7.08 TEDUGLUTIDE, Lyophilised powder 5 mg, water for injection 0.5 mL, 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 by the resubmission (changes compared with the November 2017 submission are underlined).

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

Component	Description
Population	Patients with Type III (chronic) short bowel syndrome with intestinal failure due to major intestinal resection; dependent on parenteral support for at least 12 months; stable parenteral support requirements (volume and frequency) for at least four consecutive weeks.
Intervention	Teduglutide 0.05 mg/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 ≥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. Teduglutide plus standard care is at least non-inferior in term of safety compared to standard of care alone; acknowledging teduglutide reduces the need for parenteral support and the associated severe side effects.

Source: Table 1.1.1, p.2 of the resubmission.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	DPMQ Public	DPMQ Private	Proprietary Name and Manufacturer	
Teduglutide 5mg lyophilised powder, 0.5 mL water for injection	28	5	$[redacted]	$[redacted]	Revestive®	Shire Australia

Category / Program:	Section 100 – Highly Specialised Drugs Program
PBS Indication:	Type III (chronic) intestinal failure associated with short bowel syndrome
Treatment phase:	Initial treatment – new patients
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. Patient must not receive more than 12 months of treatment under this restriction. The written authority application must include: (1) Documentation of parenteral support volume administered over the 4 weeks preceding application. (2) Documentation of the number of days on parental support in the 4 weeks preceding application.
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 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

Treatment phase:	Continuing treatment
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 must demonstrate ongoing treatment response to be eligible for continuing treatment. Treatment response is defined as a reduction in parenteral support volume of at least 20% from baseline, where baseline is measured immediately prior to initiating treatment with teduglutide.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition

Treatment phase:	Extended initial treatment
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. Patient must not receive more than 12 months of treatment under this restriction. For initiating patients who do not demonstrate a reduction in parenteral support volume of at least 20% from baseline following 12 months of teduglutide treatment, the patient may be eligible for extended initial treatment if they meet the following criteria: (1) In the opinion of the treating clinician, the patient is receiving a clinically relevant improvement that is attributable to teduglutide treatment, and the patient is likely to achieve a reduction in parenteral support volume of at least 20% from baseline during the extended initial treatment period
Clinical criteria:	The patient must have previously received PBS-subsidised treatment with teduglutide for the treatment of short bowel syndrome with intestinal failure

2.1 The resubmission requested a pay-for-performance scheme to help address the risks associated with the uncertain long-term benefit of teduglutide, with the cost of teduglutide rebated at varying levels according to changes in the number of days per week on parenteral support.

2.2 Under the pay-for-performance scheme proposed in the resubmission, an [redacted]% rebate would be applicable for patients who achieve parenteral support reductions of less than 1 day per week, a [redacted]% rebate for patients who achieve at least a 1 day per week reduction but remain dependent on parenteral support, and no rebate for patients who achieve parenteral support independence. The resubmission assumed the price of teduglutide to be $[redacted] in the economic model and financial estimates, based on an estimated average rebate of [redacted]% under the pay-for-performance scheme. The ESC considered that this level of rebate, which was based on the change in parenteral support requirements from baseline to Week 104 among patients in the STEPS/STEPS-2 trial, was highly unlikely to be achieved in clinical practice (refer to Paragraph 6.45).

2.3 The ESC noted that the Pre-Sub-Committee Response (PSCR) suggested three approaches to achieve a lower effective price for teduglutide, by a flat rebate or a pay-for-performance arrangement based on either the average number of days (per the resubmission) or weekly volume reduction in parenteral support (see Paragraph 6.71). The ESC advised that the type of pay-for-performance arrangement may have implications on the PBS restriction, particularly the wording of the initial and continuing treatment criteria.

2.4 Unlike the previous submission, the resubmission did not propose a published versus effective price (Special Pricing Arrangement). In the absence of any pay-for-performance rebates, the proposed DPMQ ($[redacted]) was [redacted]% higher than the effective DPMQ in the previous submission ($[redacted] effective DPMQ; $[redacted] published DPMQ).

2.5 The pre-PBAC response proposed a flat rebate of [redacted]% via a Special Pricing Arrangement as an alternative to the proposed pay-for-performance arrangement, to provide more certainty in the budget impact of listing teduglutide.

2.6 Compared to the November 2017 submission, there was a change in the requested authority level from Authority Required (Streamlined) to Authority Required (In Writing). The written authority application must include documentation of the parenteral support volume administered and the number of days on parental support in the 4 weeks preceding the application.

2.7 The revised restriction includes a requirement for at least 12 months of parenteral support dependence prior to initiation of teduglutide. The PBAC previously considered that given the natural history of disease associated with short bowel syndrome, identification of the appropriate patient population may be difficult to

establish in patients with less than 12 continuous months of parenteral support (Paragraph 7.3, November 2017 PSD). The ESC considered that there remains a risk of treating patients with reversible intestinal failure who would otherwise have weaned off parenteral support spontaneously.

2.8 The PSCR indicated a willingness to extend the required period of parenteral support dependence from 12 months to 18 or 24 months, if the PBAC considered this to be more appropriate. It stated that extending the period of dependence on parenteral support in the eligibility criteria will not impact the majority of patients with existing short bowel syndrome with intestinal failure. The PSCR cautioned, however, that an extended period of parenteral support dependence would need to be balanced against clinician feedback that some patients could be stable from six months after surgery, and could benefit from earlier treatment with teduglutide.

2.9 The PBAC noted the variability in the underlying natural course of the condition and that the clinical evidence was based on patients with one to 16 years of prior parenteral support and so may reflect outcomes in patients with a longer time-since-resection than the potential PBS population.

2.10 The proposed restriction does not limit treatment on the basis of the number of days per week of parenteral support. In the STEPS trial, patients were required to be receiving parenteral support on at least 3 days per week. The resubmission argued that the TGA-approved indication for teduglutide does not specify any restriction on baseline parenteral support requirements, and claimed that a summary of real world evidence provided in the resubmission included patients on fewer than 3 days per week of parenteral support. However, no specific analyses were presented in the resubmission and there appears to be little clinical evidence and quality of life data available for this subgroup. The evaluation and the ESC considered that inclusion of this subgroup may impact the level of rebate achieved through the proposed pay-for-performance scheme that had been proposed in the resubmission (refer to Paragraph 6.45).

2.11 In order to qualify for continuing treatment with teduglutide, the resubmission proposed that patients must demonstrate a reduction in parenteral support volume of at least 20% from baseline at 12 months. The PBAC previously considered that the submission's proposal that a 20% reduction in weekly parenteral support volume is a clinically important change may not be substantiated for all patients if volume reductions did not result in fewer days per week of parenteral support (Paragraph 7.7, November 2017 teduglutide PSD). The appropriateness of a 20% reduction in weekly parenteral support volume as a basis for the continuation restriction is unclear, as is the basis for reliance on the 12 month time-point.

2.12 The ESC noted that the NICE 'Appraisal consultation document' for teduglutide (Paragraph 3.23) indicated a 6 month time-point for continuation criteria in adults, and 12 weeks in children, based on the marketing authorisation for teduglutide in

England.[1,2] The ESC further noted that the European Medicines Agency (EMA) "Summary of Product Characteristics" for teduglutide stated that the "Treatment effect should be evaluated after 6 months. Limited data from clinical studies have shown that some patients may take longer to respond to treatment (i.e., those who still have presence of colon-in-continuity or distal/terminal ileum); if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered" (noting that the EMA has only indicated teduglutide for use in adults).[3] Overall, the ESC considered that the basis for the restriction's proposed 12 month time-point for assessment of response was unclear.

