ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Revestive 1.25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 1.25 mg of teduglutide*.
After reconstitution, each vial contains 1.25 mg teduglutide in 0.5 ml of solution, corresponding to a concentration of 2.5 mg/ml.

*A glucagon-like peptide-2 (GLP-2) analogue produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is white and the solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revestive 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.

4.2 Posology and method of administration

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

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 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.

Posology
Paediatric population (≥1 year)
Treatment should be initiated under the supervision of a medical professional with experience in the treatment of paediatric SBS.

The recommended dose of Revestive in children and adolescents (aged 1 to 17 years) is 0.05 mg/kg body weight once daily. The injection volume per body weight when using the 1.25 mg strength vial is

provided in Table 1 below. For paediatric patients with a body weight >20 kg, the 5 mg strength vial should be used.

If a dose is missed, that dose should be injected as soon as possible on that day. A treatment period of 6 months is recommended after which treatment effect should be evaluated. In children below the age of two years, treatment should be evaluated after 12 weeks. There are no data available in paediatric patients after 6 months (see section 5.1).

Table 1

Body weight	**1.25 mg strength** Volume to be injected
5-6 kg	0.10 ml
7-8 kg	0.14 ml
9-10 kg	0.18 ml
11-12 kg	0.22 ml
13-14 kg	0.26 ml
15-16 kg	0.30 ml
17-18 kg	0.34 ml
19-20 kg	0.38 ml
>20 kg	Use the 5 mg strength vial

The safety and efficacy of Revestive in children below 1 year of age have not been established. No data are available.

Special populations
Renal impairment
No dose adjustment is necessary for paediatric patients with mild renal impairment. In paediatric patients with moderate and severe renal impairment (creatinine clearance less than 50 ml/min), and end-stage renal disease, the daily dose should be reduced by 50% (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for paediatric patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B adult subjects. Revestive has not been studied in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Method of administration
The reconstituted solution should be administered by subcutaneous injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen. In case the injection into the abdomen is hampered by pain, scarring or hardening of the tissue, the thigh can also be used. Revestive should not be administered intravenously or intramuscularly.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or trace residues of tetracycline.

Active or suspected malignancy.

Patients with a history of malignancies in the gastrointestinal tract, including the hepatobiliary system and pancreas within the last five years.

4.4 Special warnings and precautions for use

It is strongly recommended that every time Revestive is administered to a patient, the name and lot number of the product are recorded in order to maintain a link between the patient and the lot of the product.

Adults

Colo-rectal polyps
A colonoscopy with removal of polyps should be performed at the time of starting treatment with Revestive. Once yearly follow-up colonoscopies (or alternate imaging) are recommended during the first 2 years of Revestive treatment. Subsequent colonoscopies are recommended at a minimum of five year intervals. An individual assessment whether increased frequency of surveillance is necessary should be performed based on the patient characteristics (e.g., age, underlying disease). See also section 5.1. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of malignancy, Revestive therapy must be discontinued (see section 4.3).

Gastrointestinal neoplasia including hepatobiliary tract
In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. These observations were not confirmed in clinical studies of more than one year duration. If a neoplasia is detected, it should be removed. In case of malignancy, Revestive treatment must be discontinued (see sections 4.3 and 5.3).

Gallbladder and bile ducts
Cases of cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies. In case of gallbladder or bile duct-related symptoms, the need for continued Revestive treatment should be reassessed.

Pancreatic diseases
Pancreatic adverse events such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase have been reported in clinical studies. In case of pancreatic adverse events, the need for continued Revestive treatment should be reassessed.

Monitoring of small bowel, gallbladder and bile ducts, and pancreas
SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of small bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques.

Intestinal obstruction
Cases of intestinal obstruction have been reported in clinical studies. In case of recurrent intestinal obstructions, the need for continued Revestive treatment should be reassessed.

Fluid overload
Fluid overload has been observed in clinical trials. Fluid overload adverse events occurred most frequently during the first 4 weeks of therapy and decreased over time.

Due to increased fluid absorption, patients with cardiovascular disease, such as cardiac insufficiency and hypertension, should be monitored with regard to fluid overload, especially during initiation of therapy. Patients should be advised to contact their physician in case of sudden weight gain, swollen ankles and/or dyspnoea. In general, fluid overload can be prevented by appropriate and timely assessment of parenteral nutrition needs. This assessment should be conducted more frequently within the first months of treatment.

