SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
www.scottishmedicines.org.uk
NHS SCOTLAND
Delta House • 50 West Nile Street • Glasgow • G1 2NP • Tel 0141 225 6999 • Chairman: Dr Alan G MacDonald

teduglutide 5mg and 1.25mg vials of powder and solvent for solution for injection (Revestive®)

SMC No 1139/16

Shire Pharmaceuticals Ltd

12 January 2018 *(Issued 9 March 2018)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the ultra-orphan medicine process

teduglutide (Revestive®) is accepted for restricted use within NHS Scotland.

Indication under review: for the treatment of patients aged one year and above with short bowel syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

SMC restriction: initiation in paediatric patients (aged 1 to 17 years).

Results of one phase III randomised study in adults demonstrated that significantly more patients treated with teduglutide compared with placebo achieved at least a 20% reduction in parenteral support at weeks 20 and 24. A 12-week open-label, non-randomised study in paediatric patients also found parenteral support was reduced with teduglutide compared with standard of care.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of teduglutide. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of patients aged one year and above with short bowel syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

Dosing Information

The recommended dose for adults, children and adolescents (aged one to 17 years) is 0.05mg/kg body weight subcutaneously (SC) once daily. The summary of product characteristics (SPC) includes details of injection volume per body weight using the 5mg vial. A 1.25mg vial is also available for paediatric use (patients with a body weight <20kg).

In adults, the treatment effect should be evaluated after six months. Limited data from clinical studies have shown that some patients may take longer to respond to treatment (i.e., those who still have presence of colon-in-continuity or distal/terminal ileum); if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered. Continued treatment is recommended for patients who have weaned off parenteral nutrition. Due to the heterogeneity of the SBS population, a carefully monitored down-titration of the daily dose may be considered for some patients to optimise tolerability of the treatment.

In paediatric patients (≥one year), a treatment period of 12 weeks is recommended after which treatment effect should be evaluated. There are no data available in paediatric patients after 12 weeks.

Treatment should not be initiated until it is reasonable to assume that a patient is stable following a period of intestinal adaptation. Optimisation and stabilisation of intravenous (IV) fluid and nutrition support should be performed before initiation of treatment. Clinical assessment by the physician should consider individual treatment objectives and patient preferences. Treatment should be stopped if no overall improvement of the patient condition is achieved. Efficacy and safety in all patients should be closely monitored on an ongoing basis according to clinical treatment guidelines.

Treatment should be initiated under the supervision of a medical professional with experience in the treatment of SBS.[1]

Product availability date

September 2014 for 5mg vial. March 2018 for the 1.25mg vial.

Teduglutide has been designated an orphan medicine for the treatment of SBS by the European Medicines Agency (EMA).

Teduglutide also meets SMC ultra-orphan criteria.

Background

Teduglutide is a glucagon-like-peptide-2 (GLP-2) analogue which is licensed for the treatment of short bowel syndrome (SBS) in patients who are aged at least one year and are stable following a period of intestinal adaptation after surgery. It has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth.[1]

Teduglutide for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

SBS is a rare condition which results from surgical resection, congenital defect or disease-related loss of absorption. It is characterised by an inability to maintain protein-energy, fluid, electrolyte or micronutrient balances when on a normal diet. The patient population affected by SBS is heterogeneous depending on the extent and location of intestinal loss. Some patients with intestinal insufficiency are able to adapt metabolically and compensate for their malabsorption by increasing oral or enteral intake. However other patients with intestinal failure depend on parenteral support which is associated with serious complications (including infections and liver damage) and has a negative impact on quality of life. Intestinal transplantation may be an alternative treatment option for a small number of selected patients when other treatments have failed.

Teduglutide is licensed for patients with SBS who are stable following a period of intestinal adaptation after surgery and on parenteral support. The company has indicated that the licensed population represents patients with type III intestinal failure which is defined in guidelines as a chronic condition, in metabolically stable patients, requiring IV supplementation over months or years. It may be reversible or irreversible.[2] Clinical experts consulted by SMC consider that there is an unmet need due to lack of available treatment options for patients with SBS. Teduglutide is the only medicine licensed for the treatment of SBS and it meets SMC ultra-orphan criteria.