2.13 The ESC considered that the clinical and patient relevance of a reduction in volume versus days per week of parenteral support may depend on the patient's baseline parenteral support requirements. For example, it may be more meaningful for a patient who is on 7 days of parenteral support per week to achieve days off parenteral support rather than a volume reduction; whereas for a patient who is on 3 days of parenteral support per week, a further reduction in the number of days may not be likely, but a 20% volume reduction may still be clinically meaningful. The ESC advised that this has important implications in the consideration of the approach to the pay-for-performance scheme. The ESC noted that the continuation criteria proposed in the restriction was based on volume rather than days reduction from baseline, which may present a greater risk of continuation bias and be more administratively difficult to monitor.

2.14 The ESC noted that the NICE committee "heard from the patient experts that they would value even 1 day less of parenteral nutrition, and that this is smaller than a 20% reduction in the frequency of parenteral support per week for a patient who needs nutrition daily (1.4 fewer days). The NICE committee therefore concluded that it would be reasonable to apply a stopping rule that was based on a change in parenteral-support frequency of 1 day or 20%, whichever is smaller".[2] The ESC considered that further consumer input regarding the meaningfulness of reductions in parenteral support requirements would be informative.

2.15 The PSCR stated that decisions about the best way to reduce parenteral support volume in a particular patient were multifaceted, and should take into account both clinical factors such as intestinal function, and patient lifestyle factors, such as a

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[1] *Teduglutide Summary of Product Characteristics, Accessed at: https://www.medicines.org.uk/emc/product/3382/smpc*

[2] *'Teduglutide for treating short bowel syndrome', Appraisal consultation document; National Institute for Health and Care Excellence; November 2017. Accessed at: https://www.nice.org.uk/guidance/GID-TA10048/documents/appraisal-consultation-document*

[3] *Teduglutide Summary of Product Characteristics, European public assessment report, European Medicines Agency. Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002345/WC500132926.pdf:*

preference for reduced volume per infusion (i.e. equating to a shorter infusion time per day) versus fewer infusions per week (Carlsson 2003; Jeppesen 2009). The PSCR stated that there are direct physical and psychosocial benefits in reducing the number of hours per day of parenteral support (i.e. improved sleep, reduced fatigue, greater socialisation) (Jeppesen 2013). The PSCR presented a plot of the average weekly parenteral support volume compared with the average days per week on parenteral support over the duration of the STEPS-2 study. The PSCR claimed that the comparison shows that reductions in volume and days follow a similar trajectory and are well correlated.

2.16 However, the ESC considered that the PSCR's claim was not reasonable as the plot did not include the initial 24 weeks of treatment in the STEPS trial and was dependent on the choice of scale used on the two y-axes. The ESC noted that the number of patients with at least a 20% reduction in weekly parenteral support volume at 12 months (i.e. 24 weeks treatment in STEPS plus an additional 6 months treatment in STEPS-2) was [redacted] ([redacted]%); whereas only [redacted] patients ([redacted]%) were reported to have achieved at least one additional day off parenteral support at this time point. Overall, the ESC considered the two measures (volume versus days) may produce different results; thus the ESC considered that the same definition (either volume or days) should be used in both the restriction and the RSA.

2.17 There was insufficient guidance in the proposed restriction regarding the measurement and documentation of parenteral support volumes, or the timing and duration of the required change from baseline. Though additional information was provided in the PSCR about the documentation requirements (refer to Paragraph 6.71), the ESC considered that this did not adequately address the concerns.

2.18 The proposed restriction also allows up to an additional 12 months of teduglutide treatment for patients who, in the opinion of the treating clinician, are receiving a clinically relevant improvement that is attributable to teduglutide treatment, and are considered likely to achieve a reduction in parenteral support volume of at least 20% from baseline during the extended initial treatment period. The ESC and the PBAC considered that the additional criterion was not appropriate as it would extend the allowable treatment period prior to demonstration of a 20% reduction in weekly parenteral support volume to 2 years based on subjective criteria. The ESC considered that it was also unclear how many patients would benefit from such a criterion, especially in the context of the restriction requiring 12 months dependency on parenteral support before teduglutide initiation and therefore the ESC considered there was a reasonable expectation that any teduglutide benefits would be seen in the initial twelve months of therapy.

2.19 The ESC noted that the resubmission had not proposed a stopping rule despite the PBAC previously advising that "a stopping rule was an important consideration for the PBS restriction, to ensure that patients do not continue on treatment that may

be unnecessary" (Paragraph 7.12, PBAC Minutes November 2017). The resubmission argued there was limited information available regarding patient outcomes following treatment cessation. The resubmission acknowledged that studies had found that teduglutide cessation was followed by either no change or was associated with an increase in parenteral support volume which did not return to baseline levels (Compher et al, 2011 and Sobocki et al, 2016). However, it argued that due to the limitations of both studies, including small sample sizes and a lack of data to make an appropriate assessment of patient clinical status, the results should not be used to inform assumptions regarding ceasing teduglutide. The ESC considered that it was unclear what patient risks and benefits might arise in the event of treatment cessation, particularly for patients in whom independence from parenteral support has been achieved, or in whom no further improvement is expected. Overall, the ESC considered that limited data were available given the costs of long term therapy.

2.20 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, paediatric populations, or in patients who do have at least 12 months of prior parenteral support dependence. There may be ongoing use of teduglutide despite not having achieved the required improvements specified in the proposed restriction. The increase in authority level proposed in the resubmission may mitigate some of the risk of use outside of the proposed restriction. The ESC and PBAC considered that use of teduglutide outside the restriction may be constrained by the limited number of clinicians experienced in the treatment of this condition. Notwithstanding this, the ESC and PBAC advised that an Authority Required (Writing) restriction was necessary for the initial and continuing treatment listings.

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 4 weeks prior to initiating teduglutide.

Previous PBAC consideration

3.3 Teduglutide was previously considered for the treatment of intestinal failure associated with short bowel syndrome at the November 2017 PBAC meeting. The outstanding matters of concern are summarised in Table 2.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern	How the resubmission proposed to address it
Clinical place in therapy	The PBAC considered that overall, due to the variability in the underlying natural disease course of short bowel syndrome, the variable time on parenteral support prior to achieving a response and the variable length of treatment among different patients, that the clinical position for teduglutide, and hence the PBS eligibility criteria, was difficult to define (Paragraph 7.5, November 2017 teduglutide PSD).	The resubmission included a revised restriction which requires patients to be dependent on parental support for at least 12 months prior to initiating teduglutide treatment. The PSCR suggested that the sponsor is amenable to extending the required period of parenteral support dependence to greater than 12 months.
Requested PBS listing	The PBAC considered that the requested restriction was not consistent with the pivotal clinical trial. The PBAC considered that given the natural history of disease associated with short bowel syndrome, identification of the appropriate patient population may be difficult to establish in patients with less than 12 continuous months of parenteral support (Paragraph 7.3, November 2017 teduglutide PSD).	The resubmission included a revised restriction which requires patients to be dependent on parental support for at least 12 months prior to initiating teduglutide treatment.
	The PBAC noted that the requested restriction did not contain a stopping rule. The PBAC was concerned that the assessment of the magnitude, timing, and duration of clinical benefit that would support ongoing treatment with teduglutide was uncertain, and that other factors such as intestinal adaptation and intestinal rehabilitation programs may also contribute to clinical improvements (Paragraph 7.4, November 2017 teduglutide PSD)	The resubmission proposed continuation criteria as part of the revised restriction. Patients must achieve at least a 20% reduction in weekly parenteral nutrition volume in the first 12 months of treatment in order to qualify for ongoing treatment with teduglutide. An additional 12 months of treatment (beyond the initial 12 months) based on clinician discretion was also proposed in the revised restriction.
Clinical effectiveness	The PBAC considered that the submission's proposal that a 20% reduction in weekly parenteral support volume is a clinically important change may not be substantiated for all patients if volume reductions did not result in fewer days per week of parenteral support.	The resubmission proposed a pay-for-performance scheme to help address the risks associated with the uncertain long-term benefit of teduglutide. The sponsor proposed that the cost of teduglutide be rebated at varying levels according to changes in the number of days per week on parenteral support. The Pre-PBAC proposed a flat rebate of [redacted]% via a Special Pricing Arrangement as an alternative to the pay-for-performance scheme.
	The PBAC considered that there was a lack of long-term comparative clinical evidence to define the magnitude of the treatment effect associated with teduglutide (Paragraph 7.8, November 2017 teduglutide PSD).	The resubmission presented the results of observational studies examining the efficacy and safety of teduglutide in routine clinical settings to support the clinical trial evidence.
Safety	The PBAC considered the claim of non-inferior safety of teduglutide over standard care was not adequately justified. The PBAC noted that in the placebo-controlled trials, treatment with teduglutide was associated with numerically higher treatment related particularly gastrointestinal adverse events, and serious adverse events (Paragraph 7.9, November 2017 teduglutide PSD).	The resubmission provided additional safety data, including the most recent PSUR (covering the period from [redacted]) and an interim report for an international registry study for patients with short bowel syndrome (TED-R13-002).

