The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using teduglutide in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Note that this document is not NICE’s final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE’s guidance on using teduglutide in the NHS in England.

For further details, see NICE’s guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 4 December 2017

Second appraisal committee meeting: 4 January 2018

Details of membership of the appraisal committee are given in section 5.
1 Recommendations

1.1 Teduglutide is not recommended, within its marketing authorisation, for treating people aged 1 year and over with short bowel syndrome that is stable following a period of intestinal adaptation after surgery.

1.2 This recommendation is not intended to affect treatment with teduglutide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by the clinician and the child or young person, or the child’s or young person’s parents or carers.

Why the committee made these recommendations

People with short bowel syndrome need intravenous (parenteral) nutrition, usually for many hours a day on several days a week. There are no therapies that reduce the frequency or duration of parenteral nutrition. Results from clinical trials suggest that teduglutide reduces, but does not remove, the need for parenteral support in adults. There is limited clinical trial evidence for how well teduglutide works in children, but it is reasonable to apply trial results on the effectiveness of teduglutide from adults to children. The most frequent complication of long-term parenteral nutrition is catheter-related infections.

The cost-effectiveness estimates for teduglutide compared with standard care are £193,549 per quality-adjusted life year (QALY) gained for adults and £111,045 per QALY gained for children. These are higher than what NICE normally considers acceptable, and even higher when corrections and preferred assumptions about catheter-related infections, and patients’ and carers’ quality of life are included. Therefore, teduglutide cannot be recommended for treating short bowel syndrome in people aged 1 year and over.
2 The technology

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3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Shire and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

**Short bowel syndrome**

This appraisal considers people with short bowel syndrome whose condition is stable on long-term parenteral nutrition

3.1 Short bowel syndrome (SBS) is a chronic and potentially life-threatening condition characterised by reduced absorption of nutrients, water and electrolytes in the intestine. A common cause is the surgical removal of large parts of the small intestine because of ischaemia, inflammatory bowel disease, injury or tumour. The remaining small bowel adapts over 2 to 3 years and grows to absorb nutrients, with children generally adapting more quickly than adults. People with SBS can develop chronic intestinal failure, also known as type III intestinal failure, and need long-
term home-based parenteral nutrition. This appraisal focuses on people whose condition is stable on long-term parenteral nutrition.

**Long-term parenteral nutrition is associated with several complications, such as catheter-related infections**

3.2 Parenteral nutrition delivers fluids and nutrients intravenously rather than via the gastrointestinal tract. Long-term parenteral nutrition is associated with complications including:

- Catheter-related infections: the committee understood that these are the most frequent complications associated with long-term parenteral nutrition, and that their occurrence does not directly correlate with the frequency of parenteral nutrition.

- Intestinal failure-related liver disease: the committee understood from the clinical experts that the data on the link between parenteral nutrition and liver disease came primarily from a French study in the 1990s, at which time in France, parenteral nutrition included a higher concentration of lipid than is currently given in the UK. The clinical experts explained that, in England, the incidence of liver disease is much lower than that reported in the study.

- Intestinal transplant: the committee understood that, if treatment with long-term parenteral nutrition fails, in certain clinical scenarios people may need an intestinal transplant, but this remains rare.

The committee heard from the clinical experts that end-stage kidney disease occurs very rarely and is not considered a standard complication of parenteral nutrition.

**Impact on patients and carers**

**Parenteral nutrition affects the quality of life of people with the SBS and their carers**

3.3 The patient experts noted that everybody with SBS on parenteral nutrition needs support, although not everybody needs a carer. About 80% of
adults with SBS have a full-time carer. For children, normally both parents have training on to care for their child. The committee heard from the patient and clinical experts that people having parenteral nutrition may need daily infusions for up to 14 hours per day. Other factors can increase how long infusions are needed for, such as dehydration. Usually, people administer their parenteral nutrition at night, which affects patients’ (and carers’) sleep, and their social and family life. The committee heard from the clinical experts that anxiety and depression are common in people with SBS. It understood that a person’s quality of life depends far more on the frequency than the volume of parenteral nutrition needed; a 1-day reduction in parenteral support is perceived to be a substantial benefit. Disrupted sleep in children may result in them not being able to go to school or attend social events. This may affect the family’s social life, and result in a parent having to stop working. The committee concluded that long-term parenteral nutrition negatively affects the quality of life of patients and their carers.

