

5.16 TEDUGLUTIDE, Lyophilised powder 5mg, water for injection 0.5mL, Revestive[®], Shire Australia Pty Ltd

1 Purpose of application

1.1 The submission 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.

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

Component	Description
Population	Patients with Type III (chronic) short bowel syndrome with intestinal failure who are stable for a period of at least four consecutive weeks on parenteral support.
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 $\geq 20\%$ reduction from baseline in weekly parenteral support fluid volume; additional days off parenteral support; number of patients weaned off parenteral support.
Clinical claim	Teduglutide plus standard care is superior in terms of effectiveness compared with standard care alone. 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 submission.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	DPMQ ¹		Proprietary Name and Manufacturer	
			Public	Private		
TEDUGLUTIDE 5mg lyophilised powder, 0.5 mL water for injection	28	5	\$ [REDACTED] (\$ [REDACTED])	\$ [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					
Restriction:	Authority Required (STREAMLINED)					
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					
Clinical criteria:	The patient must have short bowel syndrome with intestinal failure following major surgery; AND The patient must have undergone a period of intestinal rehabilitation following surgery; AND The patient should be stable at least to 4 weeks on their parenteral support regimen before initiating teduglutide therapy; AND The patient has no active gastrointestinal malignancy or history of gastrointestinal malignancy within the last five years.					

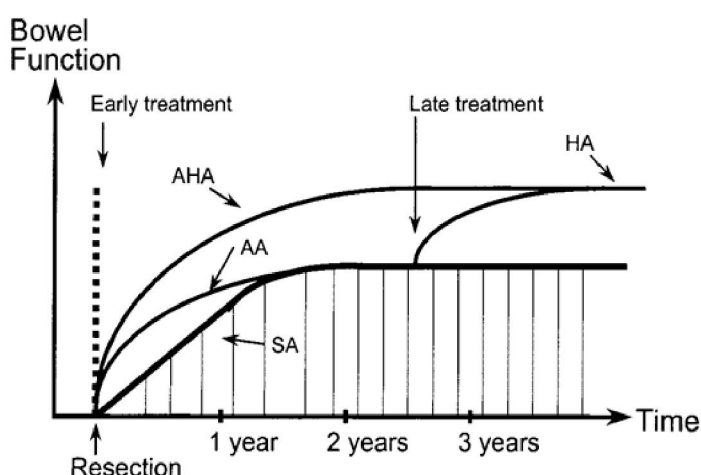
¹ Published price (effective price)

- 2.1 The submission requested a Special Pricing Arrangement (SPA) with the effective price at a [REDACTED]% discount to the proposed published price.
- 2.2 The proposed restriction does not define duration of parenteral support dependence prior to initiation of teduglutide. In the pivotal clinical trial, patients were required to have at least 12 continuous months of prior parenteral nutrition dependency, and be receiving parenteral support on at least 3 days per week.
- 2.3 The Pre-Sub-Committee Response (PSCR, p1) argued against the inclusion of criteria specifying a period of parenteral support dependence, citing clinician feedback that a 12-month period of parenteral support dependence may be too long for some patients who are likely to be stable enough to benefit from therapy. The ESC 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. The ESC considered that parenteral support dependence criteria may assist in differentiating between reversible and irreversible intestinal failure, and therefore reduce treatment of patients with potentially reversible intestinal failure. The ESC noted that the sponsor proposed to work with relevant parties to re-word the PBS eligibility criteria to ensure that eligible patients have reached a parenteral support maintenance phase and in clinical expert opinion their parenteral dependence is irreversible. The PBAC noted the clinical input given at the sponsor hearing, which suggested that six months would be a reasonable period to judge parenteral support stability.
- 2.4 The ESC agreed with the evaluation that it may be challenging to distinguish between reversible and irreversible Type III intestinal failure, which may result in treatment of patients with reversible intestinal failure who may otherwise have weaned off parenteral support spontaneously. The ESC noted the PSCR's (p1) claim that patients in the STEPS trial could be considered to have Type III irreversible intestinal failure, as stable parenteral support requirements for 4-8 weeks likely

indicated that intestinal adaptation was complete. However, the ESC considered that as intestinal adaptation is generally a slow, gradual process, stable parenteral support levels for 4-8 weeks does not necessarily indicate irreversible intestinal failure. The ESC was concerned that the criterion for at least four consecutive weeks of parenteral support, as stipulated in the proposed PBS restriction, is not long enough to ascertain an irreversible condition requiring lifelong parenteral support.

- 2.5 The pre-PBAC response (p1) stated that the vast majority of patients in STEPS had more than 18 months of parenteral support prior to enrolment, and maintained that this is likely reflective of the current Australian population. The pre-PBAC response provided a visual representation of the pathways for intestinal adaptation and the time course of each pathway (Figure 1).

Figure 1: Schematic presentation of intestinal adaption



AA=accelerated adaptation; AHA, accelerated hyperadaptation; HA=hyperadaptation; SA=spontaneous adaptation Source: Jeppesen PB 2003. J Nutrition; 133: 3721-23

- 2.6 The pre-PBAC response (p1) explained that in some patients who have high parenteral support requirements (typically following enterostomy; where <100cm of the small intestine is remaining) little intestinal rehabilitation is expected and therefore these patients would likely be eligible for teduglutide within 6 months post-surgery. In contrast, following other types of surgery, such as jejunio-ileal anastomosis, patients tend to have low parenteral support requirements and may take up to two years post-surgery to stabilise. The pre-PBAC response stated that the eligibility criteria for teduglutide should recognise the individual patient opportunity for rehabilitation due to residual anatomy post resection (such as presence of a stoma and/or length or residual bowel) as well as the duration of stable parenteral support volumes.
- 2.7 The proposed restriction does not include a stopping rule. The submission argued against a stopping rule on the grounds that some patients may achieve parenteral support volume reductions and/or wean off parenteral support beyond 12 months. The Product Information states that the treatment effect should be evaluated on an ongoing basis, with the need for continued treatment reviewed if no overall improvement is achieved after 12 months.