Congestive heart failure has been observed in clinical trials. In case of a significant deterioration of the cardiovascular disease, the need for continued treatment with Revestive should be reassessed.

Management of fluids during treatment with Revestive
In patients receiving Revestive, parenteral support should be reduced carefully and should not be discontinued abruptly. The patient's fluid status should be evaluated following parenteral support reduction and corresponding adjustment performed, as needed.

Concomitant medicinal products
Patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption (see section 4.5).

Special clinical conditions
Revestive has not been studied in patients with severe, clinically unstable concomitant diseases, (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS), or in patients with malignancies within the last five years (see section 4.3). Caution should be exercised when prescribing Revestive.

Hepatic impairment
Revestive has not been studied in patients with severe hepatic impairment. The data from use in subjects with moderate hepatic impairment do not suggest a need for restricted use.

Discontinuation of treatment
Due to the risk of dehydration, discontinuation of treatment with Revestive should be managed carefully.

Paediatric population
See also general precautions for adults under this section.

Colo-rectal polyps/Neoplasia
Prior to initiating treatment with Revestive, faecal occult blood testing should be done for all children and adolescents. Colonoscopy/sigmoidoscopy is required if there is evidence of unexplained blood in the stool. Subsequent faecal occult blood testing should be done annually in children and adolescents while they are receiving Revestive.

Colonoscopy/sigmoidoscopy is recommended for all children and adolescents after one year of treatment, every 5 years thereafter while on continuous treatment with Revestive, and if they have new or unexplained gastrointestinal bleeding.

Excipients
Revestive contains less than 1 mmol sodium (23 mg) per dose. This means that it is essentially 'sodium-free'.

Caution is needed when administering Revestive to persons with a known hypersensitivity to tetracycline (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug-drug interaction studies have been performed. An *in vitro* study indicates that teduglutide does not inhibit cytochrome P450 drug metabolising enzymes. Based upon the pharmacodynamic effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Revestive in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Revestive during pregnancy.

Breast-feeding
It is unknown whether teduglutide is excreted in human milk. In rats, mean teduglutide concentration in milk was less than 3% of the maternal plasma concentration following a single subcutaneous injection of 25 mg/kg. A risk to the breast-fed newborn/infant cannot be excluded. As a precautionary measure it is preferable to avoid the use of Revestive during breast-feeding.

Fertility
There are no data on the effects of teduglutide on human fertility. Animal data do not indicate any impairment of fertility.

4.7 Effects on ability to drive and use machines

Revestive has minor influence on the ability to drive, ride a bicycle, and use machines. However, cases of syncope have been reported in clinical studies (see section 4.8). Such events might impact the ability to drive, ride a bicycle, or use machines.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions were retrieved from 2 placebo-controlled clinical studies with teduglutide in 109 adult patients with SBS treated with doses of 0.05 mg/kg/day and 0.10 mg/kg/day for up to 24 weeks. Approximately 52% of the patients treated with teduglutide experienced adverse reactions (*versus* 36% of the patients given placebo). The most commonly reported adverse reactions were abdominal pain and distension (45%), respiratory tract infections (28%) (including nasopharyngitis, influenza, upper respiratory tract infection, and lower respiratory tract infection), nausea (26%), injection site reactions (26%), headache (16%), and vomiting (14%). Approximately 38% of the treated patients with a stoma experienced gastrointestinal stoma complications. The majority of these reactions were mild or moderate.

No new safety signals have been identified in patients exposed to 0.05 mg/kg/day of teduglutide for up to 30 months in a long-term open-label extension study.

Tabulated list of adverse reactions
Adverse reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. All adverse reactions identified in post-marketing experience are *italicised.*

Frequency **System organ class**	**Very common**	**Common**	**Uncommon**	**Not known**
Infections and infestations	Respiratory tract infection*	*Influenza-like illness*		
Immune system disorders				*Hypersensitivity*
Metabolism and nutrition disorders		Decreased appetite Fluid overload		
Psychiatric disorders		Anxiety Insomnia		
Nervous system disorders	Headache			
Cardiac disorders		Congestive heart failure		
Vascular disorders			Syncope	
Respiratory,		Cough		

Frequency **System organ class**	**Very common**	**Common**	**Uncommon**	**Not known**
thoracic and mediastinal disorders		Dyspnoea		
Gastrointestinal disorders	Abdominal distension Abdominal pain Nausea Vomiting	Colorectal polyp Colonic stenosis Flatulence Intestinal obstruction Pancreatic duct stenosis Pancreatitis† Small intestinal stenosis	Duodenal polyp	*Gastric polyp*
Hepatobiliary disorders		Cholecystitis Cholecystitis acute		
General disorders and administration site conditions	Injection site reaction‡	Oedema peripheral		*Fluid retention*
Injury, poisoning and procedural complications	Gastrointestinal stoma complication			

*Includes the following preferred terms: Nasopharyngitis, Influenza, Upper respiratory tract infection, and Lower respiratory tract infection.