**Place of teduglutide in the treatment pathway**

**Teduglutide would be used in people with SBS and type 3 chronic intestinal failure that needs long-term parenteral nutrition**

3.4 Teduglutide has a marketing authorisation for treating SBS in people 1 year and over, when their intestines have had time to adapt after surgery and the condition is stable. The committee heard from clinical experts that, in clinical practice, teduglutide would be used in a subset of this population, that is, people with SBS and type 3 chronic intestinal failure whose condition is stable and who are fit enough for home-based parenteral nutrition that is needed long term, at a frequency of 2 to 7 nights per week. The clinical experts clarified that the original cause of SBS would not determine whether or not to offer teduglutide.
Comparators

The relevant comparator for teduglutide is standard care, including parenteral nutrition

3.5 The final scope from NICE specified that the relevant comparator for teduglutide was established clinical management without teduglutide (including parenteral support, antimotility and antisecretory agents, fluid restriction and an optimal diet). The committee understood from clinical experts that teduglutide would be used in addition to parenteral nutrition. The committee was aware that there is currently no other therapy available that may allow people with SBS to reduce their parenteral nutrition needs. It concluded that, in the absence of teduglutide, people would continue to have parenteral nutrition alone.

Clinical evidence from the STEPS trial

STEPS, a double-blind, randomised controlled trial, is the main source of clinical evidence for adults

3.6 The main clinical evidence for teduglutide in adults came from STEPS, a 24-week double-blind phase III randomised controlled trial comparing 24 weeks of treatment with teduglutide (n=43) with placebo (n=43). It included adults with parenteral nutrition-dependent SBS who needed parenteral support at least 3 times per week. The primary endpoint of the trial was the percentage of patients whose condition responded at week 20 and in whom there was still a response at week 24. A response was defined as a reduction of 20% or more from baseline in the volume per week of parenteral nutrition. Secondary outcomes were the percentage and absolute change in volume of parenteral support; the number of patients who stopped parenteral support; and change in health-related quality of life, using the Short Bowel Syndrome–Quality of Life (SBS–QoL) scale. People who completed the 24-week treatment period in STEPS were enrolled into the 2-year extension study STEPS2 (n=88). Those who completed treatment in STEPS2 were enrolled into the 1-year...
extension study STEPS3 (n=14). In both extension studies, patients had teduglutide whether or not they had previously been randomised to teduglutide. The 2 extension studies focused on the change from baseline in the weekly volume of parenteral nutrition.

**CL0600-004, a randomised controlled trial, provides further clinical evidence in the adult population**

3.7 CL0600-004 was a 24-week double-blind phase III randomised controlled trial that compared 2 doses of teduglutide (0.10 mg/kg once daily, n=32; and 0.05 mg/kg once daily, n=35) with each other and with placebo (n=16). It included patients with SBS who had needed parenteral support at least 3 times per week for more than 12 months. The primary endpoint was a graduated response score that accounted for intensity and duration of response; the primary endpoint was changed during the trial. Data on health-related quality of life, using SF–36, EQ–5D and the Inflammatory Bowel Disease Questionnaire, were also collected. The extension study of CL0600-004, CL0600-005, was a single-arm study that included patients who completed the 24 weeks of CL0600-004 (n=65) regardless of which treatment they had been randomised to. The primary endpoint was the percentage of patients who reached the endpoint of CL0600-004 and who had a more than 20% reduction in parenteral support.

**Generalisability of the trial results for adults to the NHS**

The population of the clinical trials for adults reflect people who would be offered teduglutide in the NHS

3.8 The clinical experts were generally satisfied that patients in the trials reflected people who they would expect to treat with teduglutide in the NHS. However, they noted that, in UK clinical practice, colon-in-continuity (that is, when the colon is linked to the remaining part of the small intestine) is very rare, whereas in the clinical trials it was seen in around 60% of patients. The clinical experts stated that they did not know whether this would alter the clinical effectiveness of teduglutide. The committee concluded that the population informing the clinical-effectiveness evidence
reflected people in the NHS, and the results were generalisable to UK clinical practice.