A patient and clinician engagement (PACE) meeting was held to consider the added value of teduglutide in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the burden of care for SBS patients with parenteral support which may be administered via a central vein over 10 to 14 hours, three to seven times per week. Administration is usually at night and therefore has high negative impact on the quality of life of patients and carers through loss of sleep. This affects day-time functioning and concentration, making school or work difficult and greatly restricts the activities that patients and their families can be involved in, leading to a feeling of isolation. In addition, the risk of serious complications, including infection and liver failure, is a constant cause of psychological distress to patients, families and carers.

Impact of new technology

Summary of evidence on comparative efficacy

The evidence for use in adults with SBS comes from a pivotal, randomised, double-blind, phase III study (STEPS). Eligible patients were aged ≥18 years with SBS with intestinal failure after major intestinal resection due to injury, cancer, Crohn's disease, vascular disease or volvulus. Patients were dependent on parenteral support at least three times weekly for at least 12 months to meet caloric, fluid or electrolyte needs. The study comprised screening, optimisation and stabilisation periods to determine the patient's minimally tolerated stable volume of parenteral nutrition/IV fluid before randomisation to receive teduglutide (0.05mg/kg/day subcutaneously [SC], n=43) or placebo (n=43) for 24 weeks. Randomisation was stratified by baseline parenteral support volume (≤6 or >6 litres/week). During treatment, attempts were made to reduce the parenteral support volume by 10% to 30% of baseline if the 48 hour urinary volume exceeded the baseline levels by >10% and the oral intake remained constant.[3, 4]

The primary outcome was the percentage of patients who achieved a response (defined as a 20% to 100% reduction from baseline in the weekly parenteral support volume) at week 20 which was maintained at week 24 and was analysed in the intention to treat population which included all randomised patients. Response was achieved by 63% (27/43) of patients in the teduglutide group and 30% (13/43) of patients in the placebo group (p=0.002). Secondary outcomes included mean absolute change from baseline to week 24 in parenteral support, which was a reduction of 4.4 litres/week (from a baseline of 12.9 litres/week) in the teduglutide group compared with a reduction of 2.3 litres/week (from a baseline of 13.2 litres/week) in the placebo group (p<0.001) and percentage change from baseline to week 24 in parenteral support (32% versus 21% respectively, p=0.030). At week 24, no study patients were completely weaned from parenteral support. However, 54% (21/39) and 23% (9/39) of patients allocated to tedulglutide and placebo respectively who completed the study reduced parenteral support by at least one day/week and 21% (8/39) and 7.7% (3/39) respectively by at least two days/week. At baseline, 53% (46/86) patients were receiving parenteral support every day.[3, 4]

Quality of life (QoL) was assessed using the SBS-specific QoL questionnaire (SBS-QoL) which was developed by the submitting company and was considered acceptable by the European Medicines Agency (EMA). In the teduglutide group, there were numerical improvements from baseline to week 24 in all but one of the 17 single item scores and significant improvements in nine of the 17. However, there was no statistically significant difference between teduglutide and placebo in the change in overall SBS-QoL score.[3]

STEPS 2 was a 2-year, open-label, extension which included 76 patients who completed the 24-week treatment period of STEPS (37 in the teduglutide group and 39 in the placebo group) plus an additional 12 patients who completed the optimisation and stabilisation phases of STEPS but were not randomised to study treatment because the study was full. All patients received open-label teduglutide 0.05mg/kg/day SC daily for up to 24 months and 65 patients completed. At the last visit, 65% (57/88) of patients had responded to treatment (reduction of ≥20% in parenteral support). Thirteen patients (15%) were independent of parenteral support at the end of STEPS 2.[5]

Another randomised, double-blind, phase III study (CL0600-004), which was performed before STEPS, compared teduglutide SC 0.10mg/kg/day (n=32) or 0.05mg/kg/day (n=35) with placebo (n=16) in adult patients with SBS due to intestinal resection who were dependent on parenteral

support at least three times per week for at least 12 months.[7] This study also included screening, optimisation and stabilisation periods before randomisation. The primary efficacy outcome was response rate defined as reduction from baseline in parenteral volume of 20 to 100% at weeks 20 and 24 but there was no statistically significant difference between teduglutide 0.10mg/kg/day and placebo: 25% (8/32) versus 6.2% (1/16), p=0.16. The statistical plan stopped further formal testing. However, ad hoc analysis suggested a difference between teduglutide 0.05mg/kg/day and placebo: 46% (16/35) versus 6.2% (1/16), (nominal p=0.007). It was suggested that this discrepancy may have been due to the higher baseline parenteral volumes in the teduglutide 0.10mg/kg/day group. Two patients in the teduglutide 0.05mg/kg/day group were weaned off parenteral support at week 24.