- 2.8 The PSCR (p4) stated that continued treatment is necessary, as teduglutide is an analogue of and replacement for naturally occurring glucagon-like peptide-2 (GLP-2). The ESC noted the sponsor is open to working with relevant parties to achieve a stopping rule which contains cost and allows sufficient time for all patients to benefit from therapy.
- 2.9 The ESC noted a study by Compher et al 2011¹, which investigated the change in parenteral nutrition volume (and body mass index) for 12 months after stopping teduglutide, in patients who had received treatment for at least 24 weeks. The analysis included 37 patients, of which 15 had their parenteral nutrition volume increased, 15 maintained the same volume and 7 had further volume reductions in the 12 months after stopping teduglutide. The ESC noted that based on the results of this study, 59% (22/37) of patients who ceased treatment did not require increases in parenteral nutrition volume within the next 12 months. The ESC acknowledged the limitations of the study, however, nonetheless considered that the study findings had important implications for consideration of the PBS eligibility criteria, which as currently proposed in the submission, does not include a stopping rule. The ESC further noted the importance of colon length in relation to the need for continued teduglutide therapy (i.e. the trend for patients with longer colon to be less likely to require increases in parenteral nutrition volume up to 12 months following cessation of teduglutide).
- 2.10 The pre-PBAC response (p3) argued that due to the limitations of the Compher 2011 paper, including a small sample size and a lack of clinical data to make an appropriate assessment of clinical status, these results cannot be used reliably inform assumptions regarding ceasing teduglutide.
- 2.11 The PBAC considered that given the limited treatment options available, the difficulty in identifying the appropriate patient population, and the high cost of treatment with teduglutide, detailed PBS restriction criteria are necessary to ensure eligibility for teduglutide in the PBS setting is reflective of the trial eligibility criteria, to reduce the risk of leakage and treatment in patients who may have other means to reducing parenteral support dependency. The PBAC advised that the consideration of a stopping rule was important for the PBS restriction, to ensure that patients do not continue on treatment with no or negligible benefit.

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.

¹ Charlene Compher, P. R. (2011). Maintenance of Parenteral Nutrition Volume Reduction, Without Weight Loss, After Stopping Teduglutide in a Subset of Patients With Short Bowel Syndrome. *Journal of Parenteral and Enteral Nutrition* , 603-609.

- 3.2 Teduglutide was registered on the ARTG on 19 May 2017 for the treatment of adult patients with short bowel syndrome who are dependent on parenteral support. Patients should be stable on their parenteral support regimen for at least to 4 weeks prior to initiating teduglutide.

Previous PBAC consideration

- 3.3 Teduglutide has not previously been considered by the PBAC.

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 Intestinal failure associated with short bowel syndrome may be reversible due to intestinal adaptation, and intestinal rehabilitation programs.
- 4.3 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.
- 4.4 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.
- 4.5 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. The ESC noted that patients have an important role in the self-management of parenteral nutrition, including determination of the required parenteral support volumes.
- 4.6 The submission positioned teduglutide as a treatment option for patients with Type III (chronic) short bowel syndrome receiving home parenteral nutrition.

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

5 Comparator

- 5.1 The submission nominated standard care (comprising enteral feeding, parenteral nutrition, dietary interventions, oral rehydration solutions, and anti-diarrhoeal/anti-secretory agents) as the main comparator. The ESC considered that standard care was an appropriate main comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The clinician explained that the time to intestinal adaptation could take two years, however it was possible that patients may reach metabolic stability by six months, depending on the length of small bowel remaining and concomitant fluid and electrolyte management. The PBAC noted the clinician's preference to commence treatment sooner rather than later to increase the chance of intestinal adaptation. The PBAC also noted the clinician's advice that at least six months was required to establish optimisation of patients' fluid and nutrition requirements, to assess patients' parenteral support needs and suitability for teduglutide. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease with a heterogeneous patient population.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health professionals (5) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with teduglutide associated with reduced need for parenteral support, including the improvement in quality of life for patients, carers and the whole family, ability to participate in social events, and the reduction of complications associated with parenteral support.
- 6.3 The PBAC noted input received from Parenteral Nutrition Down Under Inc. (PNDU) in support of subsidising teduglutide through the PBS. The PNDU described the restrictive impact of parenteral nutrition on patients' lives, due to the time commitments and clinical requirements of daily infusions. The PNDU explained how the need for daily parenteral nutrition not only impacted on patients' quality of life, but also their carers and families. The PNDU highlighted the significance of a treatment option that may provide days off parenteral nutrition, which would allow patients and their carers and family the opportunity to have a "break" and participate in normal social interactions. The PNDU also described the risks and complications associated with parenteral nutrition.

Clinical trials

- 6.4 The submission 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.
- 6.5 Details of the trials presented in the submission are provided in the table below.