**Results of the clinical trials for adults**

**Teduglutide reduces the need for parenteral support in patients with SBS**

3.9 The committee discussed the results of the clinical trials noting that:

- Accidental unblinding occurred in the trial because of stomal swelling in the teduglutide group.
- STEPS showed that the percentage of patients with a response (20% or more reduction in the need for parenteral support) was higher with teduglutide than with placebo (62.8% compared with 30.2%, p=0.002). It also showed that more patients had at least a 1 day reduction per week in the need for parenteral support with teduglutide than with placebo (53.8% compared with 23.1%, p=0.005). The results of STEPS2 showed that the reduction in parenteral-support volume was maintained during the 2-year study period.
- In the 0.05 mg/kg/day arm of the CL0600-004 trial, the results showed that a higher percentage of people had at least a 20% or more reduction in the need for parenteral support with teduglutide than with placebo (45.7% compared with 6.3%, p=0.005). More patients randomised to teduglutide had a reduced need for parenteral support by 1 or more days per week than those randomised to placebo (31.4% compared with 25%, p=0.684).

The committee concluded that functional unblinding was unlikely to have biased the results, and that teduglutide is a clinically effective treatment for SBS in adults in reducing both the volume and number of days of parenteral nutrition.
Meta-analysis

The company did not meta-analyse the results from STEPS and CL0600-004

3.10 The company did not meta-analyse the STEPS and CL0600-004 trials because:

- The hierarchical statistical analysis plan of CL060-004 required that there was a statistically significantly greater graded response score with teduglutide at a dose of 0.10 mg/kg/day (subsequently not a licensed dose) compared with placebo before the 0.05 mg/kg/day dose was evaluated. However, the first analysis was negative, so there was no formal comparison between teduglutide 0.05 mg/kg/day and placebo; which the company compared in a post-hoc analysis.
- There were methodological differences between STEPS and CL0600-004:
  - Patients in STEPS were weaned off parenteral support earlier than in CL0600-004 because investigators assessed reduction in parenteral-support volume at weeks 1, 2, 4 and then every 4 weeks in STEPS compared with every 4 weeks in CL0600-004.
  - In STEPS, patients could reduce parenteral support by 10% to 30% of their stabilised baseline up to a clinically appropriate amount, whereas in CL0600-004, no patients reduced their parenteral-support volume by more than 10%.

Results of a meta-analysis based on STEPS and CL0600-004 trials would strengthen the evidence

3.11 The committee discussed the difference between STEPS and CL0600-004, but considered that reducing uncertainty with more data would outweigh the problems arising from heterogeneity between the trials, particularly with trials with small population sizes. It agreed with meta-analysing the 2 trials. It noted that the ERG meta-analysed the number of ‘responders’ at week 20 and 24 in both trials. The results confirmed that teduglutide was more effective than placebo. However,
these results could not be used in the economic model, because the model used a different outcome (that is, reduction in the number of days of parenteral support needed) to reflect clinical effectiveness. The committee concluded that a meta-analysis of STEPS and CL060-0004 strengthened the evidence and that, ideally, the results of such an analysis should inform the model.

**Clinical trial evidence for children**

**TED-C13-003 was an open-label study that compared teduglutide with standard care in children between 1 year and 17 years**

3.12 TED-C13-003 was a phase III open-label study that enrolled children with parenteral nutrition-dependent SBS who needed parenteral support at least 3 times a week and weighed at least 10 kg. It compared 3 doses of teduglutide, 0.0125 mg/kg (n=8), 0.025 mg/kg (n=14) and the licensed dose of 0.05 mg/kg per day (n=15), with standard care (n=5). The study lasted 12 weeks and measured the pharmacokinetics and pharmacodynamics of teduglutide, and its safety and tolerability. Health-related quality of life was not measured in the study.

**Generalisability of trial results for children to the NHS**

The results of the clinical study for children have limited value for decision-making

3.13 The baseline patient characteristics of the TED-C13-003 trial were imbalanced between the study arms in terms of age, sex and years on parenteral nutrition. The committee heard from the company that it was difficult to recruit patients to the standard-care group because parents saw little benefit from their children being in that group. As a result, only 5 patients had standard care. The committee questioned the need to be a minimum weight of 10 kg to be included in the trial. It heard from the clinical experts that, although arbitrarily chosen, this weight seemed appropriate. In general, the clinical experts agreed that the population in TED-C13-003 represented NHS patients in England well. However, the
committee considered that the study had limited value for establishing the effectiveness of teduglutide in children and for decision-making.