Evidence for use in paediatric patients with SBS comes from an open-label, non-randomised, phase III study. Eligible patients were aged one to 17 years and had a history of at least 12 months of SBS due to major intestinal resection requiring parenteral support for at least 30% of caloric and/or fluid/electrolyte needs which had been stable for at least three months. The study compared three doses of teduglutide (0.0125mg/kg/day, 0.025mg/kg/day, and 0.05mg/kg/day) with standard of care. There was a screening period of at least two weeks before treatment started to ensure eligibility and parenteral support requirements. The treatment period used a staggered sequential approach where safety was assessed in the lowest dose group before the next dose group started treatment. [8, 9]

The primary outcome was the percentage change from baseline to week 12 in parenteral support in terms of volume and calories. The study protocol included guidelines for adjusting volume and calories during the treatment period. Results are presented for the licensed dose of teduglutide (0.05mg/kg/day) and the standard of care groups only and are based on physician-prescribed data. Due to the small study population, statistical analysis was descriptive only. The percentage of patients with ≥10% reduction from baseline to week 12 in parenteral nutrition volume was 53% (8/15) in the teduglutide group and 0% (0/5) in the standard of care group. The percentage of patients with ≥10% reduction from baseline to week 12 in parenteral nutrition calories was 67% (10/15) in the teduglutide group and 0% (0/5) in the standard of care group.[8] Other outcomes included, the percentage of patients with ≥20% reduction from baseline to week 12 in parenteral nutrition volume (53% [8/15] versus 0% (0/5) respectively), the percentage of patients with ≥20% reduction from baseline to week 12 in parenteral nutrition calories (60% [9/15] versus 0% [0/5] respectively) and the mean absolute change from baseline to week 12 in parenteral nutrition volume (-2.57 litres/week [corresponding to a 39% reduction] versus +0.43 litres/week [corresponding to a 7.4% increase]). At week 12, 20% (3/15) of teduglutide patients were weaned off parenteral nutrition. However after a 4-week washout period, two of these patients had reinitiated parenteral nutrition support.[1, 8]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

During the STEPS study, 83% (35/42) of patients treated with teduglutide and 79% (34/43) of patients treated with placebo reported an adverse event and these were serious adverse events in 36% and 28% of patients respectively. Adverse events led to discontinuation in 4.8% of patients treated with teduglutide and 7.0% of patients treated with placebo. The most commonly reported adverse events in the teduglutide and placebo groups respectively were: abdominal pain (31% versus 23%), nausea (29% versus 19%), gastrointestinal stoma change (24% versus 7.0%), abdominal distention (21% versus 2.3%), systemic central line infections (17% versus 16%), peripheral oedema (17% versus 4.7%), urinary tract infection (14% versus 9.3%), flatulence (12% versus 7.0%), vomiting (12% versus 9.3%), fatigue (9.5% versus 7.0%), pyrexia

(9.5% versus 9.3%), diarrhoea (7.1% versus 12%), weight increase (7.1% versus 7.0%), dyspnoea (7.1% versus 0) and nasopharyngitis (7.1% versus 0%).[4]

In the paediatric study, all patients reported at least one adverse event which were generally mild to moderate in severity. Severe adverse events were reported in 33% (5/15) of patients treated with teduglutide (licensed dose) and 20% (1/5) of patients treated with standard of care. There were no discontinuations from the study due to adverse events. The most frequently reported adverse events in the teduglutide (licensed dose) and standard of care groups respectively were: vomiting (47% versus 0%), pyrexia (47% versus 40%), upper respiratory tract infection (27% versus 40%), catheter-related complication (13% versus 20%), abdominal pain (27% versus 20%), fatigue (27% versus 0%), decreased blood bicarbonate (20% versus 40%), diarrhoea (20% versus 20%), injection-site haemorrhage (20% versus 0%), cough (19% versus 20%), headache (14% versus 0%), nausea (13% versus 0%), increased faecal volume (13% versus 0%), viral gastroenteritis (13% versus 20%), dizziness (13% versus 0%) and rash (13% versus 0%). Overall gastro-intestinal-related adverse events were reported in 67% of patients treated with tedulglutide and 20% of patients treated with standard of care.[8, 9]

