

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

# Teduglutide for treating short bowel syndrome

## 1 Recommendations

- 1.1 Teduglutide is recommended, within its marketing authorisation, as an option for treating short bowel syndrome (SBS) in people 1 year and above. People should be stable following a period of intestinal adaptation after surgery before having teduglutide. Teduglutide is recommended only if the company provides it according to the commercial arrangement (see section 2).

### Why the committee made these recommendations

Current treatment for SBS is parenteral support (giving nutrients and fluids intravenously) with best supportive care. Best supportive care includes antimotility and antisecretory medicines, fluid restriction and diet changes.

Clinical trial evidence shows that teduglutide reduces the number of days a week people with SBS need parenteral support compared with placebo. However, how much it reduces this is uncertain because the trial design may not reflect NHS practice.

Because of the uncertainties in the clinical evidence, the cost-effectiveness estimates are uncertain. However, even when accounting for the uncertainties, these estimates are below what NICE normally considers an acceptable use of NHS resources. Therefore, teduglutide is recommended.

## 2 Information about teduglutide

### Marketing authorisation indication

- 2.1 Teduglutide (Revestive, Takeda) is 'indicated for the treatment of patients aged 1 year and above with short bowel syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.'

### Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics for teduglutide](#).

### Price

- 2.3 The list price of a 5 mg vial of teduglutide is £521.98. The list price of a 1.25 mg vial of teduglutide is £260.99 (excluding VAT; BNF online, accessed April 2022).
- 2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes teduglutide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

## 3 Committee discussion

The [appraisal committee](#) considered evidence submitted by Takeda, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

### The condition

#### Short bowel syndrome is a chronic condition with limited treatment options

- 3.1 Short bowel syndrome (SBS) is a chronic and potentially life-threatening condition characterised by reduced absorption of nutrients, water and

electrolytes. SBS is commonly caused by surgery that has been needed to remove abnormal bowel. In adults, this surgery may be needed for a range of conditions, including mesenteric ischaemia, Crohn's disease and radiation enteritis. In children, it is often because of necrotising enterocolitis in premature babies, or other conditions such as volvulus or gastroschisis. Some children can be born with a short bowel. SBS can lead to intestinal failure. This is when the length of intestine remaining means the intestinal functions drops below the necessary level for absorption of nutrients, water and electrolytes. Intestinal failure is classified as type 3 when it is chronic and people need to have parenteral support over months or years. Current treatment for SBS includes parenteral support, in which nutrients and fluids are given intravenously for an average of 10 to 14 hours a day for between 2 and 7 days a week. Most people have parenteral support at home using a permanent intravenous tube. While parenteral support is life-saving, it is very time-consuming, highly complex and its complications can be life-threatening. These include blood infections, blood clots, and kidney and liver failure. Clinical and patient experts both noted that there are currently supply issues with parenteral support, and people with SBS are having to adapt their care to manage this. They also highlighted that administering parenteral support is complicated and challenging for people with SBS and their carers. They emphasised a need for new treatments that offer more normality for those affected by SBS. The committee concluded that SBS is a chronic condition with limited treatment options that can cause further adverse complications.

### **People would welcome new treatment options for short bowel syndrome that reduce the number of days of parenteral support**

3.2 SBS is not only burdensome for the person with the condition, but for their carers too. This burden is often linked to the need to use parenteral support. Patient experts confirmed that parenteral support limits a normal life in many ways, including family, work and social life. Most people with SBS have parenteral support at home, and either administer this

themselves or with a carer's assistance. Patient experts highlighted that this places a huge burden on people with SBS and their carers, because the responsibility of doing complicated procedures at home can be overwhelming. They feel that the impact on carers is often overlooked, and that many families have not had a night off from giving parenteral support in many years. Carers also often feel guilt when people with SBS experience complications such as blood infections because they feel that these would have been avoided if they had done their caring duties correctly. Clinical experts highlighted that there is potential for teduglutide to allow some people with SBS to wean off parenteral support completely, or at least reduce the number of nights per week when they need it. This would greatly increase the quality of life of both people with SBS and their carers. Both clinical and patient experts noted that there is an unmet need to reduce the time spent on parenteral support to increase the quality of life for people with SBS and their carers. The experts emphasised that this was a continuous burden, with little or no respite. They advised that any reduction in the number of nights of treatment would give people respite, which would give them and their family and carers some time to do other activities. Clinical experts explained that a person with SBS would usually have bespoke home parenteral nutrition formulations through compounded parenteral nutrition bags. However, because of the increased demand for parenteral support in England, some people do not have access to these formulations. Instead they are given standard preparations that are more complex to infuse and could result in reduced health. Clinical experts also highlighted that this is likely to incur a higher cost because people are prescribed multiple types of bags to replace what would usually be provided in their compounded parenteral nutrition. The committee agreed that the impact of parenteral support on people with SBS and their carers was high. It concluded that people would welcome new treatment options for SBS that reduce the number of days of parenteral support.