†Includes the following preferred terms: Pancreatitis, *Pancreatitis acute*, and Pancreatitis chronic.

‡Includes the following preferred terms: Injection site haematoma, Injection site erythema, Injection site pain, Injection site swelling and Injection site haemorrhage.

Description of selected adverse reactions

Immunogenicity

Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of Revestive may potentially trigger the development of antibodies. Based on integrated data from two trials in adults with SBS (a 6-month randomised placebo-controlled trial, followed by a 24-month open-label trial), the development of anti-teduglutide antibodies in subjects who received subcutaneous administration of 0.05 mg/kg teduglutide once daily was 3% (2/60) at Month 3, 17% (13/77) at Month 6, 24% (16/67) at Month 12, 33% (11/33) at Month 24, and 48% (14/29) at Month 30. In phase 3 studies with SBS patients who received teduglutide for ≥2 years, 28% of patients developed antibodies against *E. coli* protein (residual host cell protein from the manufacture). The antibody formation has not been associated with clinically relevant safety findings, reduced efficacy or changed pharmacokinetics of Revestive.

Injection site reactions

Injection site reactions occurred in 26% of SBS patients treated with teduglutide, compared to 5% of patients in the placebo arm. The reactions included injection site haematoma, injection site erythema, injection site pain, injection site swelling and injection site haemorrhage (see also section 5.3). The majority of reactions were moderate in severity and no occurrences led to drug discontinuation.

C-reactive protein

Modest increases of C-reactive protein of approximately 25 mg/l have been observed within the first seven days of teduglutide treatment, which decreased continuously under ongoing daily injections. After 24 weeks of teduglutide treatment, patients showed small overall increase in C-reactive protein of approximately 1.5 mg/l on average. These changes were neither associated with any changes in other laboratory parameters nor with any reported clinical symptoms. There were no clinically relevant mean increases of C-reactive protein from baseline following long-term treatment with teduglutide for up to 30 months.

Paediatric population
In two completed clinical trials, there were 87 paediatric subjects (aged 1 to 17 years) enrolled and exposed to teduglutide for a duration of up to 6 months. No subject discontinued the studies due to an adverse event. Overall, the safety profile of teduglutide (including type and frequency of adverse reactions, and immunogenicity) in children and adolescents (ages 1-17 years) was similar to that in adults.

Long-term safety data are not yet available for this paediatric population. No data are available for children under 1 year of age.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The maximum dose of teduglutide studied during clinical development was 86 mg/day for 8 days. No unexpected systemic adverse reactions were seen (see section 4.8).

In the event of an overdose, the patient should be carefully monitored by the medical professional.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX08.

Mechanism of action
The naturally occurring human glucagon-like peptide-2 (GLP-2) is a peptide secreted by L cells of the intestine which is known to increase intestinal and portal blood flow, inhibit gastric acid secretion, and decrease intestinal motility. Teduglutide is an analogue of GLP-2. In several nonclinical studies, teduglutide 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.

Pharmacodynamic effects
Similar to GLP-2, teduglutide is 33 amino acids in length with an amino acid substitution of alanine by glycine at the second position of the N-terminus. The single amino acid substitution relative to naturally occurring GLP-2 results in resistance to *in vivo* degradation by the enzyme dipeptidyl peptidase-IV (DPP-IV), resulting in an extended half-life. Teduglutide increases villus height and crypt depth of the intestinal epithelium.

Based on the findings derived from pre-clinical studies (see sections 4.4 and 5.3) and the proposed mechanism of action with the trophic effects on intestinal mucosa, there appears to be a risk for the promotion of small intestinal and/or colonic neoplasia. The clinical studies conducted could neither exclude nor confirm such an increased risk. Several cases of benign colorectal polyps occurred during the course of the trials, however, the frequency was not increased compared to placebo-treated patients. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment (see section 4.4.), every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g., age and underlying disease, previous occurrence of polyps etc.).