Summary of clinical effectiveness issues

There are no generally accepted outcomes to assess the efficacy of treatment for SBS and the studies used reductions in parenteral support. In the initial adult study, teduglutide, at a dose higher than licensed, was not found to be significantly better than placebo. In the pivotal adult study (STEPS), this outcome was considered acceptable by the EMA since guidelines within the study protocol defined when and how to adjust the volume of parenteral support. In STEPS, teduglutide reduced the need for parenteral support compared with placebo but no patients were able to be weaned off parenteral support at week 24 which may be the most relevant clinical outcome. However, the EMA notes that this may not be realistic in a severely affected SBS population and more patients allocated to teduglutide achieved a reduction of at least one day/week in parenteral support.[3] Longer-term results in a small number of patients indicate a continued treatment effect with open-label teduglutide for up to three years.[5, 6] The response rate in the placebo group of the STEPS study was relatively high at 30% which may be a result of investigators actively attempting to reduce parenteral support.

Subgroup analyses generally found that the treatment effect was consistent across various subgroups defined by gender, age, stoma/no stoma and colon-in-continuity/colon-not-in-continuity. While responder rates for patients without and with colon-in-continuity were both higher in patients treated with teduglutide than placebo, response was numerically higher for patients without colon-in-continuity than with colon-in-continuity (76% [13/17] and 54% [14/26] respectively in the teduglutide group and 20% [4/20] and 39% [9/23] respectively in the placebo group). Response rates were also numerically higher in teduglutide patients with a stoma than without (71% [15/21] versus 55% [12/22]). The length of remaining small intestine did not affect the response rates.[3, 4] However, these analyses did not provide clear predictors of response on which to select the most suitable patients.

The study outcomes focused on reductions in parenteral support and there is limited information to indicate the impact of the resulting reductions on the nutritional status of patients and the complications of parenteral support. In the STEPS study, it was noted that albumin, as a surrogate marker of nutrition, was lower in patients treated with placebo (-1.7g/L) than with teduglutide (-1.1g/L).[2] In the 12-week paediatric study, stable levels of albumin, calcium, magnesium and phosphate and stable weight suggested that nutritional status was maintained.[7] However longer term data are needed to confirm this and to determine the effect on associated complications of parenteral support, particularly liver disease.

The STEPS study had a number of limitations including a lack of differentiation between parenteral support from parenteral nutrition or parenteral fluid/electrolytes and no recording of dietary intake including oral rehydration solutions. It is therefore unclear if these factors affect response. However the study included stabilisation and optimisation phases to ensure that the baseline parenteral support was required and stable. There was no suggested timing of teduglutide dosing with respect to food and it is unknown if pre- or post-prandial dosing would affect response.[3, 4, 10]

The SBS-QoL assessment did not identify any significant differences between teduglutide and placebo treatment which may have been due to the heterogeneous study population and lack of sensitivity of the measure. In addition, the study was not powered to detect differences in quality of life outcomes. SBS is generally heterogeneous and in the STEPS study this was illustrated by the range in parenteral support requirements (124 to 5000mL/day) and length of remaining small intestine (5 to 343cm).[3, 4]

Evidence from the paediatric study is limited by its open-label, non-randomised design and short, 12-week, duration. However the EMA considered it acceptable to extrapolate results from the adult study to children.[8, 9] Long-term data in children are lacking and the SPC notes that evidence is limited to 12 weeks.[1]

Teduglutide would provide patients with an active treatment for SBS over supportive care. This may offer patients a reduction in the parenteral volume required with the potential to reduce the number of days per week of parenteral support and in some cases avoid the need for continued parenteral support. Patients would require daily SC injections and for responding patients this would be lifelong. Clinical experts consulted by SMC advised that teduglutide offered a therapeutic advancement to reduce parenteral support in patients with SBS.