## Treatment pathway and comparators

### Teduglutide is likely to be used once people become stable on parenteral support

3.3 Teduglutide's marketing authorisation is for the treatment of SBS in people 1 year and above who are stable after a period of intestinal adaptation. The company's positioning of teduglutide was aligned with the marketing authorisation. This was highlighted as a decision point in the pathway after the adaptation phase. The adaptation phase is estimated to be up to 2 years in adults but can be longer in children. Clinical experts noted that they would want to use teduglutide for any child who needs routine parenteral support, and they would not want to wait more than 2 years to start treatment. They also highlighted that starting teduglutide might reduce the need for intestinal transplant because transplants would only be indicated for people in whom parenteral support is not working. The committee concluded that teduglutide was likely to be used for people with SBS once their parenteral support needs had been established and stabilised on a regular schedule.

### The only appropriate comparator for teduglutide is parenteral support combined with best supportive care

3.4 For people with SBS, the company submission compared teduglutide with established clinical management including parenteral support with best supportive care (antimotility and antisecretory agents, fluid restriction and dietary optimisation). Further surgical procedures can be done after parenteral support stabilisation to attempt to increase the length of remaining bowel that is in direct continuity. However, because these are rarely done in practice, they were not included as a relevant comparator. Intestinal transplant can also be done if all other treatments fail. This is done in some children, but not routinely. Surgery was not considered a comparator in this appraisal, but avoiding the need for a transplant, which has lifelong consequences, could be a benefit of teduglutide. The

committee concluded that parenteral support with best supportive care was the only appropriate comparator for teduglutide.

## Clinical evidence

### **The clinical trial evidence used in the company model is appropriate, but the patient support programme data is less certain**

3.5 The key clinical evidence for teduglutide came from 1 clinical trial and its long-term open-label extension study, and 1 non-interventional real-world study in adults with SBS:

- STEPS: a phase 3, multinational, randomised, double-blind, placebo-controlled 24-week study and STEPS-2: a 2-year, open-label, multinational extension study for people who had screening or treatment in STEPS.
- PSP: a non-interventional patient support programme (PSP) in Australia.

The company submitted clinical evidence for adults from an extension to STEPS-2 and 1 further clinical trial and its extension that were not included in the economic model:

- STEPS-3: an up to 1 year, open-label extension study for people in STEPS-2 at 5 US sites.
- 004: a phase 3, multinational, randomised, double-blind, placebo-controlled, 24-week study and 005: a 28-week, open-label, multinational, extension study for people who had treatment with teduglutide or placebo in 004.

The company decided not to include STEPS-3 data in its model because the relevant cohort of patients only contained 5 people. 004 and 005 were not included because the results have weak external validity due to the restrictive parenteral support weaning algorithm used as part of the study protocol. The company also submitted evidence from 8 non-interventional real-world studies in adults which were not included in the model.

The company submitted clinical evidence for children from 2 open-label studies and their extensions, but did not include this evidence in the economic model:

- C13: a phase 3, open-label, non-randomised, 12-week study in the UK and US and SHP633-303: its open-label, long-term extension.
- C14: a phase 3, multinational, open-label, non-randomised, 24-week study and SHP633-304: its open-label, multinational, long-term extension.

No clinical data from studies in children was used in the modelling. The company's justification for this was that the trials in children had small sample sizes and non-continuous treatment across follow-on studies. The ERG was satisfied with the company's choice of clinical evidence used in the model. It agreed that STEPS was of good methodological quality. It highlighted the small sample size of STEPS-3 and accepted that the weaning algorithm used in 004 and 005 was not closely matched to clinical practice. It also recognised the small sample numbers in C13, C14 and their extensions. The committee concluded that the clinical trial evidence chosen by the company for use in the model was appropriate.

### **Results from trials in children show that teduglutide reduces parenteral support needs, but there are limitations in the trial design, which justifies the use of adult data for children**

3.6 The company provided efficacy data for children from 2 clinical trials and their long-term extensions. This data was provided to show that the efficacy of teduglutide in children is similar to and may even exceed its efficacy in adults. In C14, the primary outcome was the percentage of people who had a 20% to 100% reduction in parenteral volume from baseline at week 24. This was defined as a 'clinical response'. Reduction in days of parenteral support per week was measured as a secondary outcome. C14 found that more children with SBS had a clinical response on teduglutide compared with the standard care group (69% compared with 11%). Children having teduglutide also had a reduction in days of

parenteral support per week from baseline, while those on standard care did not (1.3 days reduction compared with 0 days). The primary outcome for C13 was the reduction in days of parenteral support per week. The results of this are confidential and cannot be disclosed here. Reduction in parenteral support volume was measured as a secondary outcome. Results from C13 also showed reductions in parenteral volume from baseline at 12 weeks. Results from the extension studies are confidential and cannot be disclosed here. C13, C14 and their extensions were not included in the model because they had small sample sizes and non-continuous treatment with teduglutide (see section 3.5). Instead, the company used adult data to inform both the adult and child base cases. The committee concluded that the results in children did indicate that teduglutide has clinical benefits for children, but they were not suitable for use in the model because of their limitations in study design.