Table 2: 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 extension study: STEPS-2)	A long-term, open-label study with teduglutide for subjects with parenteral nutrition dependent short bowel syndrome.	Clinical Study Report, 1 August 2013.
	Schwartz LK, O'Keefe SJD, Fujioka K et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome.	Clinical and Translational Gastroenterology 2016; 7:1-9. e142.
TED-C11-001 (STEPS-2 extension study: STEPS-3)	A one-year, open-label study with teduglutide for subjects with parenteral nutrition-dependent short bowel syndrome who completed Study CL0600-021.	Clinical Study Report, 18 August 2014.
	Iyer K, Fujioka K, Boullata JI et al. Long-term safety and efficacy with teduglutide treatment in patients with intestinal failure associated with short bowel syndrome (SBS-IF): The STEPS-3 study (abstract).	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.28 of the submission.

6.6 The key features of the direct randomised trials are summarised in the table below.

Table 3: 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 $\geq 20\%$; Reduction of ≥ 1 day in weekly PS days; Patients weaned off PS	Reduction in PS days per week
Study 004	84	Randomised, double-blind, placebo-controlled multi-centre trial 24 weeks + extension	Low	Adults with short bowel syndrome dependent on PS for at least 12 months	Graded response score; Reduction in weekly PS volume of $\geq 20\%$; Reduction of ≥ 1 day in weekly PS days; Patients weaned off PS.	Not used

Source: compiled during the evaluation.

Abbreviations: PS, parenteral support.

- 6.7 The primary outcome of the STEPS trial was the percentage of subjects who achieved at least a 20% reduction in weekly parenteral support volume from baseline at Week 20, which was maintained to Week 24. The submission proposed that a 20% reduction in weekly parenteral support volume was a clinically important change (based on expert opinion). The ESC acknowledged the impact of large volumes of parenteral support and the clinical significance to patients of reducing parenteral support dependency. The ESC noted, however, that a 20% reduction in weekly parenteral support volume is not necessarily equivalent to one day less of parenteral nutrition per week.
- 6.8 Following completion of STEPS, patients could opt to continue into a two-year, open-label extension study (STEPS-2). The study also included 12 previously untreated subjects who were screened, optimised, and stabilised (but not randomised) for the STEPS trial. All subjects in STEPS-2 (N = 88) received teduglutide 0.05 mg/kg daily. Patients who received teduglutide in STEPS received up to 30 months of teduglutide treatment; patients who received placebo (and previously untreated patients) in STEPS received up to 24 months of teduglutide treatment.
- 6.9 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 The submission included Study 004 as supportive evidence as the primary outcome was based on a different dose of teduglutide (0.10 mg/kg/day). The primary outcome of Study 004 was a graded response score (a scoring algorithm taking both response intensity and duration into account between Weeks 16 and 24). The statistical analysis plan specified a step-down procedure which required teduglutide 0.10 mg/kg/day to be statistically significantly greater than placebo before evaluation of the 0.05 mg/kg/day dose. Teduglutide 0.10 mg/kg/day failed to demonstrate superiority to placebo; however, the results of the 0.05 mg/kg/day dose were explored to gain further understanding of the effect of the lower dose. The submission stated that modifications were made to the STEPS protocol based on experience gained from Study 004, to allow earlier and greater adjustment of parenteral support.

Comparative effectiveness

6.11 Table 4 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.

Table 4: 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.50 of the submission; Table 2.3.1, p.20 of Attachment 5 of the submission.

Abbreviations: CI, confidence interval.

6.12 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. 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.

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

6.14 Table 5 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 5: Responder rates for at least a 1-day reduction in days per week on parenteral support

Extension study	Teduglutide (0.05 mg/kg) n (%)	Placebo n (%)	Difference, % (95% CI)	p-value
STEPS (24 weeks)	21/39 (53.8)	9/39 (23.1)	30.7% (9%, 50%)	p = 0.005
Study 004 (24 weeks)	██████████	██████████	██████████	██████████

Confidence intervals calculated during the evaluation using StatsDirect software.

Source: Table 2.5.2, p.56 of the submission; Table 2.3.5, p.22 of Attachment 5 of the submission.

Abbreviations: CI, confidence interval.

6.15 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.

6.16 The PSCR (p2) suggested that the active 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. However, the ESC considered that the extent to which an increase in oral fluid intake accounts for the reduction in parenteral support volumes demonstrated in the placebo group is unclear.

- 6.17 The pre-PBAC response (p2) reaffirmed that oral fluid intake in placebo patients was increased to compensate for reduced parenteral support. The pre-PBAC response claimed that the response rates in the placebo arm of the STEPS trial was a protocol driven treatment response that is unique to the study environment and would not be replicated in the real-world setting.
- 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 subject 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 6 presents the results for the number of patients who completely weaned off parenteral support across the placebo-controlled trials.

Table 6: 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: p.56 of the submission.

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 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.
- 6.24 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, as presented in Table 7. In Study 004 the overall results from three quality of life

assessments (SF-36, EQ-5D, and IBDQ) indicated no major effect on quality of life parameters.

Table 7: Results for SBS-QoL in the STEPS trial

	Teduglutide (n=35)				Placebo (n=35)				p-value (between groups)
	Baseline	Week 24	Change	p-value (within group)	Baseline	Week 24	Change	p-value (within group)	
Sum score	79.7	69.0	-5.9	0.0038	73.7	78.3	-1.7	0.3168	0.2286
Subscale 1	53.1	48.4	-6.1	0.0109	50.1	48.4	-1.5	0.2824	0.3124
Subscale 2	26.7	24.2	-2.1	0.0225	28.7	25.7	-1.4	0.3168	0.2620

Source: Table 2.5.6, p.60 of the submission.