At the PACE meeting, it was noted that even a small reduction in the level of parenteral support (e.g. of one day per week) could have a high impact in terms of reducing the burden of care and lead to improved quality of life. The potential to reduce central line use could also reduce the risk of infection and associated hospital admissions and antibiotic use.

Patient and clinician engagement (PACE)

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of teduglutide, as an ultra-orphan medicine in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Patient with SBS intestinal failure are dependent on parenteral support to maintain their nutritional requirements. This has a huge impact on the quality of life of patients, families and carers. Loss of sleep due to night-time infusions impairs normal life and makes school or work difficult. The constant threat of complications of parenteral support, including infection risk and liver failure, cause substantial psychological distress to patients, families and carers. These complications are serious and in some cases life-threatening.

- Teduglutide was considered to address an unmet need as there are currently no alternative medicines licensed for treatment of SBS.

- The quality of life for patients, families and carers would be improved by even a small reduction in parenteral support requirements. Any relief from the burden of nightly infusions would improve sleep and family life and allow some patients and carers to return to work or school, all of which raise patient self-esteem and dignity.

- Any reduction in parenteral support would offer the potential to reduce central access, lowering the risk of infection and need for hospitalisation or antibiotics. This would reduce the worry and stress associated with the administration and complications of parenteral support for patients, families and carers.

- A small number of patients may be able to stop parenteral support completely.

- PACE participants considered that teduglutide may be particularly useful for patients with ultra-short bowel or with failed line sites.

Additional Patient and Carer Involvement
We received patient group submissions from PINNT and Short Bowel Survivor and Friends. PINNT is a Charitable Incorporated Organisation. Short Bowel Survivor and Friends is a registered charity. PINNT has received 46.9% pharmaceutical company funding in the past two years, including from the submitting company. Short Bowel Survivor and Friends has not received any pharmaceutical company funding in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of both submissions have been included in the full PACE statement considered by SMC.

Value for money

The company presented a cost-utility analysis which assessed the cost-effectiveness of teduglutide plus standard of care (SoC) versus standard of care alone in adults and paediatrics (aged 1 to 17 years) respectively with SBS. Standard of care included administration of parenteral support (parenteral nutrition, fluids/electrolytes), antimotility and antisecretory agents, fluid restriction and dietary optimisation.

A Markov model was used in both the adult and paediatric patient populations and the structure of the economic models was relatively similar.

The adult model used a 40 year time horizon and consisted of 17 mutually exclusive health states: eight states represented the intensity of parenteral support patients required (from 'no parenteral support required' to 'parenteral support required seven days a week') which were further divided into 'on treatment' and 'off treatment' in the teduglutide arm, and death. Patients could transition from one to any other parenteral support health state during each cycle, remain in their current parenteral support health state, or die. Two non-mutually exclusive health states were introduced to capture potential complications associated with SBS and long-term administration of parenteral support, i.e. intestinal failure-associated liver disease (IFALD) and chronic kidney disease (CKD). Patients could enter the complication health states with a probability determined by level of parenteral support dependence and were subsequently

assigned elevated probability of death and associated medical cost. In sensitivity analysis, a tunnel-state simulating intestinal transplantation was also included in the economic model.

The paediatric model was adapted from the adult model by reducing the number of PS health states due to scarcity of clinical data available and used a 96 year time horizon. The intestinal transplantation tunnel-state was included in the base case analysis as it was considered to be the most important complication in paediatric SBS patients. Based on answers from a Delphi panel of UK experts, four health states were included in the model which represented the intensity of requirements of parenteral support (from 'no parenteral support' to 'high parenteral support').

A stopping rule for teduglutide was applied in the analysis which assumed treatment evaluation at 6 months in adults and 12 weeks in paediatric patients, after which treatment was discontinued if patients did not achieve at least a 20% reduction in volume of parenteral support. Patients who discontinued teduglutide due to insufficient response continued to receive SoC. At the point of discontinuation adult patients were subsequently assigned SoC transition probabilities and reverted to baseline parenteral support requirements. Paediatric patients reverted to the high parenteral support health state after discontinuation. It is also worth noting that patients initiated to teduglutide in the paediatric model who did not discontinue treatment, received teduglutide into adulthood.