Component	Matter of concern	How the resubmission proposed to address it
Cost effectiveness	The PBAC considered that the incremental cost per QALY gained of more than $200,000 for teduglutide over placebo, presented in the submission's base case analysis, was uncertain and likely to be underestimated due to several issues with the economic model (Paragraph 2.10, November 2017 teduglutide PBAC minutes)	The resubmission included a discount to the published price of teduglutide ($[redacted]), with a lower expected rebated price under the proposed price-per-performance scheme. Updates to the economic model resulted in a base case incremental cost per QALY gained of more than $200,000.
	The treatment effect applied in the model was not reflective of trial data: the model assumed that placebo patients would remain at their baseline parenteral support requirements and could only transition to the dead state, which was not consistent with the improvements demonstrated in the placebo arm of STEPS, or the natural history of intestinal failure, where some patients may have reversible disease. The model also assumed that improvements in parenteral support requirements would continue for up to 20 years and that patients become completely weaned off parenteral support, which was not supported by the trial evidence and is unlikely to occur in clinical practice. (Paragraph 7.10, November 2017 teduglutide PSD).	No change. The resubmission claimed that based on expert clinical advice, it would be inappropriate to model the impact from patients who received placebo in the trial. Transitions in the teduglutide arm beyond 104 weeks are based on Week 91 to 104 transitions in the resubmission (previously based on Week 52 to 104 transitions).
	The PBAC considered that it was inappropriate to assume a survival difference between the teduglutide and placebo arms of economic model, given that no survival difference was demonstrated in the STEPS trial (Paragraph 7.10, November 2017 teduglutide PSD).	No change. The resubmission claimed that the STEPS trial was not powered to detect a difference in mortality at 24 weeks, and that the study by Amiot et al (2013) demonstrated a difference in mortality due to parenteral support dependency.
	The PBAC considered that the modelled population was not consistent with the proposed PBS population as it only included patients with a baseline ≥3 days per week of parenteral nutrition (Paragraph 7.10, November 2017 teduglutide PSD).	No change. The resubmission argued that most patients in Australia who will be eligible to receive teduglutide are expected to receive more than 3 days of parenteral support at baseline. The resubmission also claimed that a summary of real world evidence provided in the resubmission included patients on fewer than 3 days per week of parenteral support.
	The submission did not adequately justify the application of utilities from Ballinger et al 2016 rather than Lachaine et al 2016 in the submission's base case analysis, and that this likely favoured teduglutide (Paragraph 7.10, November 2017 teduglutide PSD).	No change. The resubmission claimed that the values from the UK time trade-off study are the most appropriate to include in the economic analysis.
	It was inappropriate to assume future price reductions for teduglutide in the model and noted that this was not consistent with the PBAC guidelines (Paragraph 7.10, November 2017 teduglutide PSD).	The resubmission removed the drug price discounts due to 'loss of exclusivity' (i.e. reductions of 20% at 5 and 10 years). The resubmission applied expected future statutory price reductions of 5%, 10% and 5% at 5, 10 and 15 years, respectively.

Component	Matter of concern	How the resubmission proposed to address it
Financial impacts	The PBAC noted that the financial estimates are particularly sensitive to a change in patient numbers and that given the high cost of teduglutide; any use outside of the PBS restriction may have a substantial impact on the budget impact estimates (Paragraph 7.11, November 2017 teduglutide PSD).	The resubmission requested a change in Authority level from Authority Required (Streamlined) to Authority Required (In Writing).

Source: Pages XI-XII and Table 3.11.1, p.108 of the resubmission.
Abbreviations: PSD, public summary document; PSUR, Periodic Safety Update Report; QALY, quality adjusted life year.

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. It may be reversible or irreversible. The submission positioned teduglutide as a treatment option for patients with Type III (chronic) short bowel syndrome receiving home parenteral nutrition.

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 November 2017 submission. The PBAC has previously accepted standard care as the appropriate comparator (Paragraph 7.6, November 2017 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 health care professionals (5) and an organisation via the Consumer Comments facility on the PBS website.

6.3 Representatives of the PBAC met with a representative of Parenteral Nutrition Down Under (PDNU) prior to the PBAC meeting. The representative of PDNU provided their perspective about the condition and its impacts.

6.4 The representative of PDNU noted that a reliance on parenteral support has a significant impact on a patient's quality of life, due to:

- the time impact including while connected to parenteral support (e.g. a patient may be connected to parenteral support for 12 hours every day, which would occur overnight) plus the time taken to connect and disconnect, organise supplies and logistics, attend medical appointments, and (if applicable) care for a stoma;
- the worry of infection;
- immobility while connected to the infusion pump and bag and the weight of the infusion pump and bag (which can be carried by backpack, trolley or IV pole) especially given the fatigue associated with the condition;
- interrupted sleep due to toilet visits and pump alarms;
- dehydration and lack of energy;
- social impact including limited ability to leave the house in the evening or go away on holidays; and
- carer impact.

6.5 The PDNU representative indicated that a reduction in the number of days of parenteral support required, and to a lesser extent the volume required, would potentially reduce the time impact, immobility and interrupted sleep while connected to parenteral support, and also reduce the social and carer impacts. The representative highlighted that the most meaningful impact would be a full night off parenteral support.

Clinical trials

6.6 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) were also included. These trials were previously considered as part of the November 2017 submission. No additional relevant randomised controlled trials were identified in the updated literature search.

6.7 Details of the randomised trials are provided in the table below (unchanged from November 2017 submission).

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.	Gastroenterology 2012; 143(6):1473-1481.e1473.
	Jeppesen PB, Pertkiewicz M, Forbes A et al. (2013). 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.	Clinical Nutrition 2013; 32(5):13-721.
CL0600-021 (STEPS ext 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.	Clinical and Translational Gastroenterology 2016; 7:1-9. e142.
TED-C11-001 (STEPS-2 ext 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.	Clinical Nutrition 2014; 33:S167-S168.
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.	Gut (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.	Clinical Gastroenterology and Hepatology 2013; 11(7):815-823.

Source: Table 2.2.2, p.37 of the resubmission.

6.8 The key features of the direct randomised trials are summarised in Table 4 (unchanged from November 2017 submission).

Table 4: Key features of the included evidence, 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 ≥ 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 ≥ 20%; Reduction of ≥ 1 day in weekly PS days; Patients weaned off PS.	Not used

Source: Source: Table 2.4.1, pp46-47 and Table 2.4.8, pp56-58 of the resubmission; Table 2.2.1, p.7 and Table 2.2.3, pp16-18 of Attachment 7 of the submission.
Abbreviations: PS, parenteral support.

6.9 Following completion of STEPS, patients could opt to continue into a two-year, open-label extension study (STEPS-2, N = 88). The study also included 12 previously untreated patients who were screened, optimised, and stabilised (but not randomised) for the STEPS trial. Patients who completed STEPS-2 at North American sites could opt to participate in an additional one-year extension study (STEPS-3; N = 14).