### **Clinical evidence from adult trials shows that teduglutide reduces parenteral support needs**

3.7 In STEPS and STEPS-2, the primary outcome was the percentage of people with SBS who had a 20% to 100% reduction of parenteral volume from baseline at week 20 maintained to week 24. This was defined by the company as a 'clinical response'. A key secondary outcome was the change in days per week of parenteral support from baseline. Both STEPS and STEPS-2 assessed the safety of teduglutide. Outcomes considered from PSP were a 20% to 100% reduction in parenteral support volume from baseline ('clinical response') and change in days per week of parenteral support from baseline. The ERG noted the definition of 'clinical response' differed slightly between STEPS and PSP, but did not consider that it would affect the trial results. Both clinical and patient experts agreed that a reduction in days on parenteral support per week is more valuable to patients than reducing parenteral volume alone. People in the STEPS trial had an average number of days on parenteral support of 5.6 and 5.9 days (teduglutide and placebo arms respectively) before treatment. After treatment, significantly more people with SBS had a 1-day



or more reduction in weekly parenteral support on teduglutide over placebo (53.8% compared with 23.1%). The results from PSP are confidential and cannot be disclosed here. The committee concluded that the clinical evidence indicates that teduglutide reduces parenteral support needs in adults with SBS.

### **The weaning algorithm in STEPS may have affected generalisability of the results in both arms**

3.8 People with SBS taking teduglutide can potentially reduce parenteral support and increase their oral diet through a process known as weaning. The STEPS trial used a weaning algorithm to decide if people with SBS should have their parenteral support reduced. A feature of the STEPS results is the apparent efficacy of placebo, with 23.1% of the placebo arm reducing their days of parenteral support by 1 day or more. The company commented that this is unrealistic, and that any reduction in days of parenteral support per week in the placebo arm were unlikely to be because of improved intestinal function. It emphasised that people entering STEPS had undergone parenteral support optimisation and stabilisation before starting teduglutide or placebo, so any differences in parenteral support over time in the placebo arm could not be explained by further optimisation of care. It suggested that the observed placebo effect is instead a result of the strict weaning algorithm used in the trial that was solely based on urine output. The ERG noted that the company's argument was plausible, and that changes in parenteral support do not rely on urine output alone in clinical practice. The company also stated that people in the placebo arm lost weight over the course of the trial and this indicates that they were not having adequate parenteral support. The committee queried whether this placebo effect reflected clinical practice. The clinical experts explained that in clinical practice clinicians do not know urine output on a day-to-day basis, and so weaning is less precise than in STEPS. They added that the weaning algorithm relying entirely on urine output was unrealistic and that maintaining weight should also be part of the weaning criteria. They clarified that while it may be possible for

adults with SBS temporarily to reduce their parenteral support while having current standard care, this would not be sustainable if medical advice was followed correctly. This means that the placebo effect seen in STEPS did not reflect clinical practice. Conversely, the company also commented that the weaning algorithm used in STEPS in the teduglutide arm underestimated the extent to which parenteral support could be reduced, thereby underestimating the effect of teduglutide. The company's view was that the strict nature of this algorithm was therefore likely to underestimate the relative treatment effect of teduglutide compared with placebo. Also, the weaning algorithm constrained how quickly people were able to wean off parenteral support if they improved on teduglutide. The ERG highlighted that while the weaning algorithm is restrictive and may not reflect clinical practice, it was applied to both arms of the STEPS trial. Therefore, the internal validity of the results could be considered robust, but the absolute effects of teduglutide and placebo may not be valid. The ERG also received clinical feedback that adults on standard care were unlikely to reduce their parenteral support. The committee then explored whether teduglutide might allow some people with SBS to stop parenteral support altogether. Clinical experts commented that they would expect some people taking teduglutide to come off parenteral support entirely, and they have seen such cases in clinical practice. They stated that while some children may be able to wean off parenteral support naturally as their bowel matures and they grow, teduglutide allows them to improve faster and avoid both the clinical and social challenges associated with parenteral support. The committee considered whether it was more important to consider benefits relating to the clinical effectiveness of teduglutide independently, or in comparison with other treatments. The ERG agreed with the company's arguments relating to the impact of the weaning algorithm on the results. Clinical experts confirmed that people on standard care were unlikely to reduce their parenteral support. The committee was unable to come to a clear conclusion on the impact of the weaning algorithm on the trial results, but noted that placebo-controlled trials are usually appropriately designed to

determine the true treatment effect of a new drug. It concluded that the weaning algorithm may have affected generalisability of the results from both arms of STEPS, which made the true relative treatment effect of teduglutide compared with placebo uncertain.

### **The frequency of adverse events is broadly similar between teduglutide and placebo for adults**

3.9 The company provided safety evidence for adults, pooled from STEPS, STEPS-2, 004 and 005. The ERG found that the pooling of safety data from these trials was appropriate. Adults on teduglutide most commonly reported abdominal pain (38.5% compared with 27.1%), gastrointestinal stoma complications (37.8% compared with 13.6%), upper respiratory tract infections (27.5% compared with 13.6%) and abdominal distension (16.5% compared with 1.7%). The frequency and severity of these adverse events were broadly similar between the people having teduglutide and placebo, except for abdominal distension. The company commented that the observed adverse events were likely to be because of pro-absorptive and intestinotrophic effects of teduglutide, insufficient parenteral support weaning or the underlying nature of SBS. The ERG accepted this reasoning following advice from clinical experts. The committee concluded that the overall frequency and severity of adverse events resemble those of the placebo group.