- 6.25 The ESC noted the patient comments within the submission and the submission's emphasis on the impact of parenteral support on patients' quality of life. The ESC noted however, that despite a statistically significant difference between the teduglutide and placebo arms in the STEPS trial, in responder rates for at least a 20% reduction in weekly parenteral support volume, and for at least a 1-day reduction in days per week on parenteral support, there was no statistically significant difference in patients' quality of life between the teduglutide and placebo arms. The ESC was concerned therefore, that the submission's proposal that a 20% reduction in weekly parenteral support volume was clinically important may not translate into fewer days per week of parenteral support and may not be adequately justified.
- 6.26 The pre-PBAC response (p2) stated that patients who have more days on parenteral support per week may achieve additional days off parenteral support with relatively modest volume reductions, while those with fewer days of parenteral support may not achieve additional days off despite volume reductions. The pre-PBAC response (p2-3) claimed that a post-hoc analysis of the STEPS trial showed that for all patients with a parenteral support volume reduction $\geq 20\%$ there was a significant improvement in SBS-QoL sum score compared to a volume reduction $< 20\%$ (-5.2 points; $p=0.017$). The pre-PBAC response hypothesised that the lack of quality of life improvement across all patients is likely due to the heterogenous patient population. The pre-PBAC response (p3) stated that among patients who responded late to treatment in STEPS and STEPS-2, the mean time to sustained parenteral support volume reduction was 10 months. These patients were more likely to have a colon in continuity, ileo-caecal valve, and higher percentage of remaining colon than early responders. The pre-PBAC response argued that no improvement in quality of life at 6 months would be expected in these patients as, at this time point, they would not yet have responded to treatment. A $\geq 20\%$ reduction of parenteral support volume at Week 20 that was maintained at Week 24 was achieved in the majority (73%) of patients with inflammatory bowel disease as an underlying cause of SBS-IF treated with teduglutide in STEPS (2). In this subgroup of "early responders", teduglutide treatment was significantly associated with a SBS-QoL sum score improvement (-18.9 points; $p<0.001$) at Week 24 compared with placebo.

Comparative harms

- 6.27 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.

- 6.28 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.
- 6.29 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.
- 6.30 The ESC noted that there was significant uncertainty regarding the extended assessment of harms associated with long term teduglutide treatment.

Benefits and harms

- 6.31 A summary of the comparative benefits and harms for teduglutide versus placebo is presented in the table below.

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

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

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

Source: Table 2.5.1, p.50; Table 2.5.2, p.56; Table 2.5.10, pp65-66 of the submission. Table 2.3.1, p.20; Table 2.3.5, p.22; Table 2.3.11, p.33 of Attachment 5 of the submission.

¹ Teduglutide 0.05 mg/kg arm of Study 004.

- 6.32 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.
- 6.33 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 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.
- 6.34 The ESC noted that the submission did not include discussion on the benefits and harms associated with ceasing teduglutide. The ESC advised that this may be an important consideration if a stopping rule for treatment cessation was included in the PBS restriction. The PBAC agreed with the ESC's views.

Interpretation of clinical evidence

- 6.35 The submission described teduglutide 0.05 mg/kg daily plus standard care as superior in terms of effectiveness, and at least non-inferior in term of safety compared to standard of care alone. The submission also claimed that treatment with teduglutide was likely to reduce parenteral support-related complications such as liver disease and catheter-related sepsis. The ESC noted that there was no direct evidence from the STEPS trial that treatment with teduglutide reduced such complications associated with parenteral support.
- 6.36 Treatment with teduglutide for 24 weeks in STEPS resulted in statistically significantly higher responder rates ($\geq 20\%$ reduction in parenteral support volume; proportion of patients with ≥ 1 day off parenteral support) and weekly parenteral support volume reductions compared to placebo.
- 6.37 However, improvements in weekly parenteral volume requirements in the placebo arm of the STEPS trial may indicate that other factors (such as intestinal adaptation) contributed to parenteral support volume improvements. The ESC noted that in clinical practice, the determination of parenteral support volume is based on various factors and involves clinician and patient decision making, rather than changes in urine output only, as was the case in STEPS.
- 6.38 Additional responders for $\geq 20\%$ reduction in parenteral support volume and the proportion of patients with ≥ 1 day off parenteral support, and further reductions in parenteral support volume occurred beyond 24 weeks in the two-year STEPS extension study (STEPS-2). In STEPS-2, 13 patients were completely weaned off parenteral support, including 10/37 (27.0%) treated with teduglutide and 2/39 (5.1%) treated with placebo in STEPS.
- 6.39 However, the magnitude of the treatment effect attributable to teduglutide is uncertain, as no comparator group was included in STEPS-2. Based on the natural history of Type III intestinal failure, some patients may have weaned off parenteral support without treatment.
- 6.40 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 treatment with 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.
- 6.41 The PSCR (p3) claimed that adverse events associated with parenteral support are likely to be higher in the real world setting compared to in the STEPS trial, where patients were receiving optimised support.
- 6.42 The ESC considered that the submission's claim of reduced parenteral support volume was supported by the clinical evidence, however, considered that the relevance to the proposed PBS population was uncertain. The ESC noted that the reductions in parenteral support were based on 48-hour urine volumes at each trial visit in STEPS (weeks 2, 4, 8, 12, 16, 20), which may not reflect usual clinical practice. The ESC noted the statistically higher responder rates in patients on teduglutide compared to placebo, however, was concerned that the statistically significant

differences may not have been clinically meaningful. In particular, the ESC noted that there was no statistically significant difference in patients’ quality of life between the teduglutide and placebo arms of the STEPS trial. The ESC agreed with the evaluation that there was a lack of comparative clinical data to support the claim of reduced parenteral support complications in patients treated with teduglutide. The ESC further noted that the length of required treatment with teduglutide was uncertain and that there was no robust evidence for the efficacy and safety of teduglutide beyond 24 weeks.