6.10 Patients who completed Study 004 could opt to continue into a 28-week extension study (Study 005, N = 65).

Comparative effectiveness

6.11 The results presented for comparative effectiveness in the resubmission were unchanged from the November 2017 submission. The resubmission also presented results of observational studies examining the effectiveness of teduglutide in patients treated in routine clinical settings.

6.12 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, across the placebo-controlled studies. This was the primary outcome of the STEPS trial.

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.60 of the resubmission; Table 2.3.1, p.20 of Attachment 7 of the resubmission.
Abbreviations: CI, confidence interval.

6.13 In STEPS, responder rates were 62.8% and 30.2% for the teduglutide and placebo groups respectively. Treatment with teduglutide was associated with a statistically

significantly higher proportion of responders compared to placebo. As noted in the November 2017 teduglutide PSD, the high proportions of patients with at least a 20% reduction in weekly parenteral support volume in the placebo arm suggest that other factors may contribute to improvements in parenteral support volume (Paragraph 6.12, November 2017 teduglutide PSD).

6.14 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 November 2017 teduglutide PSD noted that 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 6.13, November 2017 teduglutide PSD).

6.15 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

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.64 of the resubmission; Table 2.3.5, p.22 of Attachment 7 of the resubmission.
Abbreviations: CI, confidence interval.

6.16 In STEPS, responder rates 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 suggest that other factors may play a role in parenteral support reductions.

6.17 The resubmission claimed that the improvement observed in the placebo arm was protocol-driven and not reflective of the likely clinical outcomes outside of a trial setting (thus, the economic model assumed no placebo response). The basis for the resubmission's claim was that a protocol-related reduction in parenteral support volume in the placebo arm of the STEPS trial may have led to increased oral fluid intake to maintain urine output, potentially resulting in false reductions in parenteral support requirements in the placebo arm. The PBAC previously considered that "the extent to which increases in oral fluid intake in STEPS resulted in a smaller reduction in parenteral support volumes compared to that which would be achieved if teduglutide was implemented outside of a trial setting, is unclear" (Paragraph 7.8, November 2017 teduglutide PSD). The ESC noted that no evidence was presented to indicate how the responses seen in the placebo arm compared with other estimates

that might be expected in the PBS population. The ESC considered that the 'placebo response' was also of relevance to formulating an appropriate pay-for-performance approach.

6.18 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.

6.19 In STEPS, a patient was considered to have weaned off parenteral support if the investigator prescribed no parenteral support prior to the last visit, and there was no parenteral support use at the last dosing visit based on the subject diary data.

6.20 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)	p-value
STEPS (24 weeks)	0/43 (0.0)	0/43 (0.0)	0% (-8%, 8%)	NR
Study 004 (24 weeks)	2/35 (5.7)	0/16 (0.0)	5.7% (-14%, 19%)	NR

Confidence intervals calculated during the evaluation using StatsDirect software.
Source: Page 66 of the resubmission.
Abbreviations: CI, confidence interval.

6.21 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.

6.22 In STEPS-2, weaning rates were 5.1% (prior placebo-treated patients), 8.3% (previously untreated patients), and 27% (prior teduglutide-treated patients). Weaning rates were higher among patients who previously received treatment with teduglutide in STEPS.

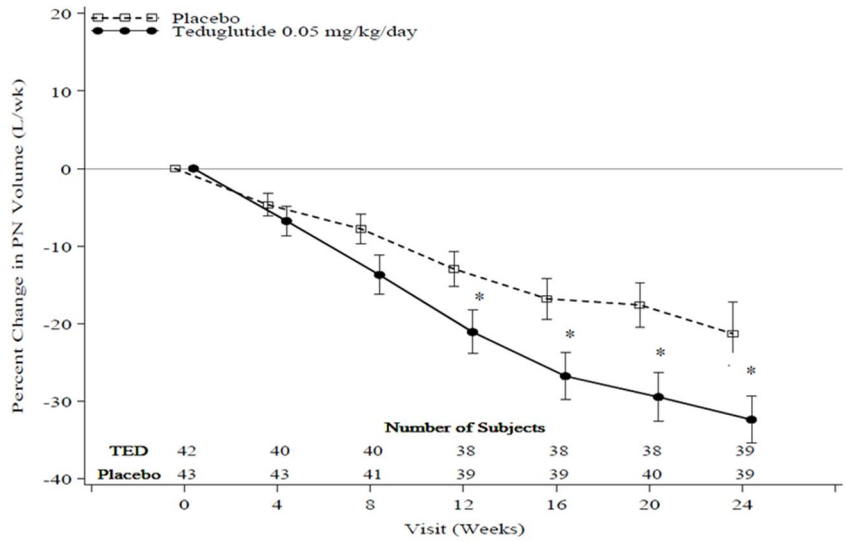
6.23 The PBAC noted that, after 24 weeks of treatment in STEPS, teduglutide and placebo-treated patients achieved mean reductions in weekly parenteral support volume of 32% and 21%, respectively. The difference between groups was statistically significant from Week 12 onwards. Both the teduglutide and placebo groups achieved mean reductions of greater than 20%.

Table 8: Reduction in weekly parenteral support volume

Study	Teduglutide (0.05 mg/kg)	Placebo	Difference	p-value
STEPS (week 24)[1]				
Baseline mean, L	12.92	13.20	- 0.28	-
Mean change from baseline, L (SD)	- 4.37 (3.81) [n = 39]	- 2.29 (2.74) [n = 39]	- 2.08	p <0.001
% change, (SD)	- 32.42 (18.86)	- 21.33 (25.43)	-11.09	P = 0.030
Study 004 (week 24)				
Baseline, L	NR	NR	-	-
Mean change from baseline, L (SD)	–2.48 (2.34) [n = 27]	–0.90 (1.41) [n = 15]	-1.41	p = 0.0768

Source: Table 11-8, p.116 of the STEPS clinical study report; Table 2.3.7, p.24 of Attachment 7 of the resubmission;
Abbreviations: L, litre; SD, standard deviation
[1] The treatment comparison for the absolute and percent change was based on an ANCOVA model with treatment and interaction of treatment by baseline PN/I.V. volume as effects and baseline PN/I.V. volume as a covariate.

Figure 1: Change in weekly parenteral support volume in the STEPS trial



Source: Figure 2.5.2, p.62 of the resubmission.
Abbreviations: TED, teduglutide; PBO, placebo.

6.24 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.

6.25 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).

6.26 The resubmission conducted a supplementary literature search to identify observational studies examining the effectiveness of teduglutide in patients treated in routine clinical settings. This was the only new clinical evidence presented in the resubmission. The resubmission claimed that the results of the observational studies were consistent with results reported in the pivotal clinical trials, and that the studies provided evidence of the effectiveness of teduglutide in patients receiving parenteral support on fewer than 3 days per week. There was limited available observational evidence to inform estimates of longer-term teduglutide effectiveness. No specific analyses were presented in the resubmission for the subgroup of patients on parenteral support on fewer than 3 days per week at baseline.

6.27 The PSCR argued that the results of the two Phase 3 trials and publications of real-world data provided a high degree of confidence in the short-term efficacy estimates for teduglutide, relative to other rare disease therapies. However, the ESC considered that the magnitude of the treatment effect attributable to teduglutide beyond 24 weeks was uncertain, as there was no control arm in the STEPS-2 extension study.

Comparative harms

6.28 As reported in the November 2017 submission, 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.

6.29 As reported in the November 2017 submission, 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.

6.30 The resubmission provided additional safety data, including the most recent PSUR (covering the period from [redacted] to [redacted]) and an interim report for an international registry study for patients with short bowel syndrome (TED-R13-002).

6.31 Based on an expanded assessment of harms, important identified risks associated with teduglutide include 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/harms

6.32 A summary of the comparative benefits and harms for teduglutide versus placebo is presented in the Table 9 (unchanged from the November 2017 submission).

