Cost-effectiveness of teduglutide (Revestive®) for the treatment of patients aged one year and above with Short Bowel Syndrome.

The NCPE has issued a recommendation regarding the cost-effectiveness of teduglutide (Revestive®). Following NCPE assessment of the applicant's submission, teduglutide (Revestive®) is not considered cost-effective for the treatment of patients aged one year and above with Short Bowel Syndrome and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Shire) economic dossier on the cost effectiveness of teduglutide (Revestive®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **March 2018**

Summary

In July 2017, Shire submitted a pharmacoeconomic assessment to the National Centre for Pharmacoeconomics (NCPE) to support the use of teduglutide for the treatment of patients aged one year and above with Short Bowel Syndrome. Short Bowel Syndrome (SBS) is a chronic and potentially life-threatening condition characterised by reduced absorption of nutrients, water and electrolytes in the intestine. People with SBS can develop chronic intestinal failure, also known as Type III intestinal failure and need long term home based parenteral nutrition. The focus of this appraisal was on patients whose condition is stable on long term parenteral nutrition (PN). In the submission, the applicant refers to parenteral support (PS) which they define as PN together with intraveneous fluids and electrolytes (IV).

Teduglutide has a marketing authorisation for treating SBS in patients aged one year and above, when their intestines have had time to adapt after surgery and the condition is stable. The applicant have proposed that teduglutide would be used in a subset of the SBS population, i.e. patients with SBS and Type III intestinal failure (SBS-IF) whose condition is stable and currently on long term parenteral nutrition.

1. Comparative effectiveness of teduglutide

The main clinical evidence for teduglutide in adults came from STEPS, a 24 week double blind Phase III RCT comparing 24 weeks of treatment with teduglutide (n=43) with placebo (n=43). It included adults with SBS-IF who needed parenteral support (PS) at least three times per week. The primary endpoint of the trial was the percentage of patients whose condition responded at week 20 and in whom there was still a response at week 24. A response was defined as a reduction of 20% or more from baseline in the volume per week of PS. Secondary outcomes were the percentage and absolute change in volume of PS and change in health related quality of life using the Short Bowel Syndrome Quality of Life (SBS-QoL) scale. Patients who completed the 24 week treatment period in STEPS were enrolled into a 2 year open label extension study STEPS2 (n=88). STEPS2 was undertaken to assess the long-term safety, tolerability, and clinical efficacy of teduglutide in patients with SBS-IF. Efficacy endpoints included the change in PS volume from baseline, the percentage

of patients achieving a response (≥20% reduction in PS volume from baseline), duration of response, reduction in days of PS per week and the number of patients who achieved independence from PS. PS volume reductions were observed across all subgroups.

The applicant's submission also included one non-randomised study in the paediatric population (**TED-C13-003**), a 12 week, open-label, multi-centre, phase III study with the objective of determining safety and efficacy/pharmacodynamics of teduglutide in children with SBS IF. The population comprised paediatric patients in the age range of 1-17 with SBS requiring PS. The study recruited 42 patients into four different treatment groups and used a 12-week treatment period only. The primary endpoint was the change in percentage of PS in terms of both volume and calories from baseline to the end of the 12- week treatment period, and results were to be reported by descriptive statistics. In the submitted study reduction in PS calories at week 12 was included as secondary endpoint. Overall, 12 weeks teduglutide treatment was associated with a reduction in PS in terms of volume and calories in children aged 1-14 years, when compared with the group of children treated with standard of care. Three different dose levels were evaluated: 0.0125, 0.025, and 0.05 mg/kg. The adult dose of 0.05 mg/kg was also chosen for the paediatric population. The number of patients achieving a 10% and 20% reduction in PS volume and calories use were higher in the 0.025 mg/kg (71%) and 0.05 mg/kg (53%) dose groups compared with the lowest dose of 0.0125 mg/kg (12.5%) and the standard of care group (0%). Days of PS usage was estimated to be reduced by 1.3 days per week in the 0.05 mg/kg dose group and 0.69 days per week in the 0.025 mg/kg group.

2. Safety of teduglutide

The primary safety analysis for the *adult population* was based on the pooled safety evaluation for all placebo controlled SBS studies (CL0600-004 and CL0600-020). At licensing, the CHMP requested that further safety data be generated through a dedicated registry (International Short Bowel Syndrome Registry).

The overall number of TEAE and TESAE was only slightly higher in the teduglutide treated patients compared to the placebo treated patients. Severity was also comparable in the two groups. However, serious adverse drug reactions (TESAEs considered possibly related to treatment) occurred more often in the teduglutide group than in the placebo group. The same was the case for TEAEs leading to discontinuation.

The most frequently reported adverse events (AEs) were reported from the GI system, e.g. abdominal pain; nausea; vomiting; abdominal distension and constipation. Hepatobiliary and pancreatic events were only reported in teduglutide patients. There was an observed modest increase in CRP which is addressed in the SPC. The proposed registry study is considered relevant for monitoring CRP/cardiovascular events.