- 6.43 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.44 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

- 6.45 The submission 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.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	20 years in the model base case versus up to 30 months treatment in STEPS/STEPS-2
Outcomes	Life years, QALYs
Methods used to generate results	Markov cohort model
Health states	No parenteral support; parenteral support 1-3 days/week; parenteral support 4-6 days/week; parenteral support 7 days/week; death.
Utilities	Based on the results of a sponsor-commissioned time trade-off study conducted in the UK
Cycle length	28 days
Transition probabilities	Transitions between levels of parenteral support based on patient level data from the STEPS trial and extension study (STEPS-2). Mortality based on extrapolated overall survival data reported by Amiot et al (2013).

Source: Table 3.1.1, pp76-77 of the submission.
 Abbreviations: QALY, quality adjusted life year.

- 6.46 The economic evaluation was a Markov cohort model with five unique health states: no parenteral support; parenteral support 1-3 days/week; parenteral support 4-6 days/week; parenteral support 7 days/week; and death. Patients start the model in one of three health states (parenteral support 1-3 days/week; parenteral support 4-6 days/week; parenteral support 7 days/week) based on the distribution of patients at baseline in the STEPS trial. In each cycle, patients can stay in the same parenteral support health state, move to any other parenteral support health state, or die. Patients were assumed to receive treatment until death. The model time horizon was 20 years.
- 6.47 Key drivers of the economic model are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Treatment effect	<p>Transition probabilities for the teduglutide arm were derived from patient level data from STEPS/STEPS-2. In the submission 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. This was not consistent with 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). Therefore, the ESC considered that the model was not representative of the clinical evidence from STEPS.</p> <p>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.</p> <p>The ESC considered it inappropriate to assume a survival difference between the teduglutide and standard care arms of the economic model, given that no survival difference was reported in the STEPS trial.</p>	High, Favours teduglutide
Modelled population	<p>The modelled population was based on the STEPS trial mean subject age and baseline days of parenteral support per week (≥ 3 days per week). The distribution of patients in the proposed PBS population will include 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.</p>	High, favours teduglutide
Extrapolation	<p>In the submission base case, 4-weekly transition probabilities beyond Week 104 were assumed to be the average of those occurring between Week 52 and Week 104. The model assumed improvements in parenteral support requirements would continue for up to 20 years. 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. Some patients may experience disease progression due to additional bowel surgery.</p> <p>The PSCR (p4) defended the use of a 20-year time horizon on the basis that the majority of the cohort were younger patients who were likely to receive benefit during the 20 year timeframe. The PSCR claimed that the trial results show consistent improvements in parenteral support volume can be achieved if treatment with teduglutide is maintained.</p> <p>The ESC agreed with the evaluation that the use of a 20-year time horizon was poorly justified. The ESC noted that Amiot et al (2013) found that deaths due to underlying disease accounted for 21% (22/105) of deaths in a cohort of 268 patients with non-malignant short bowel syndrome followed for a median 4.4 (0.3-24) years. The ESC considered extrapolation of survival benefits past 10 years based on data from Amiot et al 2013 was not adequately justified, due to small numbers. In addition, the ESC noted from a study by Messing 1999², no survival difference was observed between parenteral support free and parenteral support dependent groups in a multivariate analysis. This scenario of no difference in survival is suggested to be modelled in the base case, and a standardised mortality ratio of 0.556 for a PS free health state used in a sensitivity analysis.</p>	High, favours teduglutide
Utilities	<p>Health state utility values used in the economic model base case were derived from a sponsor-commissioned time trade-off (TTO) study conducted in the U.K. (Ballinger et al 2016, abstract). The applicability of the derived health state utilities to the Australian population was unclear. In the model base case, the submission inappropriately applied carer disutilities in addition to patient disutilities.</p> <p>The ESC considered that patients on teduglutide may still require carer support for daily subcutaneous injections, and for those patients who are not completely weaned off parenteral nutrition, carer support may still be required on days when</p>	High, favours teduglutide

² Messing B, C. P.-R. (1999). Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. *Gastroenterology*, 117(5):1043-50.

Description	Method/Value	Impact
	<p>parenteral support needs to be administered.</p> <p>The ESC noted that the model's base case applied utilities from the smaller U.K. study (n=100; Ballinger et al 2016), where the patient utility for zero days per week of parenteral support was 0.82, higher than that in the larger Canadian study (n=799; Lachaine et al 2016) of 0.74, despite both being TTO studies. The ESC considered that the application of utilities from the U.K. study rather than the Canadian study likely favoured teduglutide.</p> <p>The ESC considered that the application of different utilities between the teduglutide and BSC arms of the model were not supported by the clinical evidence from STEPS, which showed no statistically significant improvement in patients' quality of life in those on teduglutide. The ESC also noted that disutility associated with teduglutide treatment was not taken into account in the utility vignettes.</p>	
Drug costs	<p>The submission assumed a 20% reduction in the price of teduglutide assumed at 5 years due to loss of market exclusivity, with a further 20% reduction at 10 years. This assumption is not consistent with standard practice in economic evaluation or with the current PBAC guidelines.</p> <p>The PSCR (p4) maintained that the inclusion of these discounts, to "reflect the price trajectory post-listing", was reasonable.</p>	High, favours teduglutide

Source: Compiled during the evaluation.