### **The safety profile of teduglutide in children is similar to adults**

3.10 The company also provided safety data for children, pooled from C13, SHP633-303, C14 and SHP633-304. The most common adverse events were vomiting (51.7%), pyrexia (43.8%), upper respiratory tract infection (41.6%), cough (33.7%) and device-related (central venous catheter) infection (29.2%). The ERG commented that the overall rates of adverse events were similar to adults, but respiratory infections, pyrexia, vomiting and catheter complications (including infections) were more common in children than in adults. The company stated that these adverse events would be expected to be more frequent in children. The committee

commented that children are often admitted to hospital with catheter complications, because frequent diarrhoea can mean it is difficult for carers to always keep the catheter completely clean. The committee concluded that the safety profile of teduglutide is similar for adults and children.

## Economic model

### **The estimation of health-state transition probabilities within the model is a source of uncertainty, but is appropriate for decision making**

3.11 The economic model was developed using a Markov structure, comprising 9 health states defined by the days of parenteral support per week (from 7 days to parental support independence or to death). The company included a treatment stopping rule so that modelled teduglutide use would reflect its use in clinical practice as closely as possible. The summary of product characteristics recommends that treatment should be stopped if there is no overall improvement in the condition. It recommends that adults should have an evaluation after 6 months, with treatment continuation being reconsidered if there is no treatment benefit by 12 months. The model reflected this by assuming that those who had not had a reduction of at least 1 day of parenteral support per week at 12 months, compared with baseline, stop teduglutide. Once treatment is stopped, they immediately reverted to their baseline parenteral support state before teduglutide. Teduglutide is modelled to affect both cost and quality-adjusted life years (QALYs).

Costs:

- Drug treatment (teduglutide) costs are increased.
- Costs associated with parenteral support, concomitant drugs, and complications linked to parenteral support are reduced.
- Incidence of adverse events are changed compared with standard care.

QALYs:

- The number of days that people need parenteral support per week is reduced. This is modelled to improve the health-related quality of life of people with SBS and their carers.
- The incidence of complications associated with parenteral support are reduced.
- There are carer benefits.

To calculate transition probabilities for teduglutide, the company pooled clinical data from the teduglutide arms of STEPS and STEPS-2 and data from the PSP when estimating the reductions in parenteral support for the teduglutide group. It explained that it took this approach rather than using the relative treatment effect from the trial because the weaning algorithm in STEPS and STEPS-2 underestimates parenteral support reductions for teduglutide (see section 3.8). The company supported this claim by doing an analysis comparing the percentage of people stopping parenteral support entirely while taking teduglutide between STEPS, PSP, and a combination of other real-world studies. The company also assumed that there is no change in parenteral support in the standard care arm and applied the STEPS baseline parenteral support requirement over the time horizon in the standard care arm of the model. The reasoning for this was that people need to have a stable parenteral support requirement before teduglutide, and reductions in parenteral support would not be expected in clinical practice without teduglutide (see section 3.3). The ERG confirmed that the model structure is appropriate. It advised that the company's explanation for underestimation of teduglutide effectiveness in the STEPS and STEPS-2 trials was plausible, but that any comparison of effects between observational studies and randomised controlled trials should be interpreted with caution. The committee expressed some concern around the company's methodology for estimating transition probabilities. This was specifically related to breaking randomisation when pooling the real-world and teduglutide arm trial data while disregarding the relative treatment effect and placebo data from STEPS. The ERG stated that it

had done a scenario analysis exploring the relative treatment effect of teduglutide from the STEPS data alone. This had a substantial upwards impact on the incremental cost-effectiveness ratio (ICER). But because it received clinical expert feedback that people having standard care would not be expected to reduce their parenteral support needs, the ERG considered this scenario to be conservative and did not incorporate it into its base case. At its first meeting, the committee concluded that the company's approach to modelling health-state transitions in both arms was a source of uncertainty and requested further scenario analyses. In response to these concerns, the company provided 2 scenarios:

- Using STEPS placebo arm data to calculate the first 6 months of transitions within the standard of care arm of the adult base case (only 6 months was considered by the company because it did not consider the placebo effect in STEPS to be sustainable long term).
- Using only data from STEPS or STEPS-2 in the teduglutide arm of the adult base case, rather than pooling data from STEPS, STEPS-2 and PSP.

Both these scenarios had a modest upwards impact on the ICER. The ERG combined the 2 scenarios but stated that this was pessimistic and probably underestimated the benefit of teduglutide. The committee agreed that these scenarios resolved some uncertainty around the calculation of transition probabilities in the model. It concluded that the transition probabilities were a source of uncertainty but were appropriate for decision making.

### **The assumptions and data sources are very similar between the models for adults and children**

3.12 No clinical study data from studies in children was used in the modelling (see section 3.5). The company considered that children would gain more benefit from teduglutide and so using adult data would give a conservative cost-effectiveness estimate for children. Clinical experts confirmed that children have more possibility for intestinal development and their SBS

may be more responsive to treatment. The committee noted that offering teduglutide to children would reduce the likelihood of repeated line infections, because it is more difficult to avoid contamination of the catheter in children. The company decided to model the 2 populations separately. When modelling for children, treatment is allowed to continue beyond the age of 18. After the age of 18, adult model assumptions are applied to this population. The ERG agreed that the 2 populations should be considered separately. The assumptions and data sources are very similar between the models for adults and children. The differences in model assumptions to reflect children included:

- changing the starting age from 50 years to 6 years
- extending the time horizon from 50 years to 94 years
- using an alternative source of survival data (Pironi et al. 2011)
- longer hospital stays and more frequent hospitalisations (line fracture occlusion only)
- 4 specialist visits a year, with additional testing (haematology, inflammatory markers, clinical biochemistry)
- reducing the vial used for delivery from 5 mg teduglutide to 1.25 mg teduglutide
- increasing the number of carers from 1 to 2.