**Clinical trial results for children**

Teduglutide reduces the need for parenteral support in children

3.14 The trial results showed a decline in the volume of parenteral support needed with all 3 doses of teduglutide studied, whereas the volume of parenteral support needed increased in children having standard care. The committee heard from the clinical experts that, given the limitations of the study, it would be reasonable to generalise results on the effectiveness of teduglutide from adults to children. The committee concluded that teduglutide is an effective treatment for SBS in children and reduces the need for parenteral support.

**Health-related quality-of-life results**

The trials were not powered to show a difference in quality of life

3.15 In STEPS, there was no difference between teduglutide and placebo in the overall sum SBS–QoL scale or subscale scores. However, the committee was aware that STEPS was not powered to identify changes in health-related quality of life. In C0600-004, patients in the 0.1 mg/kg/day arm of the trial reported worse quality-of-life results (measured using EQ–5D) than patients in the 0.05 mg/kg/day arm but the difference between treatment groups was not statistically significant. However, the committee noted that the trial was not powered to detect a difference in this outcome.

**Adverse events**

Serious adverse events occur more frequently with teduglutide than with placebo

3.16 Treatment-emergent adverse events occurred more frequently in patients in the teduglutide arms of the trials than the placebo arms. The most frequently reported adverse events were:
gastrointestinal disorders (such as abdominal pain, nausea, abdominal distension, flatulence, vomiting, diarrhoea, gastrointestinal stoma changes and general disorders)

• administration site conditions (such as catheter-related complications, fatigue and injection site bruising, erythema and pain).

Serious adverse events occurred more frequently with teduglutide than with placebo. The committee noted that the level of adverse events was high, and concluded that it was important that the model adequately captures this. The committee was aware of the pharmacovigilance plan from the European Medicines Agency that requires the company to set up an International Short Bowel Syndrome Registry to collect more safety data, to look at the potential for risk and to identify what that risk might be. There is also a requirement that interim data are presented in every second year.

The company’s economic model

The company submitted different models for adults and children

3.17 The company used different models for adults and children:

• In adults, it used a Markov cohort model with 8 health states reflecting the number of days of parenteral support per week (that is, 0 to 7 days per week). The model compared teduglutide with standard care over 40 years using a 28-day cycle length.

• In children, it used a variation of the adult model, with fewer health states because of the limited availability of data in children. The model had 4 health states based on the frequency of parenteral support per week (that is, no need for parenteral support, and low, mid and high need for parenteral support). The company used a lifetime time horizon of 96 years and a 28-day cycle length.

The committee recognised that the model for children had a different number of states than that for adults because the available data for
children did not allow modelling for parenteral support on 0 days to 7 days per week, and not because the natural history of the disease differs in children and adults.

**Modelling complications associated with parenteral nutrition**

**End-stage chronic kidney disease is not a standard complication of parenteral nutrition**

3.18 For both adults and children, the company’s model included 2 ‘sub models’ for 2 of the complications associated with long-term parenteral nutrition: intestinal failure-related liver disease and end-stage chronic kidney disease. However, the clinician experts did not consider end-stage chronic kidney disease to be a standard complication of parenteral nutrition (see section 3.2), so the model did not reflect the natural history of disease in this regard.

**The model for adults and children did not accurately reflect the complications of parenteral nutrition**

3.19 The committee discussed how the company incorporated other complications associated with parenteral nutrition:

- Catheter-related infections: the company included these as an adverse event that could occur only in the health state in which people had parenteral support for 7 days per week. The committee understood that catheter-related infections do not correlate with the number of days on which parenteral support is given.
- Intestinal transplantation: the company only included this as a complication in the model for children. The committee discussed whether it was valid to assume adults would never have an intestinal transplant, and heard from the clinical experts that, while rare in practice, adults sometimes need a transplant (see section 3.2). The committee considered that there was no clinical rationale for making different assumptions about intestinal transplantation in adults and children.
The committee concluded that:

- catheter-related infections should be applied to any health state including parenteral nutrition.
- both models for adults and children should incorporate the same assumptions about intestinal transplantation.