6.48 The results of the modelled economic evaluation are presented in Table 11.

Table 11: Presentation of the submission base case economic evaluation

	Teduglutide plus standard care	Standard care	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life years	8.602	7.792	0.810
QALYS	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per life year gained			\$ [REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Source: Table 3.9.1, p.91 of the submission.

Abbreviations: QALY, quality adjusted life year.

6.49 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.

6.50 The ESC considered that the modelled results, which were driven by the assumption that patients become completely weaned off parenteral support, were not reflective of the trial results or what would likely happen in clinical practice, where many factors contribute to the parenteral support volume requirements. The ESC further noted that the resulting gains in QALYs were predominantly driven by (i) the modelled survival difference between the teduglutide and BSC arms, which was not supported by the clinical evidence in STEPS, and (ii) the choice of applying the U.K. utilities (Ballinger et al 2016), which likely favoured teduglutide. The ESC noted that costs associated with adverse events for teduglutide were not included in the model, which favoured teduglutide.

6.51 The submission base case included a number of inappropriate assumptions, including a 20% discount of teduglutide drug costs at 5 years with a further 20%

discount at 10 years due to ‘loss of exclusivity’; inclusion of carer disutilities; and restriction of placebo patients to baseline health states (despite improvements in parenteral support requirements demonstrated in STEPS).

6.52 During the evaluation, an alternative base case was constructed that does not include these assumptions, and applies more conservative transition probabilities to the teduglutide arm (based on transitions between Weeks 91-104; see Table 12).

Table 12: Re-specification of the model base case

	Incr costs	Incr QALYs	ICER
Submission base case	██████	████	██████
Remove 20% drug discount in years 5 and 10	██████	████	██████
Remove carer disutility	██████	████	██████
Allow placebo transitions during weeks 0-24	██████	████	██████
Extrapolate teduglutide transitions based on average of Weeks 91-104 (rather than Weeks 52-104)	██████	████	██████
Respecified base case	██████	████	██████

Source: Constructed during the evaluation using S3A1_teduglutide_Australia CUA workbook Excel spreadsheet.

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

6.53 The respecified base case retained an underlying bias in favour of teduglutide treatment due to differences in the duration of available clinical data for teduglutide and placebo. Alternative assumptions were tested in sensitivity analyses regarding the duration of treatment effect with teduglutide and placebo.

6.54 Table 13 presents the results of sensitivity analyses undertaken during the evaluation based on the re-specified base case.

Table 13: Results of sensitivity analyses conducted during the evaluation

	Incr costs	Incr QALYs	ICER
Respecified base case	████████	████	████████
Time horizon 10 years	████████	████	████████
Time horizon 15 years	████████	████	████████
Drug price			
- 25% reduction	████████	████	████████
- 50% reduction	████████	████	████████
- 75% reduction	████████	████	████████
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 time trade-off study	████████	████	████████
Allow discontinuation from teduglutide at 52 weeks	████████	████	████████
Placebo group transitions limited to 24 weeks			
- Teduglutide transitions limited to 2 years	████████	████	████████
- Teduglutide transitions limited to 5 years	████████	████	████████
- Teduglutide transitions limited to 10 years	████████	████	████████
- Placebo (0-24 weeks) and teduglutide improvements (91-104 weeks) extrapolated to 2 years	████████	████	████████
- Placebo and teduglutide improvements extrapolated to 5 years	████████	████	████████
- Placebo and teduglutide improvements extrapolated to 10 years	████████	████	████████

Source: Constructed during the evaluation using S3A1_teduglutide_Australia CUA workbook Excel spreadsheet.
Abbreviations: PS, parenteral support.

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

- 6.55 Results of sensitivity analyses undertaken during the evaluation indicate that the ICER was sensitive to assumptions regarding the time horizon, baseline health state distributions, utility values, and treatment effect extrapolations for teduglutide and placebo.
- 6.56 The ESC noted that a lower mortality rate was applied to the parental support free health state compared with the parenteral support dependent health states, and that the mortality rates were based on a single centre study (Amiot 2013). The ESC identified a second older study by Messing 1999³, which found no survival difference in a multivariate model between parenteral support free and parenteral support dependent groups. Based on this, and given no difference in mortality was observed in the trial, the ESC considered the modelled mortality benefit associated with being parenteral support free should not be included in the base case analysis.

³ Messing B, C. P.-R. (1999). Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. *Gastroenterology*, 117(5):1043-50.

- 6.57 The cost of home parenteral nutrition was based on the Independent Hospital Pricing Authority (IHPA) National Efficient Price Determination 2016-17. The ESC noted that the daily cost of home parenteral nutrition should have been calculated using 30.42 days per calendar month rather than 28 days. The assumption of 28 days per calendar month resulted in a higher daily cost of home parenteral nutrition (\$503.45/day versus \$463.40/day) which favoured the teduglutide arm. This had approximately a \$ [REDACTED] impact on the incremental cost per QALY gained (\$ [REDACTED] using 30.42 days per month; \$ [REDACTED] using 28 days per month based on the respecified base case presented in the commentary).