The cost-effectiveness results for children are much more favourable than for adults. The ERG clarified that this is because of the younger starting age and longer time horizon in the model for children. Teduglutide also reduces the costs associated with parenteral support (see section 3.11), and these 2 contributing factors mean that QALYs and cost benefits accrue for longer in the model. The committee concluded that the difference seen between the ICERs for adults and children are plausible.

### **The choice of starting age is appropriate for use in the adult base case**

3.13 The company modelled adults and children separately. To do this, it used different starting ages for the 2 populations. The starting age for the adult base case was 50 years. The company's justification for using this age

was that it was the average age of the STEPS trial population. The committee commented that it was unsure how much this age reflected the average age of adults with SBS in the clinical practice. As a result, the committee requested further justification for the company's choice of starting age and a set of scenarios with different plausible starting ages. The company responded that the mean age of adults with SBS from real-world studies ranged from 46 to 54. So, it did not change its base-case age of 50, but provided scenario analyses in which the starting age was reduced to 40 and 45 years. These scenario analyses resulted in lower ICERs. The ERG agreed with the company's choice of starting age and considered it appropriate to use in the adult base case. The committee concluded that the starting age of 50 was appropriate to use in the adult base case.

### **The company's choice of the log-normal distribution to extrapolate overall survival in adults is acceptable**

3.14 There were very few deaths during the STEPS trial, so the company explained that it was not able to extrapolate overall survival for adults from this data. Instead, overall survival in the adult model is based on extrapolation of published Kaplan–Meier data for people with SBS on long-term parenteral support (Salazar et al. 2021). An alternative source of survival data is used for modelling overall survival in children (see section 3.12). The company chose to use the log-normal curve in its adult base case, based on both statistical fit and predicted hazard functions compared with Salazar et al. 2021. The survival probabilities were adjusted using life tables for England from the Office of National Statistics, to ensure extrapolations did not cause the mortality rate to fall below that of the general population. The ERG questioned if it was plausible for a proportion of people with SBS on long-term parenteral support to have the same mortality as the general population. The ERG explored this using an exponential curve because this retains mortality at a higher level than general population for longer. However, it used the log-normal curve in its base case after accepting that it provides a better fit to the data than the



exponential curve. Clinical experts commented that people with SBS have a near normal life expectancy once weaned off parenteral support. The committee therefore considered the company's assumptions around life expectancy for people on parenteral support to be acceptable. The committee concluded that the log-normal distribution was acceptable for extrapolating overall survival.

### **The company's approach to modelling complications associated with parenteral support is acceptable for decision making**

3.15 Parenteral support can cause complications including intestinal failure associated liver disease (IFALD) and chronic kidney disease (CKD). In the company model, the risk of developing IFALD and CKD increases with days of parenteral support per week. The company explained that teduglutide reduces the incidence of these complications by reducing the number of days of parenteral support needed per week. Clinical experts agreed that teduglutide should reduce the risk of IFALD and CKD by reducing days of parenteral support and improving intestinal fluid absorption. The company did not model a mortality risk for IFALD and CKD. This was because clinical feedback stated that deaths because of these conditions in SBS are very rare, and the real-world data used to inform mortality already includes death from complications. The ERG highlighted that a lack of structural link in the model between the proportion of people with SBS living with complications and risk of death may lead to overestimation of IFALD and CKD over time. It stated that this could cause bias in both directions by overestimating costs and utility losses related to living with IFALD or CKD, and failing to capture the small, expected survival benefit for teduglutide. The committee concluded that the company's approach to modelling these complications was acceptable for decision making.

### **The company's approach to modelling adverse events is appropriate for decision making**

3.16 The company considered 2 time periods when modelling adverse events, based on STEPS (first 6 months) and STEPS-2 (after 6 months). When modelling adverse events in the teduglutide arm, observed adverse events in the teduglutide arm of STEPS were used to estimate a rate per person for the length of STEPS (6 months). This was then divided by 6 to get a per-cycle rate of individual adverse events. A similar method was used when modelling adverse events in the teduglutide arm from 6 months onwards, except the rate per person for the length of STEPS-2 (24 months) was divided by 24 to obtain a per-cycle rate of individual adverse events. When modelling adverse events in the standard care arm, observed adverse events in the placebo arm of STEPS were used. These analyses showed that adverse event rates decreased substantially from 6 months onwards in people taking teduglutide (0.98 adverse events per cycle per person to 0.43 adverse events per cycle per person). The company stated that this was because people became more tolerant to teduglutide as treatment progressed. People on teduglutide also needed less parenteral support so any adverse events relating to this would be reduced in the teduglutide arm compared with the standard care arm. The ERG highlighted that there was no standard care safety data available beyond 6 months to validate these results. However, it was satisfied with the company's explanations of reduced adverse events in the teduglutide arm. Clinical experts agreed that they would expect the rate of adverse events to decrease over time with teduglutide, but only in people who had reductions in days of parenteral support per week. The committee concluded that the company's approach to modelling adverse events was appropriate for decision making.

