submission, for every 100 patients treated with teduglutide in comparison to placebo (for standard care):

- Approximately 33 to 39 additional patients would achieve at least a 20% reduction in weekly parenteral support volume at Week 20 that is maintained to Week 24;
- Approximately 6 to 31 additional patients would achieve at least a 1-day reduction in days per week on parenteral support after 24 weeks.
- Approximately 15 to 29 additional patients would experience gastrointestinal disorders over 24 weeks;
- Approximately 3 to 17 additional patients would experience intestinal stoma complications over 24 weeks.

Clinical claim

6.29 The resubmission described teduglutide plus standard care as superior in terms of effectiveness compared to standard of care alone. The PBAC previously considered that the claim of superior comparative effectiveness of teduglutide over standard care was reasonable, based on the statistically significant difference in the primary efficacy outcome of the proportion of patients who achieved at least a 20% reduction in

weekly parenteral support volume from baseline at Week 20 that is maintained through to Week 24 (Paragraph 7.7, November 2017 teduglutide PSD). However, in July 2018 the PBAC further considered that there was a lack of long-term comparative clinical evidence to define the magnitude of the treatment effect associated with teduglutide (Paragraph 7.9, July 2018 teduglutide PSD). No additional long-term comparative evidence was presented in the resubmission.

- 6.30 The PBAC previously considered that the non-inferior safety claim was not adequately justified (Paragraph 6.37, July 2018 teduglutide PSD). The resubmission described teduglutide plus standard care as inferior in term of safety compared to standard of care alone.
- 6.31 The PBAC noted that teduglutide was associated with a statistically significantly higher proportion of patients achieving at least a 1-day reduction in parenteral support per week compared with placebo in the STEPS study (53.8% and versus 23.1%, respectively, at Week 24). The PBAC considered that the claim of superior comparative effectiveness of teduglutide plus standard care versus standard of care alone was reasonable.
- 6.32 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.33 The resubmission presented a modelled economic evaluation assessing the cost effectiveness of teduglutide plus standard care compared to standard care alone, in patients with short bowel syndrome associated with Type III intestinal failure.
- 6.34 A comparison of the economic models presented in the current resubmission and the July 2018 resubmission is presented in Table 9.

Table 9: Comparison of economic models between submissions

Component	July 2018 resubmission	Current resubmission
Type of analysis	Cost effectiveness analysis/cost utility analysis	Unchanged
Methods used to generate results	Markov cohort model in Excel	Monte Carlo microsimulation in TreeAge
Health states	<p>Teduglutide arm:</p> <ul style="list-style-type: none"> - PS 0 days/week; - PS 1-3 days/week on teduglutide; - PS 4-6 days/week on teduglutide; - PS 7 days/week on teduglutide; - PS 1-3 days/week teduglutide discontinued; - PS 4-6 days/week on teduglutide discontinued; - PS 7 days/week on teduglutide discontinued; - Death. <p>Standard care arm:</p> <ul style="list-style-type: none"> - PS 0 days/week; - PS 1-3 days/week; - PS 4-6 days/week; - Death. 	<p>Teduglutide arm (33 health states):</p> <ul style="list-style-type: none"> - PS 0, 1, 2, 3, 4, 5, 6, or 7 days/week; - Treatment; - Holiday; - Re-treatment; - Standard care; - Death. <p>Standard care arm (8 health states, though there were no patients in the PS 0 health state):</p> <ul style="list-style-type: none"> - PS 0, 1, 2, 3, 4, 5, 6, or 7 days/week; - Standard care; - Death.
Transition probabilities	<p>Teduglutide arm:</p> <ul style="list-style-type: none"> - Transitions between levels of PS based on patient level data from STEPS trial and extension study (STEPS-2) up to Week 104. - Transitions beyond 104 weeks based on STEPS-2 teduglutide-arm transitions between Weeks 91 to 104. <p>Standard care arm:</p> <ul style="list-style-type: none"> - No transitions included (patients remain in baseline health state unless they die). 	<p>Teduglutide arm:</p> <ul style="list-style-type: none"> - Transitions between levels of PS based on patient level data from STEPS trial and extension study (STEPS-2) up to Week 120. - Transitions beyond 120 weeks based on STEPS-2 teduglutide-arm transitions between Weeks 108 to 120. <p>Standard care arm:</p> <ul style="list-style-type: none"> - Transitions between Week 0 and 24 based on patient level data for the placebo arm of the STEPS trial. - No further transitions beyond 24 weeks.
Teduglutide drug costs	<ul style="list-style-type: none"> - Based on estimated teduglutide price under the proposed pay-for-performance scheme. - Included anniversary price reductions 	<ul style="list-style-type: none"> - Based on effective price (■% discount to the published price). -No anniversary price reductions applied.
Teduglutide discontinuations	<ul style="list-style-type: none"> - Continuation criteria: assumed that ■% of patients discontinue treatment at 12 months (based on proportion of patients in STEPS/STEPS-2 not achieving ≥ 20% reduction in PS at 12 months). - Stopping rule: not included. - Other discontinuations: not included. 	<ul style="list-style-type: none"> - Continuation criteria: patients not achieving ≥ 1 day/week reduction in PS at 12 months discontinue treatment (probabilities based on individual patient data from STEPS/STEPS-2). - Stopping rule: patients who have stable or increased PS days per week during a trial of treatment cessation discontinue treatment (based on Compher et al. (2011) analysis of Study 004/Study 005). - Other discontinuations: assumed a background treatment discontinuation rate of ■% per year over the life of the model (based on discontinuations due to adverse events and patient decision in the STEPS-2 study).