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

- 6.58 The estimated annual cost for teduglutide was \$ [REDACTED] (Section 100 Public Hospital) based on 13.04 packs per year. The submission stated that patients who achieve a clinical response with teduglutide are indicated to continue treatment in order to maintain the response. Based on the information presented in the submission, treatment would be life-long.

Estimated PBS usage & financial implications

- 6.59 This submission was not considered by DUSC.
- 6.60 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.
- 6.61 The sponsor conducted an online survey of 21 Australian public hospitals with a home parenteral nutrition program to determine the number of patients on home parenteral nutrition, and the number of patients expected to be eligible for teduglutide treatment. This survey was the key data source used to estimate the utilisation and financial impact of listing teduglutide. It was unclear whether all treatment centres providing home parenteral nutrition services were identified and surveyed, or whether survey respondents appropriately identified the pool of teduglutide-eligible patients based on the supplied criteria.

Table 14: 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	■	■	■	■	■	■
Uptake rate	■	■	■	■	■	■
Patient uptake of teduglutide	■	■	■	■	■	■
Total packs dispensed (13.04 per patient per year)	■	■	■	■	■	■
Estimated total costs of teduglutide (Published price, DPMQ \$■)						
Total cost to PBS	■	■	■	■	■	■
Total co-payments (\$15.42)	■	■	■	■	■	■
Total cost to PBS less co-payments*	■	■	■	■	■	■
Estimated total costs of teduglutide (Effective price, DPMQ \$■)						
Total cost to PBS	■	■	■	■	■	■
Total co-payments (\$15.42)	■	■	■	■	■	■
Total cost to PBS/RPBS less co-payments*	■	■	■	■	■	■

*Numbers corrected during the evaluation (co-payment amounts in the submission were added rather than deducted).

Abbreviations: DPMQ, dispensed price for maximum quantity

Source: Table 4.2.2, p98; Table 4.2.3, p98; Table 4.2.4, p99; Table 4.2.5, pp99-100 of the submission.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$20 - \$30 million per year, at the published price.

- 6.62 The total published cost of listing teduglutide (less patient co-payments) was estimated at less than \$10 million per year in Year 1 of listing, increasing to \$20 - \$30 million per year in Year 6, a total of more than \$100 million in the first 6 years of listing.
- 6.63 The total effective cost of listing teduglutide (less patient co-payments) was estimated at less than \$10 million per year in Year 1 of listing, increasing to \$10 - \$20 million per year in Year 6, a total of \$60 - \$100 million in the first 6 years of listing.
- 6.64 The table below presents the overall net implications for the Australian Government health budget.

Table 15: Net implications for the Australian Government health budget*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated total costs of teduglutide (Published price, DPMQ \$ [REDACTED])						
Total cost to PBS/RPBS less co-payments	[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 (Effective price, DPMQ \$ [REDACTED])						
Total cost to PBS/RPBS less co-payments	[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]

Numbers were corrected during the evaluation due to full fee for colonoscopies being used instead of 75% benefit; co-payment amounts in the submission added rather than deducted.

Abbreviations: DPMQ, dispensed price for maximum quantity

Source: Table 4.2.2, p98 of the submission.

- 6.65 Net costs to the Commonwealth government, including both PBS (effective price) and MBS costs, were estimated at less than \$10 million per year in Year 1 of listing, increasing to \$20 - \$30 million in Year 6, a total cost of \$60 - \$100 million in the first 6 years of listing.
- 6.66 The financial estimates were most sensitive to a change in the number of patients eligible for treatment with teduglutide. The evaluation considered that higher than estimated uptake may occur in the first few years of listing given the lack of alternative treatments. The PSCR (p4) claimed that it is plausible that uptake may be lower than estimated and not higher, as the rate of uptake is limited by the ability of multi-disciplinary teams to develop individual plans for eligible patients and monitor treatment outcomes. The ESC considered that the financial estimates are particularly sensitive to a change in patient numbers. Given that the proposed PBS restriction required the patient to be stable on their parenteral support regimen only for at least 4 weeks before initiating teduglutide therapy, the ESC considered patients without irreversible intestinal failure may access treatment. The ESC considered that the 4-week timeframe was insufficient to determine whether patients truly had irreversible intestinal failure.
- 6.67 There may be 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, or in paediatric populations.

Quality use of medicines

- 6.68 The sponsor proposed a patient support program, designed to supplement existing services for patients with short bowel syndrome with intestinal failure. The sponsor proposed that the program be developed in consultation with existing multidisciplinary teams to allow for individual prescribing hospital protocols and needs. 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

- 6.69 The sponsor requested a Special Pricing Arrangement, with a public price to be rebated to an effective price as used in the economic analysis.