### **The company's approach to modelling the incidence and costs of line sepsis is appropriate for decision making**

3.17 Another complication of parenteral support is line sepsis. The company model assumes that health-state costs related to line sepsis increase with

the number of days of parenteral support per week. The company explained that time spent on a catheter is recognised as being linked to sepsis incidence. Days of parenteral support per week is equivalent to days when the catheter will need to be manipulated to administer the treatment, and so it is appropriate to vary rates of line sepsis according to this in the model. The ERG commented that its understanding of catheter days is the number of days a catheter is inserted for access, not the number of days it is used for delivering parenteral support. However, it supported the plausibility of a relationship between the number of days of parenteral support per week and risk of line sepsis. Clinical experts agreed that they would expect the risk of line sepsis to be greater when parenteral support is administered more frequently. Also, they would expect some people on teduglutide to not need a central venous catheter at all, meaning related complications would be reduced. The committee concluded that the company's approach to modelling the incidence and costs of line sepsis is appropriate for decision making.

## **Utilities**

### **The health-state utilities from STEPS do not reflect the quality of life of people with SBS**

3.18 When considering impact on quality of life, patients and clinical experts both agreed that a reduction in days of parenteral support per week is the most relevant outcome of teduglutide treatment. STEPS used the SBS-quality-of-life scale, a disease-specific tool to measure quality of life in adults with SBS. People with SBS were asked to rate the influence of SBS on 17 items, including general wellbeing, leisure activities, work life and social life. The company stated that the health-related quality-of-life data collected in STEPS did not show statistically significant quality-of-life differences between teduglutide and standard care after 24 weeks of treatment. The company also argued that the STEPS health-related quality-of-life data showed an inconsistent relationship between days of parenteral support and health-state utilities. When the quality-of-life data

was stratified and mapped to utility values, the highest utility values were seen for 4 days of parenteral support per week. The company explained that this lacked face validity because there was no gain in quality of life for fewer days per week of parenteral support. As a result, the company used values used in health-state vignettes (Ballinger et al. 2018) instead of the quality-of-life data from STEPS in its base case. It also assumed that carer utilities are related to days of parenteral support per week. The ERG accepted the company's use of the vignette utilities but explored uncertainty through various scenario analyses. It stated that the company's approach may exaggerate the quality-of-life benefits from reduction in days of parenteral support per week. However, clinical and patient experts agreed that a reduction of even 1 day of parenteral support per week can have a huge impact for people with SBS. This is because it allows for respite and gives time for normal activities for the person and their family and carers. The committee noted that using vignettes instead of trial data does not meet the NICE reference case. However, it agreed with the company and ERG that the use of vignette utilities was justified in this case.

### **The company's approach to estimating carer disutility is appropriate for decision making**

3.19 Both adults and children with SBS commonly need caregivers for help with day-to-day tasks, complex medical procedures and emotional support. Carer utilities are linked to days of parenteral support per week in the modelling. The company's adult base case assumes that adults will have 1 carer, while its base case for children assumes 2 carers, based on the assumption that the child's parents would act as carers. Patient experts emphasised the challenging experience of being a carer for a person with SBS. They highlighted the amount of time taken to provide caregiving duties as well as the impact of the high responsibility and emotional burden of keeping people with SBS alive and well. They confirmed that the carer role for somebody with SBS had a huge impact on the carer's quality of life. Clinical experts confirmed that the

expectation of carers was high, and they were often formally trained to be able to undertake care that was usually only done in hospitals. The ERG accepted the company's approach to modelling carer disutility. But it did specify that the carers' utilities derived from the UK caregiver survey do not provide support for an association between days of parenteral support per week and carer health-related quality of life. Clinical and patient experts highlighted that a reduction in days of parenteral support per week can have a huge impact on carers of people with SBS. The committee raised concerns that the company may have overestimated carer disutility by assuming children would have 2 carers rather than 1, which would favour teduglutide. It also questioned whether it was appropriate for all adults to have a caregiver. The company clarified that they had calculated adult caregiver requirements using results from a multinational survey that included the UK. In this survey, 21% of adults with SBS did not have a carer, 62% had 1 carer and 17% had 2 carers. From this, a weighted average of 0.96 carers per adult was calculated. The company also provided a scenario analysis in which the carer requirement was reduced from 1 as in the base case to 0.8 carers per adult. This had a small upward impact on the ICER. The ERG agreed with the assumption of 1 caregiver per adult but provided a scenario analysis in which carer disutility and home nurse costs were removed from the model entirely. The committee noted that it would be unrealistic to expect carer requirements to be removed entirely and acknowledged that both clinicians and patient groups supported the assumption that adults need a caregiver. It concluded that the company's approach to estimating carer disutility was appropriate for decision making.