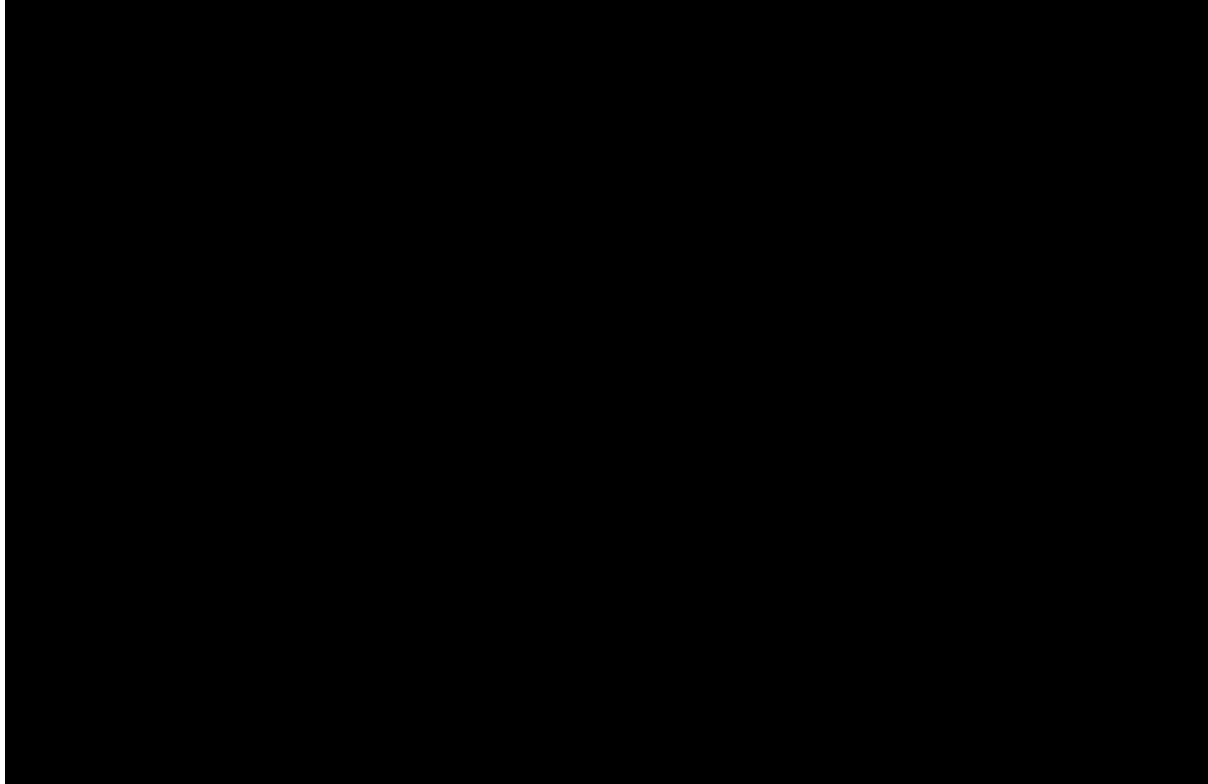
Component	July 2018 resubmission	Current resubmission
Utility values	<ul style="list-style-type: none"> - Based on sponsor-commissioned UK time trade-off study (Ballinger et al., 2016). - Applied as averaged values according to PS 0 days/week; 1-3 days/week; 4-6 days/week; 7 days per week. - Carer disutilities (base on a survey of clinical experts in the UK) included in base case. 	<ul style="list-style-type: none"> - Utility values (Ballinger et al., 2016) applied across individual PS health states. - Carer disutilities removed from the base case.

Source: Section 3.12, pp133-149 of the resubmission.

Abbreviations: PS, parenteral support.

- 6.35 As requested by the PBAC in its previous consideration, the resubmission model included transitions for the standard care arm based on the STEPS trial placebo arm (up to 24 weeks), and removed carer disutilities and anniversary price reductions from the base case. While these changes were considered to be appropriate, the PBAC noted they resulted in a conservative ICER.
- 6.36 As with the previous resubmission, the model included treatment discontinuation for patients failing to meet the restriction’s continuation criterion. However, the current model also included treatment discontinuation following a trial treatment cessation and treatment discontinuation due to adverse events.
- 6.37 After 12 months of treatment with teduglutide, patients who have not met the continuation criterion (≥ 1 day reduction in the number of parenteral support days per week) discontinue treatment with teduglutide and switch to standard care. The ESC noted that this may not be appropriate as a level of response had been included in the standard care arm (and thus patients who discontinued teduglutide because they failed to meet efficacy criteria may still accrue a health benefit but with no cost). The ESC considered that it would have been more appropriate for non-responders to remain in their baseline parenteral support health state. However, the ESC acknowledged that this was only an issue in the first 24 weeks of the model (because transitions in the standard care arm were only applied for 24 weeks, after which point patients remained in the same health state; more than █% of patients in the teduglutide arm remain on teduglutide treatment at this time point).
- 6.38 After each additional 6 months on teduglutide treatment, patients whose parenteral support requirements have remained stable or worsened undertake a trial of treatment cessation. Patients whose parenteral support requirements increase during the trial treatment cessation may reinitiate teduglutide with no further assessment required, however patients who remain stable or reduce their PS requirements during treatment cessation discontinue treatment and switch to standard care.
- 6.39 During each cycle, teduglutide patients may also discontinue treatment due to adverse events or patient preference and switch to standard care.
- 6.40 Figure 2 presents the proportion of patients on treatment with teduglutide (initial treatment and retreatment following trial of treatment cessation) over the duration of the model.

Figure 2: Model traces of the proportions of patients on teduglutide in the treatment and retreatment health states



Source: Generated during the evaluation using the 'S3A1_teduglutide_CUA' TreeAge file.

6.41 The evaluation identified a number of issues with the applicability of the modelled discontinuations:

- The evaluation and the ESC considered that the continuation and discontinuation criteria in the restriction were subjective, and the level of patient discontinuations estimated in the model may not reflect clinical practice. The PSCR and pre-PBAC response proposed additional definitions regarding the timing and measurement of response (refer to Paragraph 2.10). The PBAC considered that these additional definitions, along with the RSA proposed in the pre-PBAC response would help mitigate these concerns.
- The transition probabilities following treatment cessation derived from the Compher et al. (2011) analysis of patients in Study 004/Study 005 may not be applicable to the STEPS population and the PBS population. The duration of treatment with teduglutide was shorter than modelled in the economic model (patients received treatment for only 24 to 48 weeks in Study 004/Study 005), and the study also included patients who received the higher dose of teduglutide (0.10 mg/kg). Further, the responder analysis was based on patients achieving at least a 20% reduction in weekly parenteral support volume, rather than a reduction of ≥ 1 day per week in parenteral support modelled in the resubmission.
- Discontinuations due to adverse events or patient decision were derived from the STEPS-2 study (6/37 patients discontinued treatment over a 2 year duration – 4

due to adverse events and 2 due to patient decision), which the evaluation considered may not reflect treatment discontinuations in Australian clinical practice.