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 of an unclear clinical place in therapy and the very high and uncertain incremental cost-effectiveness ratio (ICER). The PBAC considered the use of teduglutide in clinical practice was unclear with regards to the appropriate time to commence and cease treatment, and identifying the appropriate patient population. The PBAC considered the economic model as presented in the submission to be optimistic and noted that the financial impact of listing teduglutide was uncertain due to issues with the PBS restriction.
- 7.2 The PBAC noted the consumer comments received in support of a PBS listing for teduglutide, and considered that these reflected the high clinical need for treatment options for patients with parenteral nutrition dependency and their carers and families. The PBAC noted that there are currently no PBS subsidised treatment options available to reduce patients' requirements for parenteral support.
- 7.3 The PBAC considered that the requested restriction, which did not specify a period of parenteral support dependence prior to initiation of teduglutide, was not consistent with the pivotal clinical trial, in which patients were required to have at least 12 continuous months of prior parenteral nutrition dependency, and be receiving parenteral support on at least 3 days per week. 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. Therefore the PBAC was concerned that the requirement in the requested restriction for patients to be stable for at least 4 weeks on their parenteral support regimen before initiating teduglutide may not be sufficient to identify the correct patient population.
- 7.4 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. The PBAC considered that although the requested restriction specified Type III (chronic) intestinal failure associated with short bowel syndrome, it may not be possible to distinguish between reversible and irreversible Type III intestinal failure. Therefore the PBAC was concerned that it was possible for some patients to continue treatment with no or negligible benefit, and that some patients with reversible intestinal failure may also receive treatment in the PBS setting.
- 7.5 The PBAC noted that patients who were completely weaned off parenteral support across the teduglutide studies had durations of prior parenteral support dependency

ranging from 1 year to 16 years. Weaning occurred at 12 to 130 weeks of teduglutide treatment. No patients requiring parenteral support on 7 days per week at baseline were completely weaned in the teduglutide studies. Therefore 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.

- 7.6 The PBAC accepted standard care as the appropriate comparator.
- 7.7 The PBAC noted that the submission was based on one head-to-head 24-week trial comparing teduglutide and placebo (STEPS) and associated extension studies (STEPS-2 and STEPS-3). The PBAC considered that the claim of superior comparative effectiveness of teduglutide over standard care was reasonable, based on the statistically significant difference in the primary efficacy outcome of the proportion of patients who achieved at least a 20% reduction in weekly parenteral support volume from baseline at Week 20 that is maintained through to Week 24. However, the PBAC considered that the submission's proposal that a 20% reduction in weekly parenteral support volume as 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. Additionally, the PBAC noted that in STEPS, there was no statistically significant difference in patients' quality of life between the teduglutide and placebo arms. The PBAC noted that the design and size of the trial may in part explain the lack of significant difference in this outcome, also noting that some subgroup analyses were suggestive of quality of life benefit.
- 7.8 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. In STEPS, reductions in parenteral support volume occurred in both the placebo and teduglutide groups. The placebo group achieved a mean reduction of 21%, above the 20% considered to be a clinically important change in the submission. The PBAC noted comments from the PSCR (p2) and pre-PBAC response (p2) that there was increased oral fluid intake in the placebo arm of STEPS, which may have resulted in false reductions in parenteral support requirements in the placebo arm. However, the PBAC 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.
- 7.9 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. 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. Additionally, the PBAC considered that in cases where patients' weekly volume reductions translated to reduced hours per day of parenteral nutrition rather than

complete weaning of parenteral nutrition, that the risk of complications associated with a central venous catheter would not be reduced by teduglutide.

7.10 The PBAC considered that the incremental cost per quality adjusted life year 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, including:

- 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. 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.
- The modelled population was not consistent with the proposed PBS population: the model included patients with a baseline ≥ 3 days per week of parenteral nutrition, however, the proposed PBS restriction did not limit treatment eligibility to these patients.
- Utilities: the PBAC 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, and that this likely favoured teduglutide. The PBAC considered, given that teduglutide may not reduce the number of days per week of parenteral nutrition required, that the application of carer disutilities was not justified.
- Medicine price reductions: the PBAC considered that it was inappropriate to assume future price reductions for teduglutide in the model and noted that this was not consistent with the PBAC guidelines.

The PBAC noted that sensitivity analyses conducted by the evaluation resulted in a wide range of ICERs/QALY, which highlighted the uncertainties associated with the economic model.

7.11 The PBAC noted that the estimated net cost of teduglutide was approximately \$60 - \$100 million over six years. 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 (e.g. Type II intestinal failure, paediatric patients) may have a substantial impact on the budget impact estimates. The PBAC considered that given there are currently no PBS subsidised treatment options for patients dependent on parenteral nutrition, the risk of leakage outside of the proposed PBS restriction, to patients with less severe intestinal failure associated with short bowel syndrome, was high.

7.12 The PBAC considered that any resubmission for teduglutide would require a major submission:

- Detailing restriction criteria that ensure treatment is confined to those who are most likely to have a clinically meaningful benefit. The PBAC advised 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. In developing a stopping rule, the PBAC advised that the definition of “stopping” or a “treatment break” would need to be outlined, inter alia, in the event of independence from parenteral support, significant reductions in parenteral support, no response to treatment after a defined duration.
- Addressing the PBAC’s concerns regarding the clinical significance of the primary efficacy outcome, including the relationship between a 20% reduction in weekly parenteral support volume and the number of days reduced per week of parenteral support. The PBAC advised that the claim of quality of life improvements in the longer term would need to be clarified, given the variability in time to response and extent and duration of sustained response among patients. The PBAC also advised that the clinical outcomes (both benefits and harms) be explored in the case where a stopping rule is proposed for the PBS restriction.
- Addressing the PBAC’s concerns regarding the economic model as outlined through the Minutes.

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

7.13 The PBAC considered that the PBS is the most appropriate mechanism for subsidising teduglutide for Type III (chronic) intestinal failure associated with short bowel syndrome, rather than other programs such as the Life Saving Drugs Program.

7.14 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.