## **Resource use and costs in the economic model**

### **Using the mean price of home parenteral nutrition available on the NHS is appropriate for decision making**

3.20 Parenteral support is provided by the NHS through the home parenteral nutrition (HPN) framework. The company estimated the resource use of

HPN (consisting of parenteral support bags, catheter lock solution [Taurolock] and costs for delivery and nursing) in its original submission based on resource use studies for both adults and children. It obtained prices using publicly available sources and expert input. There are several HPN providers in the HPN framework, each with different prices for the various components of HPN. These prices are confidential so cannot be disclosed here and were not available to the company at the start of the appraisal. According to the NICE methods guide, the price used should be transparent to the NHS and nationally available. When commercial discounts are to be considered, the lowest nationally available tender price should be used. Feedback from NHS England was that choosing the lowest cost HPN provider was unlikely to reflect the price paid across the NHS. The ERG provided ICERs using the lowest cost HPN provider, highest cost HPN provider and the mean price of all HPN providers to explore uncertainties around the true price of HPN in the NHS. When doing this, the ICERs ranged from cost-saving to cost-ineffective. The committee would have preferred for a weighted average of the different provider costs to have been used based on market share data but noted that this was not available. A patient expert highlighted that parenteral support provision and delivery is a very complex area and will differ according to individual needs. They also noted that supply issues add to the complexity. During the consultation period, multiple stakeholders also highlighted current issues with the HPN service, stating that the demand for parenteral support outweighs available supply. They highlighted that teduglutide could ease the parenteral support supply burden, addressing the current inequality and unfairness in the existing distribution of parenteral support. The committee considered the cost of parenteral support to be highly uncertain and noted the large impact on the cost-effectiveness results. After the first committee meeting, the top-level average cost of HPN in the NHS was provided to the company. The company updated its adult base-case analyses with this overall mean price of HPN and provided scenario analyses that varied the cost of parenteral support by plus or minus 20%. The ERG agreed that the mean

price was the most appropriate price to use, but highlighted that the company's pricing for individual components of parenteral support were different to its own because the company was only provided with a top-level average. This meant that the company overestimated the price of some parts of the service, while underestimating others. The committee concluded that using the mean price of HPN was likely to be most appropriate for decision making, because it is unlikely that the lowest HPN price would be accessed by the entire population with SBS.

### **Concomitant medication resource use and costs reflect NHS practice in both the company's and ERG's base cases**

3.21 When on parenteral support, people with SBS often take numerous concomitant medications, including proton pump inhibitors, antimotility agents (such as loperamide and codeine), fragmin and ondansetron. The company estimated the resource use of these concomitant medications following expert discussion and took their costs from the BNF. The ERG also provided scenario analyses exploring different dosing regimens and formulations for the concomitant medications in response to feedback from clinical experts before the committee meeting. During the committee meeting, clinical experts provided clarification around the resource use of concomitant medications for people on parenteral support in clinical practice:

- For adults and children:
  - The company assumed proton pump inhibitors are given intravenously. Experts clarified that they are generally oral treatments, with only around 20% of adults and children with SBS having them intravenously.
  - The company assumed that everyone gets daily fragmin, while experts confirmed that fragmin is only used in around 5% of adults and children with SBS.

- The company assumed that everyone gets daily Taurolock, while experts confirmed Taurolock is only used in about 50% of adults and children with SBS.
- For adults:
  - The company assumed that codeine (an antimotility agent) is an intramuscular injection for SBS, whereas clinical experts confirmed it is always an oral treatment.
  - The company assumed that all adults have ondansetron as a solution for injection. Clinical experts confirmed that it is used in a small proportion of adults (5%) and is usually an oral treatment. It is often offered to people with nausea and vomiting.
- For children:
  - The company assumed that children have antimotility agents daily and assumed that loperamide and codeine were used equally in practice. Clinical experts confirmed that children need less antimotility agents when on teduglutide compared with standard care, and codeine is not generally used in children.
  - The company assumed that all children have ondansetron as a solution for injection. Clinical experts confirmed that ondansetron is not generally used in children.
  - When children become adults they may have different concomitant medication needs compared with people who develop SBS in adulthood.

The clinical experts also confirmed that most concomitant medications are prescribed in primary care. Only intravenous proton pump inhibitors, ondansetron and Taurolock are available as secondary care prescriptions. The committee noted that there will be cost implications of this because of the different prices available to primary and secondary care providers. The company's original base case used higher dosing frequencies and different drug formulations than used in established clinical practice. The ERG's original base case differed from the company's in terms of assumptions surrounding associated medications. However, while the ERG's scenario analyses explored uncertainties around concomitant



medication resource use, it also overestimated the use of concomitant medicines in clinical practice, and therefore the costs (which in the model offsets some of the costs of teduglutide). The ERG confirmed that ondansetron, intravenous proton pump inhibitors, codeine by injection and fragmin were major drivers of the cost-effectiveness results. The committee considered that neither the company's nor the ERG's base case accurately reflected the use of concomitant medications in the NHS. Addressing these overestimates would substantially increase the ICER. In response to this, the company amended its adult base-case analyses to reflect the feedback given by the clinical experts. The ERG agreed with the company's amendments to the concomitant medication assumptions, but also applied eMIT pricing to intravenous proton pump inhibitors and ondansetron because these are initially prescribed in a secondary care setting. The company highlighted that while these are prescribed in secondary care, the long-term use may be through a primary care service. The committee concluded that the concomitant medication assumptions used in the updated company and ERG adult base cases reflected NHS practice, giving a more realistic ICER for teduglutide.