Clinical efficacy

Paediatric population

The efficacy data presented are derived from 2 controlled studies in paediatric patients up to 24 weeks duration. These studies included 101 patients in the following age groups: 5 patients 1-2 years, 56 patients 2 to <6 years, 32 patients 6 to <12 years, 7 patients 12 to <17 years, and 1 patient 17 to <18 years. Despite the limited sample size, which did not allow meaningful statistical comparisons, clinically meaningful, numerical reductions in the requirement for parenteral support were observed across all age groups.

Teduglutide was studied in a 12-week, open-label, clinical study in 42 paediatric subjects aged 1 year through 14 years with SBS who were dependent on parenteral nutrition. The objectives of the study were to evaluate safety, tolerability, and efficacy of teduglutide compared to standard of care. Three (3) doses of teduglutide, 0.0125 mg/kg/day (n=8), 0.025 mg/kg/day (n=14), and 0.05 mg/kg/day (n=15), were investigated for 12 weeks. Five (5) subjects were enrolled in a standard of care cohort.

Complete weaning

Three subjects (3/15, 20%) on the recommended teduglutide dose were weaned off parenteral nutrition by Week 12. After a 4-week washout period, two of these patients had reinitiated parenteral nutrition support.

Reduction in parenteral nutrition volume

The mean change in parenteral nutrition volume from baseline at Week 12 in the ITT population, based on physician-prescribed data, was -2.57 (±3.56) l/week, correlating to a -39.11% (±40.79) mean decrease, compared to 0.43 (±0.75) l/week, correlating to a 7.38% (±12.76) increase in the standard of care cohort. At Week 16 (4 weeks following the end of treatment) parenteral nutrition volume reductions were still evident but less than observed at Week 12 when subjects were still on teduglutide (mean decrease of -31.80% (±39.26) compared to a 3.92% (±16.62) increase in the standard of care group).

Reduction in parenteral nutrition calories

At Week 12, there was a -35.11% (±53.04) mean change from baseline in parenteral nutrition calorie consumption in the ITT population based on physician-prescribed data. The corresponding change in the standard of care cohort was 4.31% (±5.36). At Week 16, the parenteral nutrition calories consumption continued to decrease with percentage mean changes from baseline of -39.15% (±39.08) compared to -0.87% (±9.25) for the standard of care cohort.

Increases in enteral nutrition volume and enteral calories

Based on prescribed data, the mean percentage change from baseline at Week 12 in enteral volume, in the ITT population, was 25.82% (±41.59) compared to 53.65% (±57.01) in the standard of care cohort. The corresponding increase in enteral calories was 58.80% (±64.20), compared to 57.02% (±55.25) in the standard of care cohort.

Reduction in infusion time

The mean decrease from baseline at Week 12 in the number of days/week on parenteral nutrition, in the ITT population based on physician-prescribed data, was -1.36 (±2.37) days/week corresponding to a percentage decrease of -24.49% (±42.46). There was no change from baseline in the standard of care cohort. Four subjects (26.7%) on the recommended teduglutide dose achieved at least a three-day reduction in parenteral nutrition needs.

At Week 12, based on subject diary data, subjects showed mean percentage reductions of 35.55% (±35.23) hours per day compared to baseline, which corresponded to reductions in the hours/day of parenteral nutrition usage of -4.18 (±4.08), while subjects in the standard of care cohort showed minimal change in this parameter at the same time point.

An additional 24-week, randomised, double-blind, multicentre study was conducted in 59 paediatric subjects aged 1 year through 17 years who were dependent on parenteral support. The objective was to evaluate safety/tolerability, pharmacokinetics and efficacy of teduglutide. Two doses of teduglutide

were studied: 0.025 mg/kg/day (n=24) and 0.05 mg/kg/day (n=26); 9 subjects were enrolled in a standard of care (SOC) arm. Randomisation was stratified by age across dose groups. Results below correspond to the ITT population at the recommended dose of 0.05 mg/kg/day.

Complete weaning
Three (3) paediatric subjects in the 0.05 mg/kg group achieved the additional endpoint of enteral autonomy by week 24.

Reduction in parenteral nutrition volume
Based on subject diary data, 18 (69.2%) subjects in the 0.05 mg/kg/day group achieved the primary endpoint of ≥20% reduction in PN/IV volume at end of treatment, compared to baseline; in the SOC arm, 1 (11.1%) subject achieved this endpoint.