Table 9: 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intestinal stoma complication					
STEPS	10/42	3/43	23.8	7.0	0.17 (0.02, 0.32)
Study 004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Confidence intervals calculated during the evaluation using StatsDirect/Revman software.
Source: Table 2.5.1, p.76; Table 2.5.2, p.64; Table 2.5.10, p.76 of the resubmission. Table 2.3.1, p.20; Table 2.3.5, p.22; Table 2.3.11, p.33 of Attachment 7 of the resubmission.
[1] Teduglutide 0.05 mg/kg arm of Study 004.

6.33 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.

6.34 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 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

6.35 The clinical claim was unchanged from the November 2017 submission. The resubmission described teduglutide 0.05 mg/kg daily plus standard care as superior in terms of effectiveness, and at least non-inferior in terms of safety compared to standard of care alone. The resubmission also claimed that treatment with teduglutide was likely to reduce parenteral support-related complications such as liver disease and catheter-related sepsis. This claim was partly supported.

6.36 The PBAC re-iterated its previous consideration 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, the PBAC also re-iterated its previous advice that there was a lack of long-term comparative clinical evidence to define the magnitude of the treatment effect associated with teduglutide (Paragraph 7.8, November 2017 teduglutide PSD).

6.37 The PBAC re-iterated its previous consideration that the claim of non-inferior safety of teduglutide over standard care was not adequately justified. The PBAC again noted that in the placebo-controlled trials, treatment with teduglutide was associated with numerically higher treatment related particularly gastrointestinal adverse events, and serious adverse events. The submission's claim that teduglutide was likely to reduce parenteral nutrition-related complications such as liver disease and catheter-related sepsis was not adequately supported, given the lack of available comparative data beyond 24 weeks (Paragraph 7.9, November 2017 teduglutide PSD).

Economic analysis

6.38 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.

6.39 Key differences between the economic analysis presented in the November 2017 submission and the resubmission are summarised in Table 10.

Table 10: Summary of model structure and rationale

Component	November 2017 submission	Resubmission
Type of analysis	Cost effectiveness analysis/cost utility analysis	Unchanged
Options compared	Teduglutide plus standard care; standard care	Unchanged
Population	STEPS/STEPS-2 population	Unchanged
Outcomes	Life years, QALYs	Unchanged

Component	November 2017 submission	Resubmission
Methods used to generate results	Markov cohort model	Unchanged
Time horizon	20 years	Unchanged
Cycle length	28 days	Unchanged
Discounting	5% for costs and outcomes	Unchanged
Health states	Standard care and teduglutide arms: - Parenteral support 0 days/week; - Parenteral support 1-3 days/week; - Parenteral support 4-6 days/week; - Parenteral support 7 days/week; - Death.	Three additional health states compared to the previous model included for discontinuations in the teduglutide arm: - Parenteral support 1-3 days/week, teduglutide discontinued; - Parenteral support 4-6 days/week, teduglutide discontinued; - Parenteral support 7 days/week, teduglutide discontinued.
Transition probabilities	- Transitions between levels of parenteral support 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 52 to 104.	- Transitions beyond 104 weeks were based on STEPS-2 teduglutide-arm transitions between weeks 91 to 104, rather than weeks 52 to 104.
Overall survival	- Based on published 1, 5, and 10-year survival rates among French patients with short bowel syndrome (Amiot et al 2013). - Use three data points (1, 5, and 10-year survival) to construct an exponential survival curve. - Assumed that patients who wean off parenteral support have 55.6% mortality rate compared to patients who remain on parenteral support	Unchanged
Teduglutide drug costs	Based on proposed effective teduglutide price including 20% price reductions at years 5 and 10 to account for "loss of exclusivity".	Based on estimated average teduglutide price under the proposed pay-for-performance scheme ([redacted]% discount to proposed DPMQ). Also included "Anniversary price reductions" at 5, 10 and 15 years (5%, 10% and 5% reductions, respectively).
Teduglutide compliance	100%; assumption	Unchanged
Utility values	Based on sponsor-commissioned UK time trade-off study (Ballinger et al 2016).	Unchanged
Adverse events	Not modelled	Included costs of managing catheter-related sepsis associated with parenteral support
QALY	More than $200,000/QALY gained	More than $200,000/QALY gained

Source: Table 3.1.1, pp89-90; Section 3.11 pp107-110 of the resubmission.
Abbreviations: QALY, quality adjusted life year; UK, United Kingdom.

6.40 Table 11 summarises the key drivers of the economic model.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Modelled population	The modelled population was based on the STEPS trial mean patient age and baseline days of parenteral support per week (≥ 3 days per week). The PBS population proposed in the resubmission would have included patients on parenteral nutrition less than 3 days per week. Treatment of patients receiving parenteral support on less than 3 days per week appeared to be less cost effective. (Unchanged from November 2017 submission) To address this, the PBAC considered that the restriction should limit use of teduglutide to patients who require ≥ 3 days per week of parenteral support at baseline.	High, favours teduglutide
Treatment effect	Transition probabilities for the teduglutide arm were derived from patient level data from STEPS/STEPS-2. In the resubmission base case, it was assumed that patients in the standard care arm (placebo) remained at their baseline parenteral support requirements and could only transition to the dead state. The ESC and PBAC acknowledged the resubmission's argument that the placebo response observed in the trial was protocol-driven and not reflective of non-trial outcomes. However, the ESC and PBAC considered that the lack of incorporation of <u>any</u> placebo response was not appropriate, particularly in the context of the results of the STEPS trial (30% of patients in the placebo arm achieved a reduction of at least 20% in weekly parenteral nutrition volume at Week 20 which was maintained to Week 24). There was no available comparative efficacy data beyond 24 weeks. The economic model did not adequately account for the natural history of intestinal failure, which may be reversible in some patients due to intestinal adaptation and intestinal rehabilitation programs. (Unchanged from November 2017 submission)	High, Favours teduglutide
Extrapolation	In the submission base case, 4-weekly transition probabilities beyond Week 104 were assumed to be the average of those occurring between Week 91 and Week 104 (Week 52 and Week 104 in the November 2017 resubmission). The model assumed improvements in parenteral support requirements would continue for up to 20 years. The ESC considered that this assumption was poorly justified and not supported by clinical data. Improvements are more likely to plateau due to underlying limitations in remnant bowel anatomy and function.	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 U.K. (Ballinger et al 2016).The ESC considered there was limited applicability of the derived health state utilities to the Australian population. In the model base case, the submission inappropriately applied carer disutilities in addition to patient disutilities. The ESC and PBAC advised that carer utilities should only be applied in a sensitivity analysis and should not be included in the base case economic model, consistent with the PBAC Guidelines. (Unchanged from November 2017 submission) Alternative utilities were available from a trade-off study conducted in Canada (Lachaine et al, 2016). The PBAC previously considered that the submission did not adequately justify the application of utilities from Ballinger et al 2016 rather than Lachaine et al 2016 in the submission's base case analysis (Paragraph 7.11, November 2017 teduglutide PSD). The ESC considered that the choice of utilities favoured teduglutide and remained inadequately justified, particularly in the context of the lack of statistically significant difference in quality of life measures reported in the trials.	High, favours teduglutide

Description	Method/Value	Impact
Drug costs	The teduglutide drug cost was based on the estimated average rebate ([redacted]%) under the proposed pay-for-performance scheme. The use of the estimated average teduglutide rebate in the model is likely to have underestimated teduglutide drug costs, as the average rebate only reflected patient transitions over the first 104 weeks of STEPS/STEPS-2. In the model, teduglutide-treated patients continue to transition into the completely weaned state beyond week 104 (for up to 20 years). No rebate applies to patients who are completely weaned off parenteral support. Further, the ESC considered that patients who require < 3 days per week of parenteral support at baseline (who are proposed for inclusion in the PBS restriction, but not included in the trial) are possibly more likely to be completely weaned off parenteral support (in which case no rebate applies). On the other hand (but with a lesser impact), the ESC also acknowledged that a 20% reduction in patients on < 3 days per week could result in < 1 day reduction in parenteral support requirements (although the likelihood of this was highly uncertain). Overall, the ESC considered that these factors resulted in a likely substantial underestimation of the actual teduglutide drug costs that would apply under the proposed pay-for-performance scheme. Thus the ESC considered that the level of rebate applied ([redacted]%) should not have been included in the model as it is highly unlikely to be achieved in practice. To address these issues, the pre-PBAC response proposed a flat rebate of [redacted]% via a Special Pricing Arrangement, as an alternative to the proposed pay-for-performance arrangement. The cost also included proposed statutory price reductions of 5%, 10% and 5% applied at 5, 10 and 15 years respectively. Inclusion of Anniversary price reductions in the base case was not appropriate in this case as these are only legislated until 2022, and the potential first reduction for teduglutide may not occur until five years from the date of listing. Further the *PBAC guidelines for preparing a submission to the PBAC, Version 5.0* (p. 82) state to "Value future costs at current prices".	High, favours teduglutide

Source: Compiled during the evaluation.