The key sources of the clinical data in the adult model included the STEPS and STEPS 2 studies. The paediatric model was informed mainly by the paediatric study referenced above. In both base cases, the observed clinical data were extrapolated assuming that patients responding to the treatment with teduglutide remained in the same parenteral support health state beyond the observed periods (30 months for adult patients and 3 months for paediatric patients) until death; patients receiving SoC reverted to the baseline requirements of parenteral support. The incidence and mortality rates of IFALD and CKD were estimated by the Delphi panel. Published sources were used to estimate the transition from the parenteral support and intestinal transplantation health states to the death health state. The rate of adverse events were taken from both STEPS studies.

Patient utility values were taken from a study performed by the company in which general public representatives valued quality of life of the eight parenteral support health states. The utilities ranged from 0.36 to 0.82 depending on the health state. The analysis also included caregiver utility values which were estimated as midpoints between values reported by carers in a separate study organised by the company and values estimated by the Delphi panel. These midpoints ranged from 0.74 to 1.00 depending on the health state. Utility decrements associated with adverse events were informed by published sources.

The analysis included medicine acquisition and monitoring costs, as well as costs associated with requirements of parenteral support which varied based on number of days parenteral support was administered, and costs associated with IFALD and CKD and adverse events. The inputs were based on two costing studies carried out by the submitting company and published literature.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

With the PAS, the results in the adult population indicated that the ICER for teduglutide versus SoC was £167,331.The results in paediatric patients indicated that the ICER with PAS for teduglutide versus SoC was £49,744.

It should be noted that the company's base case results included carer utilities that would not normally be considered as part of SMC's preferred base case. Therefore, this assumption was excluded from the results referenced above. An analysis presented to include the caregivers' aspect was however relevant for SMC to consider as sensitivity analysis given the ultra-orphan nature of the medicine. The results of selected sensitivity analyses including analyses which captured carer utilities in the economic model are available in Table 1 below.

Table 1: Selected sensitivity analyses results around SMC's preferred base case

Scenario	ICER with PAS
Adult population	
Considering carer utilities in the analysis	£100,562
Reducing time horizon from 40 years to 10 years	£204,762
Assuming that SoC patients maintain PS requirements beyond 24 weeks without reverting to baseline	£217,311
Removing stopping rule for teduglutide from the analysis	£171,220
Patient utilities from mapped STEPS study data	£324,218
Discount rate for health benefits of 1.5%	£132,374
Lower bound of annual cost of PS 7 days a week	£238,730
Stopping rule as per the clinical study	£193,671
Paediatric population	
Considering carer utilities in the analysis	£34,251
Removing stopping rule for teduglutide from the analysis	£113,522
Excluding intestinal transplantation from the analysis	£195,846
Patient utilities from mapped STEPS study data	£131,589
Discount rate for health benefits of 1.5%	£32,792
Lower bound of annual cost of high PS health state	£123,283

The main limitations with the analyses presented included:

- The duration of the clinical trials was relatively short and extensive extrapolation was required to simulate the course of the disease over patients' lives. The STEPS studies informing the adult model had an overall follow-up of only 2.5 years. In addition, the paediatric study informing efficacy of teduglutide in paediatric patients was a small non-randomised, open-label study over a short period of 12 weeks It is acknowledged that the company carried out a number of additional studies (e.g. on quality of life and costs) and UK expert meetings with healthcare professionals (e.g. Delphi panel and advisory boards) to overcome substantial issues associated with the limited data available for this ultra-orphan disease. In addition, by generating further evidence this enabled the company to validate many assumptions used in the analysis and inform the economic models. However, the extrapolation of benefit over the longer term (over 40 and 96 years) remains associated with uncertainty.
- Given the short-term data available and general paucity of individual data from patients with SBS, the model may not have captured potential transitions among the various health states

over the patient's lifetime. In addition, it was assumed that all patients beyond a certain time point (e.g. 30 and 3 months for teduglutide patients in the adult and paediatric models respectively) remain at the same levels of PS requirements indefinitely. Although the company tried to model potential changes in patients moving from one health state to another over time in sensitivity analysis (e.g. using transition probabilities observed within the last monitoring interval), this still may not have captured substantial changes in nutrition requirements as patients grow older.