**Transition probabilities in the model**

The committee considered the ERG’s approach to be more appropriate

3.20 The company modelled effectiveness as reduction in the number of days of parenteral support per week. It used the following data for modelling treatment effectiveness in the economic model:

- data from the STEPS trial in the first 6 cycles for both the teduglutide standard-care arms
- data from the STEPS2 study after 6 cycles and until month 30 to reflect patients taking teduglutide
- the last observed health state carried forward after month 30 until the end of the modelling period or death in both arms
- reversion back to the original health state in which patients in the standard-care arm entered the model (baseline observation carried forward) after 6 months.

The committee heard from the ERG that the last assumption favoured teduglutide, so the ERG explored the impact of maintaining the last observed health state until the end of the time horizon of the model in the standard-care arm. The committee concluded that, for both arms, the last observed health state from the clinical trials should be maintained.
Modelling survival

The ERG’s modelling of survival in people with SBS is more appropriate than the company’s

3.21 In the adult model, the company modelled survival of people with SBS based on observational data from a French cohort (Amiot et al., 2013). The company took Kaplan–Meier curves for survival from the study and used a log-normal curve to extrapolate beyond the observed period until the end of the time horizon. In the model, the frequency of parenteral nutrition did not correlate with mortality, that is, more frequent parenteral nutrition per week did not increase the mortality rate associated with SBS. The clinical experts considered this assumption to be appropriate. Part of the company’s log-normal curve based on Amiot et al. predicted a lower mortality rate than the age-adjusted general population mortality. To address this, the company set the mortality rate of people with SBS equal to the mortality rate of the general population. The ERG explored alternative parametric curves, and suggested using the Weibull curve to model survival because it did not predict a lower mortality rate than the age-adjusted general population mortality rate at any point along the time horizon. The committee agreed that having SBS increases the risk of death, and that the model should include this. It concluded that the ERG’s suggested curve to model survival was more appropriate than the company’s because it did not need it did not need secondary modification to match the general population mortality.

3.22 In the model for children, it was assumed that the survival of children with SBS was better than that of the adult population, that is, children with SBS have a lower rate of mortality than adults with SBS. To reflect this, the company applied a hazard ratio of 2.42 for death to the survival curves of the adult model, which were based on Amiot et al. (see section 3.21). It estimated this hazard ratio based on a study by Pironi et al. (2011), which looked at the survival of patients with long-term parenteral nutrition. The ERG applied the same changes to the survival curves as in the adult
model (that is, used the Weibull curve instead of the company’s preferred log-normal curve). The committee agreed that there is merit in considering survival in children modelled using the same curve preferred by the committee for adults (that is, the Weibull curve).

**Stopping rules and continuing treatment in the model**

**It is reasonable to apply a stopping rule in the model**

3.23 The marketing authorisation for teduglutide specifies that the treatment effect of teduglutide should be evaluated after 6 months in adults and after 12 weeks in children. Treatment should be stopped if no overall improvement of the patient condition is achieved. The model applied a stopping rule based on STEPS for adults, which was to stop treatment if they did not have at least a 20% reduction in the frequency of parenteral support. For children, the rule was to stop treatment if there was no response (at least a 20% reduction in the frequency of parenteral support) after 12 weeks. The committee discussed whether the definition represented a clinically feasible endpoint in the model. It 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 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.

**Health-state costs**

**The costs of catheter-related infections should be applied to all health states in the model**

3.24 The company conducted costing studies with experts to calculate the costs associated with each health state. It calculated scenarios reflecting low-, medium- and high-cost parenteral support and then mapped them to the 7 parenteral-support health states in the adult model. In the model for children, the company did not do any mapping because the scenarios
reflected the 4 health states modelled. The committee heard from the ERG that the company’s approach assumed a correlation between certain types of resource use and the number of days of parenteral support needed, which exaggerated the cost difference between teduglutide and standard care and favoured teduglutide. In particular, the costs of catheter-related infections were only applied to the health state reflecting parenteral support administered 7 days a week. The committee considered this to be implausible because catheter-related infections can occur in any health state (also see section 3.2). It concluded that the cost of catheter-related infections should be applied to all health states in the model.