6.41 The results of the modelled economic evaluation are presented in Table 12.

Table 12: Results of the economic evaluation

	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]**

Source: Table 3.11.3, p.110 of the resubmission.
Abbreviations: QALY, quality adjusted life year.

6.42 Based on the economic model, treatment with teduglutide (plus standard care) was associated with a cost per QALY gained of more than $200,000 compared to standard care alone, in patients with short bowel syndrome associated with intestinal failure. The November 2017 submission estimated a cost per QALY gained of more than $200,000.

6.43 Table 13 summarises the impact of differences using a stepped analysis from the November 2017 base case to the resubmission base case.

Table 13: Stepped analysis from the November 2017 base case to the resubmission base case

Step	Incremental cost	Incremental QALYs	ICER
November 2017 base case	$		$
Changes to reflect November 2017 model			
Daily cost of parenteral support ($463.14) was recalculated based on 30.4 days per calendar month (previously assumed $503.45 based on 28 days per calendar month);	$		$
Transitions beyond Week 104 based on transitions between Weeks 91 and 104 (previously based on between Weeks 52 and 104);	$		$
Statutory price reductions applied at 5, 10, and 15 years of 5%, 10% and 5% respectively (previously applied 20% discounts at 5 and 10 years due to 'loss of exclusivity').	$		$
Inclusion of costs associated with catheter-related infections (previously no costs included);	$		$
Applied a % discontinuation rate at 12 months (previously no discontinuations included);	$		$
Daily cost of teduglutide was based on the average expected cost under the pay-for-performance scheme ($; previously based on effective price of $).	$		$
Resubmission base case	$		$

Source: Table 3.11.2, p.110 of the resubmission.

6.44 As with the previous submission, the ESC and PBAC considered that the inclusion of carer disutilities in the base case economic evaluation was inappropriate and inconsistent with the PBAC Guidelines, which state that applying carer disutilities is appropriate in supplementary analyses only. The ESC noted that this had a substantial impact on the cost-effectiveness ratio. The ESC considered that the base case should be respecified without the carer disutilities.

6.45 The ESC also considered that the average rebated teduglutide price under the pay-for-performance scheme (% rebate, as estimated by the resubmission) was not an appropriate input for the economic model, as it was unlikely to be achieved in practice, because:

- the rebate calculation did not account for the patients who completely wean off parenteral support beyond 104 weeks (i.e. some patients will take longer than 104 week to wean off parental support), resulting in an underestimation of the teduglutide drug costs over the longer term; and
- it was unclear whether the distribution of patients achieving reductions in parenteral support in the trial would reflect the distribution in clinical practice, particularly given that patients who require less than 3 days per week of parenteral support at baseline are proposed for inclusion in the PBS restriction, but were not included in the trial. The ESC considered that these patients may be more likely to achieve independence from parenteral support (i.e. no rebate would apply). The PSCR stated that if this remains an important uncertainty, then

the PBAC may wish to consider whether to include this requirement in the PBS eligibility criteria. However, it also argued that doing so may introduce inequity in access. On balance, the PBAC considered that the restriction should limit use of teduglutide to patients who require ≥ 3 days per week of parenteral support at baseline, given the evidence provided for this sub-population was limited.

To address these issues, and to provide more certainty in the budget impact of listing teduglutide, the pre-PBAC response proposed a flat rebate of [redacted]% via a Special Pricing Arrangement as an alternative to the proposed pay-for-performance arrangement.

6.46 The model assumed ongoing improvements in parenteral support requirements with teduglutide treatment for up to 20 years. This assumption was poorly justified and not supported by clinical data. The ESC noted that while the resubmission presented a summary of results across published observational studies, there was a lack of data available beyond the STEPS/STEPS-2 study duration of 130 weeks. The ESC and the PBAC advised that it would be more appropriate and clinically plausible to assume that reductions in parenteral support volume plateau after a certain period of treatment due to underlying limitations in remnant bowel anatomy and function.

6.47 The economic model restricted patients in the standard care arm from transitioning to other health states (apart from death), which was not consistent with improvements in the placebo arm of the STEPS trial, and was unlikely to be consistent with the natural history of the disease. While acknowledging the resubmission's argument that the placebo response observed in the trial was protocol-driven (and may not reflect non-trial outcomes), the ESC and the PBAC considered that the lack of incorporation of any placebo response was not appropriate.

6.48 During the evaluation, an alternative base case was derived by removing the applied carer disutilities, allowing trial-based placebo transitions up to 24 weeks, incorporating trial-based transitions based on STEPS-2 individual patient data to Week 130, extrapolating teduglutide transitions based on the average of Week 104 to 130 transitions, and removing the applied statutory price reductions.

6.49 Table 14 presents the derivation and results of the alternative base case constructed during the evaluation.

Table 14: Re-specification of the model base case (conducted during evaluation)

	Incr costs	Incr QALYs	ICER
Resubmission base case	$ [redacted]	[redacted]	$ [redacted]
Remove carer disutilities	$ [redacted]	[redacted]	$ [redacted]
Allow placebo transitions during weeks 0-24	$ [redacted]	[redacted]	$ [redacted]
Include data up to 130 weeks from STEPS-2 [a]	$ [redacted]	[redacted]	$ [redacted]
Extrapolate teduglutide transitions based on average of 104 to 130 week transitions	$ [redacted]	[redacted]	$ [redacted]
Remove future price reductions	$ [redacted]	[redacted]	$ [redacted]
Respecified base case	**$** [redacted]	[redacted]	**$** [redacted]

Source: Constructed during the evaluation using 'S3A6_teduglutide_Additional Data Request_CUA Wk130 Data_27Mar18', provided by the sponsor during the evaluation.

[a] During the evaluation, the sponsor was asked to clarify why only 104 weeks of individual patient data were included in the economic model. The sponsor provided an updated version of the economic model that included individual patient data up to 130 weeks. The sponsor proposed that the supplementary data be considered as a sensitivity analysis to the base case presented in the resubmission.

6.50 The ESC considered that the true ICER/QALY of teduglutide was likely to be closer to the respecified base case of more than $200,000/QALY, as calculated by the evaluation, than that proposed by the resubmission. The ESC considered that this may still underestimate the true ICER/QALY as it inappropriately included the [redacted]% rebate from the proposed pay-for-performance scheme (though the PBAC acknowledged this rebate was now more certain as the pre-PBAC response proposed an alternative Special Pricing Arrangement).

6.51 The pre-PBAC response stated that the 130 week transitions were based on small patient numbers due to a high degree of censoring, and therefore may not be reliable. The PBAC agreed that the 130 week transitions may not be sufficiently reliable to be applied in the model and used in the extrapolation.

6.52 The PBAC considered that the other re-specifications made in the alternative base case constructed during the evaluation (per Table 14 above) were appropriate, i.e. the model base case should allow placebo transitions during Weeks 0 to 24, remove future price reductions, and remove carer disutilities from the base case. The PBAC considered that the carer disutilities should instead be included in a supplementary analysis per the *Guidelines for preparing a submission to the PBAC, Version 5.0*.