- The extrapolation of discontinuations over the 20 years of the model was not adequately justified. Given the chronic nature of the disease, and the lack of alternative treatments, the evaluation considered that it may not be reasonable to assume such a high rate of discontinuations in the base case.

- 6.42 Overall, the evaluation and the ESC considered that the high rate of treatment discontinuations included in the economic model was not adequately justified and favoured the teduglutide arm, as discontinuing patients remain in the same parenteral support health state after discontinuing teduglutide, without incurring teduglutide drug costs. However, the PBAC acknowledged the lack of alternative data available to inform many of these assumptions and considered that the data used to inform the economic model was likely to be the best available data. Further, the PBAC considered that the RSA proposed in the pre-PBAC response helped to mitigate concerns that the rate of discontinuations estimated in the economic model would not be realised in clinical practice (refer to Paragraph 6.64).
- 6.43 As in the July 2018 resubmission, transition probabilities derived from the teduglutide arm of the STEPS/STEPS-2 study were used to inform transitions between individual parenteral health states in the teduglutide arm of the model. There were sparse data informing transitions between parenteral support health states in the teduglutide arm, due to the small number of patients treated with teduglutide in the STEPS/STEPS-2 study, and the incorporation of a larger number of health states than in the July 2018 model. Transitions beyond Week 120 were based on transitions between Weeks 108 to 120 of the STEPS-2 study. The evaluation considered that the extrapolated Week 108 to 120 transitions may not adequately reflect the longer-term outcomes of patients treated with teduglutide.
- 6.44 The ESC noted that the resubmission continued to use utility values that were derived from a time trade-off study conducted in the UK (Ballinger 2016). The ESC recalled that the PBAC had previously considered that the submission did not adequately justify the application of these utilities rather than alternative utilities from a trade-off study conducted in Canada (Lachaine 2016), and that this likely favoured teduglutide (Table 11, July 2018 teduglutide PSD). The ESC considered that the Canadian utilities, which were more conservative, may have been appropriate in the context of the lack of statistically significant differences in quality of life measured in the STEPS trial. The Pre-PBAC response provided additional information comparing the two utility studies, noting that a complete manuscript of the UK study was published in November 2018. The pre-PBAC response outlined that the UK study used a more robust methodology, including with regard to vignette development (health states were developed from literature reviews and interviews with patients and health care professionals and were piloted with members of the UK general public). The UK study found a higher degree

of internal consistency of results (with the mean utility values decreasing with worsening health state) compared with the Canadian study. The PBAC considered that this additional information provided a greater degree of confidence in the UK utility study. Further, the PBAC considered the utility decrement for each additional day of parenteral support in the UK study to be consistent with the comments received from consumers and clinicians about the impact of parenteral support on quality of life. Overall, the PBAC considered that the resubmission’s use of utilities from the UK study in the base case was reasonable.

6.45 Table 10 summarises the key drivers of the economic model.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Treatment effect	<p>Transition probabilities for the teduglutide arm from Week 0 to Week 120 were derived from patient level data from STEPS/STEPS-2. There were sparse data informing transitions between parenteral support health states in the teduglutide arm. Transition probabilities for the standard care arm from Week 0 to Week 24 were derived from patient level data from the STEPS trial. As there was no placebo arm in the trial beyond 24 weeks, patients in the standard of care arm of the model remain in the same parenteral support health state unless they die.</p> <p>No patients in the standard care arm of the model completely wean off parenteral support (whereas patients in the teduglutide arm could). This was because transition probabilities for the standard care arm were derived from the placebo arm of the 24-week STEPS trial, during which time no patients were completely weaned from parenteral support in either arm. The ESC considered that this is likely to bias against the standard care arm, as based on the natural history of intestinal failure, some patients may have completely weaned from parenteral support whilst on treatment with standard care.</p> <p>The ESC noted that the model included an OS gain in the teduglutide arm for those patients who completely wean off parenteral support. The ESC considered this assumption was likely reasonable given it was only applied to patients who completely wean off parenteral support.</p>	High, favours teduglutide

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Description	Method/Value	Impact
Extrapolation	Transition probabilities beyond Week 104 were assumed to be the average of those occurring between Week 108 and Week 120 (Week 91 and Week 104 in the July 2018 resubmission). The model assumed transitions in parenteral support requirements would continue for up to 20 years. The evaluation considered that the extrapolation of transition probabilities beyond 120 Weeks was uncertain due to the sparseness of data used to inform transitions between individual parenteral support health states. No sensitivity analyses using alternative data extrapolations were included in the resubmission. The ESC noted that the model relied on considerable extrapolation of data (20 year time horizon based on 120 weeks of data in the teduglutide arm, and 24 weeks of data in the standard care arm).	Moderate, favours teduglutide
Treatment discontinuations	The resubmission included trial-based discontinuations based on the number of patients in the teduglutide arm who discontinued treatment after 2 years in the STEPS-2 extension study (████%). The proportion of patients who discontinued at 2 years was converted to a per cycle rate and applied over the duration of the model. The high rate of discontinuations favoured the teduglutide arm, as discontinuing patients remain in the same parenteral support health state after discontinuing teduglutide, without incurring teduglutide drug costs.	High, favours teduglutide
Model transitions	The resubmission applied an additional transition to patients undergoing assessment, which was amended during evaluation (per Table 12). The ESC noted that the model did not allow patients who had completely weaned off parenteral support to transition back on to parenteral support. The ESC considered that it was not clear whether this would reflect clinical practice.	High, favours teduglutide
Utilities	Health state utility values used in the economic model base case were derived from a sponsor-commissioned time trade-off study conducted in the UK (Ballinger et al 2016), which had a utility of 0.82 in the PS0 (no parenteral support) health state, ranging down to 0.36 in the PS7 (7 days per week of parenteral support) health state. Alternative utilities were available from a Canadian time trade-off study (Lachaine 2016) which were 0.74 in PS0, ranging down to 0.40 in the PS7 health state.	High, favours teduglutide
Modelled population	The modelled population was based on the STEPS trial baseline days of parenteral support per week (≥ 3 days per week). Differences in the distribution of days per week of parenteral support in the STEPS trial and in Australian clinical practice may affect the cost effectiveness of teduglutide. The PSCR noted that a study describing the characteristics of Australian patients with short bowel syndrome found that, among the 90% (18/20) of patients on parenteral support ≥ 3 days per week, the average number of days of parenteral support was 5.4 days per week versus 5.7 in the STEPS trial. While the sample size was small (18 patients on parenteral support ≥ 3 days per week), the ESC considered that the impact and direction of bias of this applicability issue were difficult to determine.	Unknown

Source: Compiled during the evaluation.