**Costs for community nursing is missing in the model for children**

3.25 The committee discussed whether the company had incorporated the costs of care appropriately in the model. The company had incorporated the costs of community nurses into the model for adults but not for children. It heard from the clinical experts that every family with a child has support from community nurses. The committee concluded that the model for children should include the costs associated with community nurse support.

**Utility values in the economic model**

**Quality of life from the vignette study is the preferred source of utility data**

3.26 The company identified 3 different sources for sourcing utility values for adults with SBS: 2 based on the results from the clinical trials (STEPS and CL0600-004); and 1 from a vignette study conducted by the company after the trials were completed. A representative sample of the UK general population valued the vignettes using the time-trade-off method. Using the values from the vignette study resulted in substantially greater quality-adjusted life year (QALY) gains for teduglutide than using values derived from the STEPS trial. The committee agreed that the utility values calculated based on the STEPS trial lacked face validity. This was because they peaked in the health state reflecting 4 days of parenteral support.
support per week, and did not decline consistently across the health states reflecting 0 days to 7 days of parenteral support per week as expected. Conversely, the utility values calculated based on the vignette study declined linearly. The committee heard from the clinical experts that the reason for these results might have been the short duration of the STEPS trial (24 weeks) and the ability of patients to adapt to their condition. The ERG explored the impact of using health-state utility values based on mapping the SBS–QoL results of the STEPS trial to EQ-5D, and this resulted in smaller QALY gains for teduglutide than for standard care. The committee would have preferred the health-state utility values to come from the same source as the clinical effectiveness, that is, the trials; however, the values from STEPS lacked face validity. The utility values from the vignette study better reflected the experience of people with the condition, that is, utility decreases as the frequency of parenteral support increases.

**Utility decrement for adverse events**

**Some utility decrements for adverse events lack face validity**

3.27 The company applied utility decrements for adverse events in the model. The clinical experts advised that some of the company’s assumptions were unrealistic and too high (for example, the utility decrement associated with upper respiratory tract infections was 0.52). The committee concluded some of the utility decrements for adverse events overestimated the impact of adverse events on health-related quality of life.

**The ERG’s correction for adverse events rates is appropriate**

3.28 The company calculated the rates of adverse events based on results from STEPS and STEPS2. The committee heard from the ERG that the company made an error in applying adverse events rates and interchanged the rates for the different arms. The ERG corrected for this error, which the committee considered to be appropriate.
Modelling utility of carers

The benefit of teduglutide to carers is likely to lie between the company and ERG’s estimates

3.29 The company conducted a Delphi-panel study with experts to estimate carers’ utility values. It assumed that every patient has 1 carer. The committee heard from clinical experts that, for children with 2 parents, both parents usually act as carers, whereas about 20% of adult patients live independently and do not have a full-time carer. Therefore, the committee concluded that the model should have had more than 1 carer for children and less than 1 carer for adults. The company modelled carer utility as absolute values until the end of the modelled time horizon. The ERG considered that this approach may have overestimated the benefits of treatment with teduglutide. It explored the impact of applying utility decrements to the patient’s utility values to reflect carer disutility. This reduced the difference in QALYs between the 2 treatments (0.85 compared with 1.85 using the company’s approach). The committee concluded that the real benefit of teduglutide to carers was likely to be overestimated using the company’s approach, and underestimated using the ERG’s approach, and that it was likely to lie in between these.

Cost-effectiveness estimates

The ERG’s corrections to the company’s model resulted in higher incremental cost-effectiveness ratios (ICERs)

3.30 The committee noted that the base-case ICER using the company’s model that incorporated the patient access scheme discount for teduglutide was £193,549 per QALY gained for adults and £111,045 per QALY gained for children. After applying the ERG’s corrections to the model for the calculation of adverse events rates (see section 3.28), the cost-effectiveness estimates changed to £206,690 per QALY gained for adults and to £120,766 per QALY gained for children.
All the ERG scenarios increased the ICERs

3.31 The ERG presented a set of scenarios in which it combined various changes to the model. These were:
- re-calculating health-state costs
- amending renal dialysis costs based on NHS reference costs
- applying health-state utility values from STEPS
- maintaining the last observed health state of the observed trial period in the standard-care arm
- applying age-adjusted utility values for carers
- applying Weibull curves for modelling survival
- incorporating intestinal transplant as a complication to the model for adults
- excluding intestinal transplant as a complication from the model for children
- applying carer utility decrements for calculating overall the utility value for patients.