There were 3 reports of cancer during teduglutide treatment (including open label treatment). However, updated information provided by the applicant has highlighted no new safety signals.

Safety information in the paediatric population of 42 paediatric patients aged 1-14 years were collected for 16 weeks (12 weeks on study treatment and 4 weeks follow-up). Vomiting, nausea and diarrhoea were most frequently reported. Fatigue (very common), painful defaecation (very common), and dizziness (common) were reported at a higher frequency in paediatric subjects when compared to adults and this is mentioned in the SmPC for the attention of the prescriber. The majority of TEAEs were mild to moderate and no patients discontinued the study due to adverse events. Also, no deaths occurred during the study. The safety database in children is considered limited and this is outlined in the SmPC for the attention of the prescriber.

3. Cost effectiveness of teduglutide

Separate Markov models were developed in MS Excel for the adult and paediatric populations structured around the number of days of PS required per week for patients with SBS-IF. It is assumed that achieving a 20% reduction in PS volume equates to a day off PS.

Adult model

The adult model consists of 8 PS health states, that patients can transition between over time. Each defined health state represents patients who are at the same course of their disease, who incur the same expected level of resource use and cost and are expect to have the same overall level of HRQoL. Specifically, the health states are defined from PS0, representing the patient who is independent of PS, i.e. requiring PS for 0 days per week, through to PS7, where the patient requires some volume of PS every day, i.e. 7 days per week. The patient can transition from any PS health state to any other PS health state during each 28 day cycle, or they can remain in their existing health state. Patients can also die from any cause from

any PS health state. The transition probabilities for the adult model were derived directly from STEPS and STEPS2.

Paediatric model

The paediatric model is a variation of the adult model, with a reduced number of health states: no PS, low-PS requirement (1-3 days per week); mid-PS requirement (4-5 days per week); and high PS requirement (6-7 days per week). The grouping on the number of days was based on the results of a UK Delphi panel. The other difference between the paediatric and adult model was in relation to the time horizon considered (i.e. 40 years in the adult model *vs* 96 years in the paediatric model). The transition probabilities in the paediatric model were derived from TED-C13-003.

Results

The results from the applicant's base case analysis were as follows;

For adults, the total cost of the teduglutide treatment arm was €2,333,766 vs €1,133,314 for the PS arm. The total number of QALYs for the teduglutide arm was 4.33 vs 2.95 for the PS arm. This resulted in a deterministic ICER of €869,538/QALY. The probabilistic ICER calculated for the adult population was €1,036,412/QALY.

For paediatrics, the total cost of the teduglutide treatment arm was €1,950,938 vs €1,349,800 for the PS arm. The total number of QALYs for the teduglutide arm was 3.85 vs 2.73 for the PS arm. This resulted in a deterministic ICER of €537,873/QALY. The probabilistic ICER calculated for the paediatric population was €636,857/QALY.

In considering the applicant's submission and model, the RG noted the limited randomised evidence in the area, while also acknowledging the rarity of the condition. Assumptions regarding how treatment effects were applied in the model together with uncertainty around the impact that teduglutide may have on patients health related quality of life, resulted in a high level of upward uncertainty in the applicants reported ICERs.

Sensitivity analysis

The RG gave due consideration to the parameter uncertainty in the model, which resulted in (deterministic) ICERs ranging from €980,618/QALY to €1,650,465/QALY in the adult population and €550,165/QALY to €926,656/QALY in the paediatric population. The probability of teduglutide being cost effective at €45,000/QALY was 0% in both populations.

4. Budget impact of teduglutide

The list price of teduglutide (0.5mg/kg) is €17,116.44 and €8,558.22 for the adult and paediatric populations, respectively. The cost per patient per year is calculated as €229,439 and €115,123 for the adult and paediatric populations, respectively. The eligible population estimated by the applicant to receive teduglutide in year 1 to year 5 is; 2 (year 1), 3 (year 2), 3 (year 3), 4 (year 4), 4 (year 5). Based on this estimated eligible population, the applicant's predicted 5 year net budget impact for adults and paediatrics is €3,097,053 and €567,981 respectively. These figures are subject to considerable uncertainty.

5. Patient submissions

No patient submissions were received during the course of this appraisal.

6. Conclusion

Teduglutide is licensed for treating patients with SBS aged 1 year and over, when their bowel has had time to adapt after surgery and their condition is stable. The anticipated place in the treatment pathway for teduglutide is in addition to PS.

Following NCPE assessment of the company submission, which is based on the current level of evidence available, teduglutide (Revestive®) is not considered cost-effective for the treatment of patients aged one year and above with Short Bowel Syndrome and therefore is not recommended for reimbursement.