6.46 Table 11 presents a stepped analysis from the July 2018 PBAC revised base case to the resubmission base case.

Table 11: Stepped analysis from the July 2018 PBAC revised base case to the resubmission base case

Step	Incremental cost	Incremental QALYs	ICER
PBAC July 2018 revised base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
PBAC revised base case with new model structure including additional parenteral support health states	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Inclusion of additional treatment discontinuations ([REDACTED]% per year)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Application of continuation criteria at 12 months (at least 1 day reduction in weekly parenteral support)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Application of stopping rule (trial of treatment cessation)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Resubmission base case			\$ [REDACTED]

Source: Table 3.12.2, p.137 of the resubmission.

- 6.47 The resubmission estimated that treatment with teduglutide (plus standard care) was associated with an incremental cost per QALY gained of \$75,000 to \$105,000 compared to standard care alone. The stepped analysis could not be replicated during the evaluation as insufficient detail was provided on the changes at each step. The PSCR provided additional information regarding the changes made to the model in each stage of the stepped analysis, however the analysis still could not be replicated.
- 6.48 During the evaluation, an issue was identified with the resubmission model transitions. The resubmission applied an additional transition (to an improved, a worse or the same parenteral support health state), to patients undergoing assessment, based on their overall change in parenteral support requirements during the assessment period. The impact was an overall increase in patients transitioning to a higher health state. The results of the modelled economic evaluation after adjusting for this issue are presented in Table 12. The PSCR acknowledged that the additional transition favours teduglutide, but argued that the approach was justified to overcome limitations of the trial-based health state transition probabilities (e.g. small patient numbers), and that the effect is balanced by assuming teduglutide patients who do not meet the continuation criteria (due to worsening) will worsen further when moved to standard of care. The PSCR further argued that the evaluation’s adjustment represented a conservative approach by assuming patients do not transition during the assessment cycle. The ESC considered that the submission’s inclusion of an additional transition based on the overall change during the 6- or 12-month assessment period was not reasonable. However, the PBAC agreed with the PSCR that neither the submission’s base case, nor the evaluation’s adjustments are perfect representations of patient progression in clinical practice, and given the limited data to inform this, the PBAC considered that the evaluation’s adjustments resulted in an ICER that was conservative.

Table 12: Presentation of the resubmission base case economic evaluation with the evaluation’s adjustment to remove the additional transitions

	Teduglutide (plus standard care)	Standard care	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life years	[REDACTED]	[REDACTED]	[REDACTED]
QALYS	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per life year gained			\$ [REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

The resubmission inappropriately applied an additional transition (to a higher, lower or the same parenteral support health state), to patients undergoing assessment, based on their overall change in parenteral support requirements during the assessment period. During the evaluation, an alternative base case was generated by removing the extra transition.

Source: Constructed during the evaluation using the 'S3A1_teduglutide_CUA' TreeAge file.

Abbreviations: QALY, quality adjusted life year.

6.49 Based on the results of the economic model with the evaluation’s adjustment to remove the additional transition, teduglutide (plus standard care) was associated with an incremental cost per QALY gained of \$105,000 to \$200,000 compared to standard care alone. As outlined above, the PBAC considered that this was a conservative estimate of the ICER and that neither the submission’s base case, nor the evaluation’s adjustments are perfect representations of patient progression in clinical practice.

6.50 Table 13 presents sensitivity analyses conducted by the submission and multivariate sensitivity analyses conducted during the evaluation following adjustment to remove the additional transitions.

Table 13: Results of sensitivity analyses conducted during the evaluation

	Incr costs	Incr QALYs	ICER
Resubmission base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Carer disutilities included (supplementary analysis)	[REDACTED]	[REDACTED]	\$ [REDACTED]
Multivariate sensitivity analyses based on evaluation’s adjustment to remove the additional transitions			
Evaluation adjustment to remove the additional transitions	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Carer disutilities included (supplementary analysis)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utilities based on Canadian TTO study (Lachaine 2016)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Time horizon (base case: 20 years)			
- 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
- 15 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Teduglutide transitions (base case: extrapolated to 20 years)			
- Teduglutide transitions limited to 130 weeks	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
- Teduglutide transitions limited to 5 (or more) years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Trial-based discontinuations (base case 0.68% per cycle)			
- [REDACTED]%	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
- 0%	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 3.12.4, p140 of the resubmission; Constructed during the evaluation using the 'S3A1_teduglutide_CUA' TreeAge file.

Abbreviations: QALY, quality adjusted life year; PS, parenteral support; TTO, time trade-off.

^a The inconsistencies in these results appear to be related to the sparse data informing the transition probabilities

6.51 Results of sensitivity analyses undertaken during the evaluation indicate that the ICER was sensitive to assumptions regarding the time horizon, utility values, removal of trial-based discontinuations, and assumptions regarding parenteral support changes after a trial of treatment cessation.

- 6.52 The PBAC noted that with carer disutilities included, the ICER/QALY ranged from \$45,000 to \$75,000 in the submission's base case to \$105,000 to \$200,000 in the evaluation's adjusted base case. The PBAC further noted the consumer comments with respect to the impact on carers and therefore considered that this supplementary analysis remained useful.

Drug cost/patient/year

- 6.53 The drug cost per patient per year of treatment with teduglutide is \$ [REDACTED] (Section 100 Public Hospital) based on [REDACTED] packs per year at the proposed effective price of \$ [REDACTED] per pack (this was unchanged from the July 2018 resubmission).
- 6.54 Patients who fulfil the requirements under the proposed continuation criteria may receive lifelong treatment with teduglutide.

Estimated PBS usage & financial implications

- 6.55 This submission was not be considered by DUSC.
- 6.56 The resubmission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of teduglutide.
- 6.57 The main changes compared to the July 2018 resubmission were:
- Limiting the eligible population to patients on parenteral support on at least 3 days per week (consistent with PBAC recommendations);
 - Updates to the annual growth rate (increased) and uptake rates (increased);
 - Inclusion of treatment discontinuations related to the proposed continuation criteria and stopping rule (consistent with PBAC recommendations; the July 2018 resubmission included continuation criteria-related discontinuations only);
 - Inclusion of additional treatment discontinuations of [REDACTED]% per year due to adverse events or patient decision (consistent with the economic model).