All of the scenarios increased the ICER in both the adult and children models. The ICERs estimated by the ERG did not reflect more realistic assumptions about death from liver disease or renal failure, the disutility and risk of dying from line sepsis, the possibility of intestinal transplantation for both adults and children, and more realistic values for carer disutility.

Conclusions about cost effectiveness

3.32 The committee concluded that the cost-effectiveness results presented by the company and the ERG were well above the range normally considered to be a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained). It also considered that its preferred analysis would incorporate the following assumptions:
- reflecting the natural history of the disease in terms of incorporating standard complications associated with long-term parenteral support (see section 3.18)
• applying the ERG’s changes for calculating health-state costs (see section 3.24)
• amending renal dialysis costs based on NHS reference costs
• applying health-state utility values from the vignette study (see section 3.26)
• maintaining the last observed health state of the observed trial period in the standard-care arm (see section 3.20)
• applying age-adjusted utility values for carers
• applying Weibull curves for modelling survival (see sections 3.21 and 3.22)
• applying the same method for incorporating intestinal transplant as a complication to both the model for adults and children (see section 3.19)
• assuming that the benefit of teduglutide to carers is between the company and ERG’s estimates (see section 3.29).

Other factors

Teduglutide is an innovative treatment

The committee heard from the company that teduglutide is an innovative treatment. It is the first and only pharmacological therapy available for treating SBS in both adults and children that addresses intestinal rehabilitation rather than only managing symptoms. It effectively reduces the frequency and volume of parenteral support. The committee noted that the clinical and patient experts also emphasised that teduglutide is effective in reducing the symptoms and complications of SBS with chronic intestinal failure. The committee heard that, for children, fewer night-time disruptions would improve school attendance and performance. The committee discussed the possible stigma associated with having SBS in children. It appreciated that teduglutide likely improves the quality of life of patients and their carers, allowing them to live more independent lives. The committee therefore concluded that teduglutide is an innovative
treatment, and that there are benefits to utility that were not otherwise accounted for in the modelling.

The committee considered the needs of children and their families in its decision-making

3.34 The committee discussed whether any special consideration should be made to reflect the fact that the population in this appraisal includes children. It was aware that SBS is a chronic, potentially life-threatening condition, that people with the condition as well as their families and carers are affected in all aspects of life, and that children with the condition may incur stigma and potentially do less well in school (see section 3.3). A reduction in parenteral nutrition needs may increase a child’s ability to attend school, and increased educational attainment usually leads to health-related quality-of-life benefits. Therefore, the committee acknowledged that there were health-related benefits associated with the effect of teduglutide that were not otherwise accounted for in the modelling, and that it should consider these in its decision-making. However, including these benefits is highly unlikely to lower the ICER several fold, such that it would fall within the acceptable threshold range. The committee concluded that it had considered the needs of children and their families in its decision-making, and did not need to alter its recommendations.

Equality issues

3.35 No equality issues relating to the use of teduglutide were identified.

Life expectancy

3.36 NICE’s advice about life-extending treatments for people with a short life expectancy did not apply.

Discount rate

3.37 The committee was aware that NICE’s guide to the methods of technology appraisal (2013) specifies that the reference case discount rate is 3.5%, but that a discount rate of 1.5% may be used when: treatment restores
people to full or near-full health when they would otherwise die or have severely impaired lives; if it is highly likely that there will be long-term benefits; and if the treatment does not commit the NHS to significant irrecoverable costs. The committee considered whether teduglutide fulfils these criteria. It recognised that the main aim of treatment with teduglutide is to reduce the number of parenteral nutrition days in people with SBS. The committee did not consider this to amount to restoring people to full or near-full health, even when people are weaned off parenteral support, because their underlying condition and its complications are likely to need further treatment. Therefore, the committee concluded that use of a 1.5% discount rate would not be appropriate.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
October, 2017

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.
Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

**NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Boglarka Mikudina**
Technical Lead

**Ahmed Elsada**
Technical Adviser

**Jeremy Powell**
Project Manager

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