6.53 The PBAC considered that the economic model should also be updated to incorporate the impact of the stopping rule and continuation criteria (when finalised).

6.54 Alternative assumptions were tested in sensitivity analyses regarding the duration of treatment effect with teduglutide and placebo, and the impact of varying the average rebated teduglutide drug price. Table 15 presents the results of sensitivity analyses undertaken during the evaluation based on the re-specified base case.

Table 15: Results of sensitivity analyses conducted during the evaluation

	Incr costs	Incr QALYs	ICER
Respecified base case	$		$
Inclusion of carer disutilities (supplementary analysis)	$		$
Time horizon 10 years	$		$
Time horizon 15 years	$		$
Proportion of patients starting in each health state base case: PS 1-3 days: 0%; 4-6 days: 37%; 7 days: 52%.			
- PS 1-3 days: 100%; 4-6 days: 0%; 7 days: 0%	$		$
- PS 1-3 days: 0%; 4-6 days: 100%; 7 days: 0%	$		$
- PS 1-3 days: 0%; 4-6 days: 0%; 7 days: 100%	$		$
- PS 1-3 days: 33%; 4-6 days: 33%; 7 days: 33%	$		$
Utilities based on Canadian TTO study	$		$
Teduglutide discontinuations at 12 months (base case %)			
- % (non-responders for STEPS/STEPS-2 at 12 months)	$		$
- 0%	$		$
Placebo group transitions limited to 24 weeks			
- Teduglutide transitions limited to 130 weeks	$		$
- Teduglutide transitions limited to 5 years	$		$
- Teduglutide transitions limited to 10 years	$		$
- Placebo (0-24 weeks) and teduglutide improvements (104-130 weeks) extrapolated to 130 weeks	$		$
- Placebo and teduglutide improvements extrapolated to 5 years	$		$
- Placebo and teduglutide improvements extrapolated to 10 years	$		$
Relative risk of mortality for PS 0 days per week vs PS 1-7 days per week:			
- 75%	$		$
- 100%	$		$
Average teduglutide cost, base case % rebate; $/day (104-week STEPS data, including discontinuations)			
- % rebate; $/day (rebate level for)	$		$
- % rebate; $/day ( )	$		$
- % rebate; $/day (rebate level for)	$		$
- % rebate; $/day ( )	$		$
- % rebate; $/day ( )	$		$
Catheter-related infection costs (base case: $25,145.18 per episode based on AR-DRG T60A - septicaemia, major complexity).			
- $13,081.16 (T60B, septicaemia with intermediate complexity)	$		$
- $7,247.23 (T60C, septicaemia with minor complexity)	$		$
- Remove sepsis cost	$		$
Catheter-related infection frequency (base case: 0.935/year for PS 7 days; 0.668/year for PS 4-6 days; 0.267/year for PS 1-3 days)			
- 0.935/year for PS 7 days, PS4-6 days and PS 1-3 days	$		$
- 0.139/year PS 7 days, PS4-6 days and PS 1-3 days	$		$

Source: Constructed during the evaluation using the 'S3A6_teduglutide_Additional Data Request_CUA Wk130 Data_27Mar18', provided by the sponsor during the evaluation.
Abbreviations: PS, parenteral support.

The redacted table shows ICERs in the range of $45,000/QALY – more than $200,000/QALY.

6.55 Results of sensitivity analyses undertaken during the evaluation indicated that the ICER was sensitive to assumptions regarding the time horizon, baseline health state distributions, utility values, treatment effect extrapolations for teduglutide and placebo, and the average rebate associated with the proposed pay-for-performance scheme.

Drug cost/patient/year: $[redacted]

6.56 The estimated drug cost per patient per year for treatment with teduglutide is $[redacted], based on 13.04 packs per year, at the proposed Section 100 Public Hospital DPMQ of $[redacted]. The estimated drug cost per patient per year using the estimated average rebate under the proposed pay-for-performance scheme or Special Pricing Arrangement proposed in the pre-PBAC response ([redacted]%) is $[redacted].

6.57 Based on the information presented in the resubmission, patients who fulfil the requirements under the proposed continuation criteria are expected to receive lifelong treatment with teduglutide.

Estimated PBS usage & financial implications

6.58 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of teduglutide for the treatment of patients with short bowel syndrome associated with Type III intestinal failure.

6.59 The main differences from the November 2017 submission were changes to the teduglutide drug price (resubmission price based on the estimated rebated teduglutide price under the proposed pay-for-performance scheme), and the inclusion of discontinuations ([redacted]%) at 12 months to reflect the continuation criteria in the proposed restriction.

Table 16: Total utilisation and cost to PBS of listing teduglutide

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patients, incorporating 6% annual net growth in patient numbers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Patient uptake of teduglutide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations ([redacted]% at 1 year)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative discontinuations	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total packs dispensed (13.04 per patient per year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated total costs of teduglutide (DPMQ $[redacted], without pay-for-performance rebates)						
Total cost to PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total copayments ($15.69)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated total costs of teduglutide under pay-for-performance scheme ([redacted]% rebate; $[redacted])						
Total cost to PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total copayments ($15.69)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
November 2017 submission (based on proposed effective price, DPMQ $[redacted])						
Total cost to PBS/RPBS less co-payments*	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4.2.2, p98; Table 4.2.3, p98; Table 4.2.4, p99; Table 4.2.5, pp99-100 of the resubmission; Table 14 of the November 2017 PBAC Minutes.
Abbreviations: DPMQ, dispensed price for maximum quantity.

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

6.60 The total cost to the PBS/RPBS of listing teduglutide (less patient copayments), without pay-for-performance rebates, was estimated to be less than $10 million in Year 1 of listing, increasing to $20 -$30 million in Year 6, a total of $60 - $100 million in the first 6 years of listing. The November 2017 submission estimated a cost of $60 - $100 million (based on the proposed effective price) over the first 6 years of listing.

6.61 Based on an estimated rebated price of teduglutide of $[redacted] (assuming an average rebate of [redacted]% under the proposed pay-for-performance scheme), the total PBS/RPBS cost of listing teduglutide (less patient co-payments) was estimated at less than $10 million in Year 1 of listing, increasing to $10 - $20 million in Year 6, a total of $30 - $60 million in the first 6 years of listing.

6.62 Table 17 presents the overall net implications for the Australian Government health budget. The resubmission included the cost of colonoscopies (MBS item 32090) at teduglutide treatment initiation for all patients, at the end of the first year of treatment for all patients, and in the sixth year of treatment for patients who initiate teduglutide in Year 1.

Table 17: Net implications for health budget (using effective price of teduglutide)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated total costs of teduglutide (DPMQ $ [redacted] without pay-for-performance rebates						
Total cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Costs to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net costs for health budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated total costs of teduglutide under pay-for-performance scheme ([redacted]% rebate; $[redacted])						
Total cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Costs to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net costs for health budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4.2.2, p98 of the resubmission.
Abbreviations: DPMQ, dispensed price for maximum quantity.

6.63 Net costs to the Commonwealth government (without pay-for-performance rebates) were estimated at less than $10 million in Year 1 of listing, increasing to $20 - $30 million in Year 6, a total of $60 - $100 million over the first 6 years of listing. The November 2017 submission estimated a net cost to the Commonwealth government of $60 - $100 million (based on the proposed effective price) in the first 6 years of listing.

6.64 Net costs to the Commonwealth government based on the estimated rebated price of teduglutide under the proposed pay-for-performance scheme were estimated at less than $10 million in Year 1 of listing, increasing to $10 - $20 million in Year 6, a total cost of $30 - $60 million in the first 6 years of listing.

6.65 The financial estimates were most sensitive to a change in the number of patients eligible for treatment with teduglutide, and the average rebate applied to the teduglutide drug price.