Table 14: Total utilisation and cost to PBS of listing teduglutide (as presented in resubmission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible population						
Total HPN patients (█% annual growth)	█	█	█	█	█	█
Total eligible patients (█% of total HPN patients)	█	█	█	█	█	█
Initiating patients						
Eligible patients	█	█	█	█	█	█
Uptake rate	█% ^a	█%	█%	█%	█%	█%
New patient uptake of teduglutide	█	█	█	█	█	█
Patients who meet continuation criteria at 12 months (█%)	█	█	█	█	█	█
Patients qualifying for permanent treatment (█%) ¹	█	█	█	█	█	█
Total treated patients						
Total treated patients ²	█	█	█	█	█	█
- Non-permanent	█	█	█	█	█	█
- Permanent	█	█	█	█	█	█
Mortality (█%/year)	█	█	█	█	█	█
Discontinuing patients (█%)	█	█	█	█	█	█
Total treated patients	█	█	█	█	█	█
Total treated patients July 2018 resubmission	█	█	█	█	█	█
Total packs dispensed (█/patient/year)	█	█	█	█	█	█
Estimated total cost of teduglutide to PBS (Effective price, DPMQ \$█)						
Total cost to PBS/RPBS less co-payments	\$█	\$█	\$█	\$█	\$█	\$█
Total cost to PBS/RPBS less co-payments July 2018 resubmission	\$█	\$█	\$█	\$█	\$█	\$█
Estimated total cost of teduglutide to Government						
Total cost to PBS/RPBS less co-payments	\$█	\$█	\$█	\$█	\$█	\$█
Costs to MBS	\$█	\$█	\$█	\$█	\$█	\$█
Net costs for PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█	\$█

Source: Table 4.9.1, pp164-165; Table 4.9.2, p.166; Table 4.9.3, p.166; Table 4.9.4, p.167; Table 4.9.5, p.169; Table 4.9.6, p.171; Table 4.9.7, p.172; Table 4.9.8, p.173 of the resubmission.

Abbreviations: DPMQ, dispensed price for maximum quantity; HPN, home parenteral nutrition.

¹ Number of new patients at the end of each year.

² Average number of patients per year.

^a Increased to █% in the pre-PBAC response

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS/RPBS would be less than \$10 million.

6.58 The total cost to the PBS/RPBS of listing teduglutide (less patient co-payments) was estimated less than \$10 million in Year 1 of listing, increasing to less than 10 million in Year 6, a total of \$30 to \$60 million in the first 6 years of listing. The evaluation considered that these estimates were likely underestimates given:

- uptake rates in the first few years of listing are likely to be higher than estimated due to the lack of other available treatments;

- the high rate of discontinuation due to adverse events (patients who discontinue treatment may recommence at a later time; discontinuations due to adverse events are likely to occur more frequently during the initial treatment period); and
 - there may be also be use outside of the PBS restriction among patients who have not achieved the required improvements specified in the proposed continuation criteria and stopping rule.
- 6.59 To address the evaluation’s concerns that uptake was underestimated, the pre-PBAC response increased the uptake rate in Year 1 from █% to █%. The pre-PBAC response stated this was intended to capture grandfathered patients who will transition to PBS-subsidised teduglutide, while also acknowledging that uptake will be limited by the capacity of clinics and the limited number of clinicians experienced in the treatment of this condition.
- 6.60 The PBAC noted that the financial estimates had reduced since the previous submission (the July 2018 submission estimated a cost to the PBS/RPBS of \$30 to \$60 million in the first 6 years).
- 6.61 The financial estimates were most sensitive to a change in the number of patients eligible for treatment with teduglutide, the proportion of patients meeting the continuation criteria, the proportion of patients meeting the stopping rule, and changes to uptake rates in the first few years of listing.

Quality use of medicines

- 6.62 The sponsor proposed a patient support program, designed to supplement existing services for patients with short bowel syndrome with intestinal failure. The program is proposed to offer adherence support by providing information on product administration and managing treatment emergent adverse events.

Financial management – risk sharing arrangements

- 6.63 No risk-sharing arrangements (RSA) were proposed in the resubmission or the PSCR. The evaluation and the ESC considered that an RSA with caps on prescription numbers may be required given the cost-effectiveness estimate relies on a large proportion of patients discontinuing treatment (with a maintained treatment effect), which in practice would rely on potentially subjective PBS restriction criteria.
- 6.64 The pre-PBAC response proposed an RSA, with a two-tier rebate structure. The first expenditure threshold (Tier 1) was based on █ “defined in the economic evaluation” (█ but with uptake increased from █ % to █ % in Year 1). The second expenditure threshold (Tier 2) was based on █ but excluding the █. The pre-PBAC response stated that usage between the Tier 1 and Tier 2 thresholds is “considered within the agreed PBS population, but is due to treatment effects which

differ from those modelled in the economic evaluation (i.e. more patients recommence treatment, or fewer discontinue, resulting in higher utilisation)”. Thus, the sponsor proposed a [redacted] % rebate apply to the agreed net price above the Tier 1 threshold. A [redacted] % rebate was proposed for all expenditure above the Tier 2 threshold.

Table 15: Total utilisation and cost to PBS of listing teduglutide (as presented in pre-PBAC response)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Tier 1 cap (expenditure between Tier 1 and Tier 2 was proposed to be rebated at [redacted] %)						
Total treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total packs dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Tier 2 cap (expenditure above Tier 2 was proposed to be rebated at [redacted] %)						
Total treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total packs dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Maximum Commonwealth expenditure under proposed RSA						
	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Source: Table 2, p.3 pre-PBAC response

6.65 The pre-PBAC response proposed that total PBS expenditure on teduglutide would not exceed \$10 million in Year 6, or \$30 to \$60 million over the first 6 years of listing.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of teduglutide as a Section 100 (Highly Specialised Drug Program) benefit for the treatment of patients with Type III (chronic) intestinal failure associated with short bowel syndrome. The PBAC recognised the high clinical need in this small patient group, and considered that teduglutide may reduce the patient burden associated with the current therapy, parenteral support. The PBAC considered that, with the revised restriction and the RSA proposed, teduglutide was cost-effective compared with standard care.