## **Cost-effectiveness estimate**

### **Uncertainties associated with the cost-effectiveness estimates for adults were addressed by the company**

3.22 [NICE's guide to the methods of technology appraisal](#) notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICERs. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. At its first meeting, the committee recommended teduglutide for children despite uncertainties in the evidence, because the cost-effectiveness estimates were well below what NICE normally considers an acceptable use of NHS resources. However, the committee requested further clarification and analyses from the company for adults because the ICER was likely to be

above an acceptable use of NHS resources when its preferences were incorporated. After changes made in response to consultation, the company's updated analyses for adults reflected the committee's preferences as follows:

- an updated base case for adults that aligns dosing and administration assumptions for concomitant medications with NHS practice
- scenario analyses considering different starting ages in the adult model, alongside justification for the starting age used
- scenario analyses applying the placebo arm data from STEPS rather than assuming a steady state for those not on teduglutide.

The company also provided further justification for its adult carer requirement assumptions and increased its patient access scheme discount. The committee noted some uncertainties with the model inputs remained after its second meeting, namely:

- the generalisability of clinical-effectiveness results of both the teduglutide and placebo arms of STEPS (section 3.8)
- the company's approach to estimating health-state transition probabilities for both the teduglutide and standard care arms (section 3.11).

The committee considered that the uncertainty about the generalisability of clinical-effectiveness results from both the teduglutide and placebo arms of STEPS, and other areas of uncertainty in the modelling, would mean that the ICER would have to be comfortably within the acceptable range of cost effectiveness before recommending teduglutide. The committee concluded that while uncertainty remained within the clinical evidence, the company had provided a sufficient response to resolve some of the uncertainties.

## **Teduglutide is likely to be cost effective in both children and adults with SBS**

3.23 At its first meeting, the committee concluded that the company's and ERG's cost-effectiveness estimates for teduglutide in children with SBS were well below what NICE normally considers an acceptable use of NHS resources. Because of confidential commercial arrangements for teduglutide and comparator treatments, the cost-effectiveness results cannot be reported here. However, the committee needed further evidence and analysis relating to adults, and at its first meeting was unable to recommend teduglutide for adults. It considered that the ICER was highly dependent on the costs related to the concomitant medications given alongside parenteral support, and the original ICERs did not reflect concomitant medications given in NHS practice. When the company updated its base case in response to consultation to reflect the committee's preferred assumptions, and increased its patient access scheme discount, the ICER for adults was below an acceptable use of NHS resources (see section 3.21). Scenario analyses exploring the other areas of uncertainty (see section 3.22) did not increase the ICER above an acceptable use of NHS resources. Therefore, teduglutide is considered cost effective for children and adults with the current analyses.

### **Other factors**

3.24 There were no equality issues identified for teduglutide.

### **There may be additional benefits of teduglutide that are not captured in the cost-effectiveness analysis**

3.25 The company considers teduglutide to be innovative because it represents a step change in the treatment of SBS and existing treatment (parenteral support) only manages the symptoms of the disease. The ERG commented that the economic base case for teduglutide hinges on an evidence base with many uncertainties that cannot easily be resolved given the rarity and heterogeneity of SBS. The committee highlighted that there may be an uncaptured benefit to teduglutide in that it may prevent

the need for intestinal transplant when parenteral support has not worked. The ERG noted that this was an important point to consider, but it was not possible to model this because of a lack of data on teduglutide's ability to reduce the need for intestinal transplant. The company stated that its base case for children is conservative because children may benefit more from teduglutide (see section 3.6). But the extent of this benefit is uncertain and may be countered by the fact that some children on standard care also have the potential to reduce their parenteral support needs (see section 3.8). The company also stated that their model only considers people with SBS to have improved quality of life when they reduce their parenteral support needs by 1 day or more. Because of this, people with SBS who reduce their weekly parenteral support volume, but not the number of days they have it across, are assumed to have no benefit. They highlighted that this is unlikely to be the case, because people with SBS will have a better quality of life when having parenteral support for fewer hours per day. Reduced hours of parenteral support per day means more flexibility and people can use the extra time to sleep or enjoy their usual activities. The company stated that these changes in lifestyle are not currently captured in the model. The committee concluded that there may be additional benefits of teduglutide that are not captured in the cost-effectiveness analysis. But the extent of these benefits is unclear because of uncertainties in the evidence.

## **Conclusion**

### **Teduglutide is recommended for treating short bowel syndrome in people aged 1 year or above**

3.26 Teduglutide is recommended for use in the NHS for treating SBS in people aged 1 year or above. The cost-effectiveness estimates for people with SBS were uncertain because of uncertainties within the clinical evidence. But they were highly likely to remain below what is considered an acceptable use of NHS resources, even when accounting for uncertainties.

## 4 Implementation

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has short bowel syndrome and the doctor responsible for their care thinks that teduglutide is the right treatment, it should be available for use, in line with NICE’s recommendations.

## 5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators..

Jane Adam  
Chair, appraisal committee A  
May 2022

## 6 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 A](#).

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.

#### **Emily Leckenby, Sarah Wilkes**

Technical leads

#### **Hannah Nicholas, Ewa Rupniewska**

Technical advisers

#### **Jeremy Powell, Shonagh D'Sylva**

Project manager

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