- There was some inconsistency regarding how parenteral support requirements of SoC and teduglutide groups are dealt with in the base case analysis. Patients receiving SoC reverted to the baseline values after 24 weeks as compared to the responders in the teduglutide arm, in which patients continued to benefit from the treatment based on data from a single arm of the extension study. Although the decrease in days on parenteral support in the teduglutide arm was based on clinical evidence, it is not known whether some changes in the SoC arm could happen over the long-term as well. In a sensitivity analysis, maintaining the same requirements of parenteral support for patients receiving SoC as observed at week 24 over the time horizon increased the ICER (see Table 1 above).
- Utility values were generated mainly from adult participants and transferring them to a paediatric population may not be appropriate, as clinical experts consulted by the company stated that the quality of life in children could be better than that of adults. In addition the base case utility values assigned to patients were gathered from lay members of the general public rather than patients with the condition which may have introduced some bias into the analysis. The company provide a sensitivity analysis which used patient quality of life data from the STEPS study (see Table 1 above); however it is noted that this data source is also associated with limitations when estimating utility values.

*Other data were also assessed but remain commercially confidential.**

Impact beyond direct health benefits and on specialist services

Treatment with teduglutide has the potential to reduce the burden of parenteral support for families and carers of patients with SBS and improve quality of life. Families and carers may be able to enjoy family life and activities and return to work. Reduction in parenteral support associated with teduglutide would be expected to impact on nutritional services. Reduced central line access may also reduce the risk of infection and associated hospital admissions and antibiotic use.

Costs to NHS and Personal Social Services

Population A – Adult
The submitting company estimated there would be 28 patients eligible for treatment with teduglutide in year 1 rising to 45 patients in year 5. The estimated uptake rate was 19% in year 1 (5 patients) and 19% in year 5 (9 patients).

Population B – Paediatric
The submitting company estimated there would be 5 patients eligible for treatment with teduglutide in year 1 rising to 8 patients in year 5. The estimated uptake rate was 19% in year 1 (1 patient) and 19% in year 5 (1 patient).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

Conclusion

The Committee considered the benefits of teduglutide in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as teduglutide is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted teduglutide for restricted use in NHS Scotland.

Additional information: guidelines and protocols

The British Society of Gastroenterology published clinical guidance on the management of patients with a short bowel in 2006.[11] This guideline predates the availability of teduglutide and therefore no recommendations are made regarding its use. However, the guidance does make recommendations regarding nutritional requirements of patients with SBS.

The European Society for Clinical Nutrition and Metabolism (ESPEN) published guidance on chronic intestinal failure in adults in 2016.[2] The guideline makes the following relevant recommendations:

- that patients with chronic intestinal failure due to SBS be carefully informed of the potential benefits and risks associated with growth factor treatments including probabilities of reducing the need for or the weaning from home parenteral nutrition, of quality of life improvement, the expected duration of treatment and expected effects after stopping treatment, the potential adverse effects and risks of and the need for regular monitoring.
- that for carefully selected patients with SBS who are candidates for growth factor treatment, the GPL2-analogue, teduglutide, be the first choice.
- that efficacy of growth factor treatment should be evaluated according to standardised protocols measuring fluids, electrolytes and, whenever possible, energy balance.
- that intestinal growth factors are only prescribed by experts who are experienced in the diagnosis and management of SBS and who have the ability and the facilities to objectively evaluate and balance the benefit and clinical meaningfulness of the interventions versus the inconveniences, adverse effects, potential risks, and cost-effectiveness.

Additional information: comparators

There are no relevant active comparators.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Teduglutide	0.05mg/kg/day by subcutaneous injection	Adult or child weighing between 20kg and 100kg: 190,000 Child weighing up to 20kg*: 94,997

*Cost of 5mg vial from eMIMS on 5 October 2017; cost of 1.25mg vial from company submission. * The 1.25mg vial may provide a sufficient dose for a child weighing up to 25kg but the SPC indicates that this vial is available for patients weighing <20kg. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.*

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This assessment is based on data submitted by the applicant company up to and including 21 November 2017.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG

operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.