7.2 The PBAC is satisfied that teduglutide provides, for some patients, a significant improvement in efficacy over the current standard care, parenteral support alone.

7.3 The PBAC noted the consumer comments that outlined the detrimental quality of life impacts associated with parenteral support particularly due to the significant time impact, immobility while connected to parenteral support, dehydration, lack of energy and the social and carer impacts. The PBAC re-iterated its previous consideration that there was a high clinical need for an effective therapy that reduces the patient burden associated with parenteral support.

7.4 The PBAC recalled its previous advice that teduglutide treatment should be confined to those patients most likely to achieve a clinically meaningful benefit, with the treatment duration limited to that necessary to achieve meaningful benefits. The PBAC noted that the resubmission had significantly revised the restriction to address this, particularly by:

- revising the restrictions to be based on the key patient relevant outcome of days per week (rather than volume of parenteral support) to determine eligibility and treatment response.
- revising the initiation criteria to limit use of teduglutide to patients who have a history of dependence on parenteral support for at least 12 months, require ≥ 3 days per week of parenteral support, and have stable parenteral support requirements for at least four consecutive weeks prior to initiating teduglutide.
- including a continuation restriction that requires patients to demonstrate a reduction of ≥ 1 day per week in parenteral support requirements after the first 12 months of teduglutide therapy to be eligible for continuing use.
- including a stopping rule so that patients do not continue on treatment that may be unnecessary. A ‘trial of treatment cessation’ is required for patients who have a stable frequency of days per week of parenteral support in the preceding 6 months. The PBAC considered that patients who have completely weaned off parenteral support should be exempt from the requirement to undergo a trial of treatment cessation. Further, the PBAC considered that patients who are continuing to improve should not be required to undergo a trial of treatment cessation (i.e. patients who have a reduction in the number of days per week of parenteral support since the last assessment should be eligible for continuing access to teduglutide). The PBAC considered that patients whose parenteral support requirements increase (i.e. at least one day per week increase in parenteral support over a consecutive 4-week period) while on teduglutide under the continuing restriction should be required to cease teduglutide therapy permanently.
- including a recommencement restriction wherein patients can recommence teduglutide if their condition deteriorates during the trial cessation period. The PBAC considered that recommencement of teduglutide should be based on clinician judgement as there are no simple objective measures for assessing deterioration. As such, justification of recommencement may include parameters such as an increase in parenteral support requirements by one or more days, changes in renal function or urinary sodium levels, or changes in body weight. The PBAC also considered that there should be no time limit on accessing the recommencement restriction.

7.5 To provide guidance on the timing and assessment of patient parenteral support requirements (to determine eligibility, response and stability) in the restriction, the PSCR and pre-PBAC response proposed that the number of days per week of parenteral support at each assessment point could be based on the mean number of days per week over the preceding 4 weeks of treatment. The PBAC considered that it may be more appropriate for the mean number of days to be calculated over the whole duration of the preceding treatment period (between authority applications) to account for any fluctuations in parenteral support requirements more accurately,

but that the clinical appropriateness and practical feasibility of calculating the mean number of days over a 6-12 month period should be confirmed by expert clinician advice prior to implementation.

- 7.6 The PBAC considered that the restriction should not specify any age criteria, noting that teduglutide has been studied in paediatric patients and was shown to be well tolerated.
- 7.7 The PBAC recalled its previous advice that a reduction in the number of days per week of parenteral support was a more clinically relevant outcome than a reduction in volume of parenteral support without days off. The PBAC noted that teduglutide was associated with a statistically significantly higher proportion of patients achieving at least a 1-day reduction in parenteral support per week compared with placebo in the STEPS study (53.8% and versus 23.1%, respectively, at Week 24). After 30 months of teduglutide treatment (which included single-arm extension studies), 70% of patients achieved at least a 1-day reduction in parenteral support per week and 33% weaned off parenteral support completely. The PBAC considered these were clinically meaningful benefits, but acknowledged that there is a lack of long-term comparative evidence to define the magnitude of the treatment effect associated with teduglutide versus standard care alone beyond 24 weeks.
- 7.8 The PBAC considered that, for some patients, teduglutide would result in a clinically meaningful reduction in the number of days per week of parenteral support. Overall, the PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data.
- 7.9 The PBAC considered that the claim of inferior comparative safety versus standard of care alone was adequately supported by the data.
- 7.10 The PBAC noted that the ICER/QALY was considerably lower than estimated in the previous submission predominantly due to the inclusion of the impact of treatment discontinuations due to adverse events and the trial treatment cessation criteria proposed in the restriction. Further, the PBAC considered that the resubmission had appropriately addressed the majority of issues raised about the economic evaluation in its previous considerations.
- 7.11 The PBAC noted that the resubmission presented a base case ICER of \$75,000/QALY to \$105,000/QALY, and the evaluation had adjusted this to \$105,000/QALY to \$200,000/QALY to remove an additional health state transition (to an improved, a worse or the same parenteral support health state) for patients undergoing assessment. The PBAC considered that this additional transition may be reasonable in some patients, and considered that neither the submission's base case, nor the evaluation's adjustments were accurate representations of patient progression in clinical practice. Overall, the PBAC considered that the evaluation's adjustments resulted in an ICER that was conservative.