6.66 The financial estimates assumed uptake rates of [redacted]% and [redacted]% in the first two years of listing. The PBAC considered that higher than estimated uptake may occur in the first few years of listing given the lack of alternative treatments.

Quality Use of Medicines

6.67 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

6.68 The resubmission proposed a pay-for-performance scheme to help address the risks associated with the uncertain long-term benefit of teduglutide. The sponsor proposed that the cost of teduglutide be rebated at varying levels according to changes in the number of days per week on parenteral support. The pay-for-performance scheme is referred to as a managed entry scheme in the resubmission; however the criteria included in the Managed Entry Scheme Framework have not been addressed.

6.69 The resubmission [redacted]

[redacted]

The ESC noted that no effective price was proposed in the PSCR (a Special Pricing Arrangement with an effective price of $[redacted] was proposed in the November 2017 submission).

6.70 As in the November 2017 submission, the resubmission suggested that teduglutide could be considered as a rule of rescue therapy. The resubmission also requested consideration for funding of teduglutide under the Life Saving Drugs Program.

6.71 As outlined above, the pre-PBAC response proposed a flat rebate of [redacted]% via a Special Pricing Arrangement, as an alternative to the proposed pay-for-performance arrangement, to provide more certainty in the budget impact of listing teduglutide.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of teduglutide for the treatment of patients with Type III (chronic) intestinal failure associated with short bowel syndrome on the basis that the patient group most likely to achieve a clinically meaningful benefit was unclear, the treatment duration required to achieve these benefits was unclear and the ICER was uncertain and unacceptably high. The PBAC accepted the high clinical need and limited treatment options available for people with this condition. The PBAC recommended stakeholder consultation regarding the patient group most likely to benefit, criteria for stopping and continuing teduglutide and clarification of economic model parameters.

7.2 The PBAC noted the consumer comments which outlined the burden associated with the current therapy (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. While consumers indicated that a reduction in the volume of parenteral support without days off would be beneficial (e.g. it would mean less time connected per night), consumers indicated a strong preference for fewer days of parenteral support as the key patient-relevant outcome. The PBAC accepted the high clinical need for an effective therapy that reduces the patient burden associated with parenteral support, particularly one that results in patients needing fewer days per week of parenteral support.

7.3 The PBAC considered 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.

7.4 As such, the PBAC considered initiation of teduglutide should be limited to patients who require at least three days per week of parenteral support at baseline given the lack of clinical evidence in patients with lesser requirements, who are likely to have a lower clinical need.

7.5 The PBAC noted that the proposed restriction required patients to have at least 12 months prior parenteral nutrition dependence and acknowledged there was a risk of treating patients with reversible intestinal failure who would otherwise have weaned off parenteral support spontaneously. On balance, the PBAC considered that 12 months prior parenteral nutrition dependence, which aligned with the inclusion criteria of the key trial, was appropriate.

7.6 The PBAC noted that the proposed restriction included an 'extended initial treatment' phase that would allow an additional 12 months of teduglutide for patients who have not achieved an adequate response. The PBAC considered that the additional criterion was not appropriate as it would extend the allowable treatment period prior to demonstration of response to 2 years based on subjective criteria.

7.7 The PBAC noted that, under the proposed restriction, patients who achieve a clinical benefit whilst on teduglutide are indicated to continue treatment indefinitely. However, other factors such as endogenous intestinal adaptation and intestinal rehabilitation programs may contribute to clinical improvements. Thus, the PBAC considered 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, and also given the high cost of treatment. The PBAC acknowledged limited data were available to inform decisions about a stopping rule, but noted that small studies have shown that when teduglutide is ceased, parenteral support requirements have remained lower than they were at baseline. The PBAC considered that further information and consultation was required as to the appropriate parameters for a stopping rule, such as provisions for patients to re-trial teduglutide if the condition worsens and whether re-trial should be based on a volume reduction (more accurate for detecting smaller changes) or days reduction (more patient-relevant) in parenteral support requirements.

7.8 The PBAC considered that a separate continuation rule would also be required (i.e. where patients with an inadequate response are required to cease teduglutide). The PBAC noted that the continuation criteria in the resubmission's proposed restriction were based on volume, rather than days, reduction from baseline. The PBAC noted that the two measures (volume versus days) may produce different results, with the studies (STEPS plus STEPS-2) finding that, at 12 months, 92% of patients achieved a 20% volume reduction, whereas only 53% achieved at least one additional day off. Overall, the PBAC considered it was 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. The PBAC also noted the differences in international recommendations regarding the time-point for assessing response, and considered that further stakeholder consultation would be required in developing the continuation criteria.

7.9 The PBAC re-iterated its previous advice that the claim of superior comparative effectiveness of teduglutide over standard care was reasonable, but considered there was a lack of long-term comparative clinical evidence to define the magnitude of the treatment effect associated with teduglutide. Overall, the PBAC considered that the actual patient-relevant benefit (particularly over an extended time period) was difficult to determine based on the clinical data provided in the resubmission.

7.10 The PBAC re-iterated its previous advice that the claim of non-inferior safety of teduglutide over standard care was not adequately justified, particularly given the lack of comparative clinical data to support the claim of reduced parenteral support complications.

7.11 The PBAC considered that the pay-for-performance scheme proposed in the resubmission was highly unlikely to achieve a [redacted]% rebate, thus this level of rebate should not have been applied as a discount in the economic model and financial estimates. The PBAC noted that, as an alternative to the proposed pay-for-performance arrangement, the pre-PBAC response proposed a flat rebate of [redacted]% via a Special Pricing Arrangement, which the PBAC considered would provide more certainty.

7.12 The PBAC considered that the ICER/QALY presented in the resubmission was uncertain due to:

- The economic model restricted patients in the standard care arm from transitioning to other health states (apart from death), which was not consistent with improvements in the placebo arm of the STEPS trial, and is unlikely to be consistent with the natural history of the disease. The PBAC considered that placebo response should be included in the economic model.
- Carer disutilities were included in the base case economic evaluation. The PBAC considered these should instead be included in a supplementary analysis (as per the PBAC Guidelines).
- The teduglutide drug costs included Anniversary Price Reductions in the base case. The PBAC considered this was not appropriate in this case as these are only legislated until 2022 (i.e. prior to the potential first reduction for teduglutide, which if applied would occur five years from the date of listing).
- The economic model assumed ongoing improvements in parenteral support requirements with teduglutide treatment for up to 20 years. The PBAC considered that it may be clinically plausible to assume that reductions in parenteral support volume plateau after a certain period of treatment due to underlying limitations in remnant bowel anatomy and function.

7.13 The PBAC considered that, even with the [redacted]% rebate proposed (via a Special Pricing Arrangement) in the pre-PBAC response, the ICER was unacceptably high (more than $200,000/QALY in the resubmission base case i.e. before addressing the PBAC's concerns as outlined above).

7.14 The PBAC considered that the economic model and financial estimates should be updated to incorporate the impact of the stopping rule and continuation criteria (when finalised).

7.15 Further, the PBAC considered that the financial estimates should also be updated to reflect the requirement for patients to be on at least three days per week of parenteral support at baseline.

7.16 The PBAC considered that the following issues would need to be addressed in a resubmission, some of which would require stakeholder consultation:

- restriction criteria that ensure treatment is confined to those who are most likely to experience a clinically meaningful benefit. In particular: initiation should be limited to patients who require at least three days per week of parenteral support; and both a stopping and a continuation rule are required;.
- address the PBAC's concerns regarding the economic model (as outlined above), with stakeholder input as necessary (e.g. to ascertain the impact of the stopping and continuation rules on the cost-effectiveness);
- update the financial estimates based on the revised restriction; and

The PBAC also considered that a substantial price reduction was required to achieve a cost-effective listing for teduglutide.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

SHIRE will continue to work with the Department of Health and the PBAC so that Australian patients living with SBS-IF may access teduglutide treatment.