- 7.12 The PBAC considered that a number of other conservative assumptions were included in the economic model (many of which were included to address issues raised in the PBAC’s previous considerations of teduglutide) such as: the complete account of the trial placebo response was included in the standard treatment arm (up to 24 weeks); carer disutilities were removed from the base case; costs of adverse events with parenteral support were not included except sepsis (catheter-related infections); and the long-term impacts of parenteral support on morbidity and mortality were not included except for in patients who completely weaned off parenteral support. Thus, while the estimated ICERs/QALY presented in the resubmission and the evaluation were high, the PBAC considered that these were likely to overestimate the true ICER/QALY.
- 7.13 The PBAC considered that additional information provided in the pre-PBAC response had adequately justified the resubmission’s use of utility values from a UK study, Ballinger 2016, in the base case (refer to Paragraph 6.44). Further, the PBAC considered the utility decrement for each additional day of parenteral support in the UK study to be consistent with the comments received from consumers and clinicians about the impact of parenteral support on quality of life.
- 7.14 The PBAC noted that with carer disutilities included, the ICER/QALY ranged from \$45,000 to \$75,000 in the submission’s model to \$105,000 to \$200,000 in the evaluation’s adjusted analysis. The PBAC considered that these supplementary analyses were informative given the significant impact that parenteral support requirements have on carers.
- 7.15 Overall, the PBAC considered that the ICER/QALY was high but acceptable given: the ICER was likely overestimated; supplementary analyses showed that inclusion of the impact on carers significantly reduced the ICER; and the high clinical need in this small patient group.
- 7.16 The PBAC considered that the resubmission had addressed its previous concerns regarding the financial estimates by updating the growth and uptake rates, and by including the impact of treatment discontinuations consistent with the proposed PBS restriction.
- 7.17 The PBAC noted that the pre-PBAC response proposed an RSA based on the estimates of use that would limit total PBS expenditure on teduglutide over the first ■ years of listing. The PBAC considered that an RSA that capped expenditure would adequately mitigate the uncertainties about the estimated utilisation, and in particular would help to mitigate concerns that the rate of discontinuations estimated in the economic model would not be realised in clinical practice.
- 7.18 The PBAC recommended that teduglutide should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.19 The PBAC advised that teduglutide is not suitable for prescribing by nurse practitioners.

7.20 The PBAC recommended that the Early Supply Rule should apply.

7.21 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item: Restriction to be finalised. Indicative restrictions are outlined below.

Initial 12 months of treatment

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Proprietary name and manufacturer	
TEDUGLUTIDE 5 mg injection [28 vials] (&) inert substance diluent [28 x 0.5 mL syringes], 1 pack	28	11	Revestive®	Shire Australia Pty Limited

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Severity:	Type III
Condition	Short bowel syndrome with intestinal failure
PBS Indication:	Type III short bowel syndrome with intestinal failure
Treatment phase:	Initial treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist gastroenterologist
Clinical criteria:	<p>Patient must have short bowel syndrome with intestinal failure following major surgery; AND Patient must have a history of dependence on parenteral support for at least 12 months; AND Patient must have received a stable parenteral support regimen for at least 3 days per week in the previous 4 weeks AND Patient must not have active gastrointestinal malignancy or history of gastrointestinal malignancy within the last five years AND The treatment must not exceed 12 months under this restriction AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition.</p>
Prescriber Instructions	<p>A stable parenteral support regimen is defined as the same number of days of parenteral support (parenteral nutrition ± IV fluids) per week for 4 consecutive weeks to meet caloric, fluid or electrolyte needs.</p> <p>The authority application must be made in writing and must include: (1) a completed authority prescription form; (2) a completed Short bowel syndrome with intestinal failure form; and (3) documentation of the number of days on parenteral support per week for 4 consecutive weeks immediately preceding this application. (4) documented duration in months of prior dependence on parenteral support</p>

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Administrative advice	<p>A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply</p>
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Initial treatment – balance of supply

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Proprietary name and manufacturer
TEDUGLUTIDE 5 mg injection [28 vials] (& inert substance diluent [28 x 0.5 mL syringes], 1 pack	28	0	Revestive® Shire Australia Pty Limited

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Severity:	Type III
Condition	Short bowel syndrome with intestinal failure
PBS Indication:	Type III short bowel syndrome with intestinal failure
Treatment phase:	Initial treatment – balance of supply
Restriction:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	Must be treated by a specialist gastroenterologist
Clinical criteria:	Patient must have received insufficient therapy with this drug under the initial treatment restriction to complete the maximum duration of 12 months of initial treatment AND The treatment must provide no more than the balance of up to 12 months of treatment.
Administrative advice	Authority approval for sufficient therapy to complete the balance of supply may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Special Pricing Arrangements apply

First continuing treatment

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Proprietary name and manufacturer
TEDUGLUTIDE 5 mg injection [28 vials] (& inert substance diluent [28 x 0.5 mL syringes], 1 pack	28	5	Revestive® Shire Australia Pty Limited

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Severity:	Type III
Condition	Short bowel syndrome with intestinal failure
PBS Indication:	Type III Short bowel syndrome with intestinal failure
Treatment phase:	First continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist gastroenterologist
Clinical criteria:	<p>Patient must have previously received initial PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must have a reduction in parenteral support frequency of at least one day per week from baseline</p> <p>AND</p> <p>The treatment must not exceed 6 months under this restriction</p>
Prescriber Instructions	<p>Baseline is measured in the four weeks immediately prior to initiating treatment with teduglutide under the PBS initial treatment restriction.</p> <p>The number of days of parenteral support is calculated as the mean number of days in which any parenteral support is required (parenteral nutrition ± IV fluids) per week to meet caloric, fluid or electrolyte needs over the preceding treatment period.</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form;</p> <p>(2) a completed Short bowel syndrome with intestinal failure Form; and</p> <p>(3) Documentation of the mean number of days of parenteral support (parenteral nutrition ± IV fluids) per week to meet caloric, fluid or electrolyte needs. This will be compared with the number of days per week at baseline.</p>
Administrative Advice	<p>A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

Subsequent continuing treatment

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Proprietary name and manufacturer	
TEDUGLUTIDE 5 mg injection [28 vials] (&) inert substance diluent [28 x 0.5 mL syringes], 1 pack	28	5	Revestive®	Shire Australia Pty Limited

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Severity:	Type III
Condition:	Short bowel syndrome with intestinal failure
PBS Indication:	Type III Short bowel syndrome with intestinal failure
Treatment phase:	Subsequent continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist gastroenterologist
Clinical criteria:	<p>Patient must have received PBS-subsidised first-continuing treatment with this drug for this condition OR</p> <p>Patient must have received PBS-subsidised recommencement of treatment with this drug for this condition following a trial cessation period</p> <p>OR</p> <p>Patient must have received PBS-subsidised treatment with this drug for this condition as a grandfathered patient.</p> <p>AND</p> <p>Patient must have achieved a treatment response in the preceding treatment period</p> <p>AND</p> <p>Patient must not have previously experienced a failure to respond to treatment with this drug for this condition</p>
Prescriber Instructions	<p><u>Treatment response</u></p> <p>For applications for subsequent continuing treatment, a patient has met the criteria for treatment response when there is a reduction in the number of days of parenteral support of at least 1 day per week since the last assessment for PBS-subsidised treatment, or where a patient has completely ceased treatment with parenteral support for a period of at least 4 consecutive weeks. The number of days of parenteral support at each assessment point is calculated as the mean number of days in which any parenteral support is required (parenteral nutrition ± IV fluids) per week to meet caloric, fluid or electrolyte needs over the preceding treatment period.</p> <p><u>Treatment failure</u></p> <p>Failure of treatment is defined as at least one day per week increase in parenteral support (parenteral nutrition ± IV fluids) to meet caloric, fluid or electrolyte needs over the treatment period.</p> <p>Patients who experience failure of treatment must permanently discontinue treatment.</p> <p>Patients who neither demonstrate a treatment response nor a treatment failure are considered to have a stable parenteral support regimen, defined as the same number of days of parenteral support (parenteral nutrition ± IV fluids) per week to meet caloric, fluid or electrolyte needs over the treatment period, where the number of days is greater than zero. Patients with a stable parenteral support regimen must undertake a trial cessation period.</p> <p>The authority application must be made in writing and must include:</p>

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	<p>(1) a completed authority prescription form; (2) a completed Short bowel syndrome with intestinal failure Form; and (3) Documentation of the mean number of days of parenteral support (parenteral nutrition ± IV fluids) per week to meet caloric, fluid or electrolyte needs over the preceding treatment period. This will be compared with the mean number of days per week written on the most recent authority application form.</p>
Administrative Advice	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

Re-commencement after a trial cessation period

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Proprietary name and manufacturer	
TEDUGLUTIDE 5 mg injection [28 vials] (&) inert substance diluent [28 x 0.5 mL syringes], 1 pack	28	5	Revestive®	Shire Australia Pty Limited

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Severity:	Type III
Condition	Short bowel syndrome with intestinal failure
PBS Indication:	Type III Short bowel syndrome with intestinal failure
Treatment phase:	Recommencement of treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist gastroenterologist
Clinical criteria:	Patient must have received PBS-subsidised treatment with this drug for this condition AND Patient must have undertaken a trial cessation period AND Patient must have experienced deterioration during a trial cessation period AND Patient must not have previously experienced a failure to respond to PBS-subsidised treatment with this drug for this condition

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<p>Prescriber Instructions</p>	<p>Deterioration during the trial cessation period includes an increase in parenteral support frequency of ≥ 1 day per week from the pre-cessation level, or other clinical parameters suggestive of deterioration.</p> <p>Failure of treatment is defined as at least one day per week increase in parenteral support (parenteral nutrition \pm IV fluids) to meet caloric, fluid or electrolyte needs over the treatment period.</p> <p>Patients who experience failure of treatment must permanently discontinue treatment.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) a completed authority prescription form; (2) a completed Short bowel syndrome with intestinal failure Form; and (3) Documentation of the reason for recommencement after trial cessation (4) Prescriber declaration that the patient was undertaking a trial cessation period due to experiencing a stable parenteral support regimen in the first continuing or subsequent continuing treatment phase, and not due to a treatment failure.
<p>Administrative Advice</p>	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

Grandfathered patients

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Proprietary name and manufacturer	
TEDUGLUTIDE 5 mg injection [28 vials] (& inert substance diluent [28 x 0.5 mL syringes], 1 pack	28	5	Revestive®	Shire Australia Pty Limited

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Severity:	Type III
Condition	Short bowel syndrome with intestinal failure
PBS Indication:	Type III Short bowel syndrome with intestinal failure
Treatment phase:	Grandfathered patients
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist gastroenterologist
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [date of PBS listing]

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	<p>AND Patient must have short bowel syndrome with intestinal failure following major surgery; AND Patient must have had a history of dependence on parenteral support for at least 12 months prior to initiating non-PBS subsidised treatment with this drug for this condition; AND Patient must have received a stable parenteral support regimen for at least 3 days per week in the 4 weeks prior to initiating non-PBS subsidised treatment with this drug for this condition; AND Patient must not have active gastrointestinal malignancy or history of gastrointestinal malignancy within the last five years; AND If the patient has been on non-PBS subsidised therapy with this drug for more than 12 months, the patient must have achieved a treatment response. AND Patient must not have previously experienced a failure to respond to non-PBS subsidised treatment with this drug for this condition.</p>
<p>Prescriber instructions:</p>	<p>Baseline is measured in the four weeks immediately prior to initiating treatment with non-PBS subsidised teduglutide.</p> <p>A patient has met the criteria for treatment response when there is a reduction in the number of days of parenteral support of at least 1 day per week since initiating non-PBS-subsidised treatment, or where a patient has completely ceased treatment with parenteral support for a period of at least 4 consecutive weeks prior to application for PBS-subsidised treatment.</p> <p>Failure of treatment is defined as at least one day per week increase in parenteral support (parenteral nutrition ± IV fluids) to meet caloric, fluid or electrolyte needs since initiating non-PBS subsidised treatment.</p> <p>The number of days of parenteral support is calculated as the mean number of days in which any parenteral support is required (parenteral nutrition ± IV fluids) per week to meet caloric, fluid or electrolyte needs between commencement of non-PBS subsidised teduglutide and application for PBS-subsidised treatment.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) a completed authority prescription form; (2) a completed Short bowel syndrome with intestinal failure Grandfather PBS Authority Application - Supporting Information Form; (3) documentation of teduglutide treatment start date (4) documentation of the number of days on parenteral support per week for 4 consecutive weeks prior to initiating non-PBS subsidised therapy (5) documented duration in months of prior dependence on parenteral support (6) documentation of response to teduglutide treatment (if relevant). <p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For patients who have been on this drug for less than 12 months, the maximum number of repeats that will be approved will be for an amount equivalent to an initial 12 month supply of PBS and non-PBS subsidised treatment. For patients who have been on this drug for more than 12 months, a maximum of 5 repeats will be approved. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Subsequent continuing treatment criteria.</p>

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Shire Australia (now part of Takeda) welcomes the PBAC's recommendation to list teduglutide for patients living with Short Bowel Syndrome with Intestinal Failure. Shire Australia also acknowledges the input provided by the HPN clinician community and by Parenteral Nutrition Down Under (PNDU) and thanks them for their engagement with the reimbursement process.