The mean change in parenteral nutrition volume from baseline at Week 24, based on subject diary data, was -23.30 (±17.50) mL/kg/day, corresponding to -41.57% (±28.90); the mean change in the SOC arm was -6.03 (±4.5) mL/kg/day (corresponding to a -10.21% [±13.59]).

Reduction in infusion time
At week 24, there was a decrease in the infusion time of -3.03 (±3.84) hours/day in the 0.05 mg/kg/day arm, corresponding to a percentage change of -26.09% (±36.14). The change from baseline in the SOC cohort was -0.21 (±0.69) hours/day (-1.75% [±5.89]).

The mean decrease from baseline at Week 24 in the number of days/week on parenteral nutrition, based on subject diary data, was -1.34 (±2.24) days/week corresponding to a percentage decrease of -21.33% (±34.09). There was no reduction in PN/IV infusion days per week in the SOC arm.

Adults
Teduglutide was studied in 17 patients with SBS allocated to five treatment groups using doses of 0.03, 0.10 or 0.15 mg/kg teduglutide once daily, or 0.05 or 0.075 mg/kg bid in a 21-day open-label, multicenter, dose-ranging study. Treatment resulted in enhanced gastrointestinal fluid absorption of approximately 750-1000 ml/day with improvements in the absorption of macronutrients and electrolytes, decreased stomal or faecal fluid and macronutrients excretion, and enhanced key structural and functional adaptations in the intestinal mucosa. Structural adaptations were transient in nature and returned to baseline levels within three weeks of discontinuing the treatment.

In the pivotal phase 3 double-blind, placebo-controlled study in patients with SBS, who required parenteral nutrition, 43 patients were randomised to a 0.05 mg/kg/day dose of teduglutide and 43 patients to placebo for up to 24 weeks.

The proportion of teduglutide-treated subjects achieving a 20% to 100% reduction of parenteral nutrition at Week 20 and 24 was statistically significantly different from placebo (27 out of 43 subjects, 62.8% *versus* 13 out of 43 patients, 30.2%, p=0.002). Treatment with teduglutide resulted in a 4.4 l/week reduction in parenteral nutrition requirements (from a pre-treatment baseline of 12.9 litres) *versus* 2.3 l/week (from a pre-treatment baseline of 13.2 litres) for placebo at 24 weeks. Twenty-one (21) patients treated with teduglutide (48.8%) *versus* 9 on placebo (20.9%) achieved at least a one day reduction in parenteral nutrition administration (p=0.008).

Ninety-seven percent (97%) of patients (37 out of 39 patients treated with teduglutide) that completed the placebo-controlled study entered a long-term extension study where all patients received 0.05 mg/kg of Revestive daily for up to an additional 2 years. In total 88 patients participated in this extension study, thereof 39 treated with placebo and 12 enrolled, but not randomised, in the previous study; 65 of 88 patients completed the extension study. There continued to be evidence of increased response to treatment for up 2.5 years in all groups exposed to teduglutide in terms of parenteral nutrition volume reduction, gaining additional days off parenteral nutrition per week, and achieving weaning of parenteral support.

Thirty (30) of the 43 teduglutide-treated patients from the pivotal study who entered the extension study completed a total of 30 months of treatment. Of these, 28 patients (93%) achieved a 20% or greater reduction of parenteral support. Of responders in the pivotal study who completed the extension study, 21 out of 22 (96%) sustained their response to teduglutide after an additional 2 years of continuous treatment.

The mean reduction in parenteral nutrition (n=30) was 7.55 l/week (a 65.6% reduction from baseline). Ten (10) subjects were weaned off their parenteral support while on teduglutide treatment for 30 months. Subjects were maintained on teduglutide even if no longer requiring parenteral nutrition. These 10 subjects had required parenteral nutrition support for 1.2 to 15.5 years, and prior to treatment with teduglutide had required between 3.5 l/week and 13.4 l/week of parenteral nutrition support. At the end of study, 21 (70%), 18 (60%) and 18 (60%) of the 30 completers achieved a reduction of 1, 2, or 3 days per week in parenteral support, respectively.

Of the 39 placebo subjects, 29 completed 24 months of treatment with teduglutide. The mean reduction in parenteral nutrition was 3.11 l/week (an additional 28.3% reduction). Sixteen (16, 55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral nutrition. At the end of study, 14 (48.3%), 7 (24.1%) and 5 (17.2%) patients achieved a reduction of 1, 2, or 3 days per week in parenteral nutrition, respectively. Two (2) subjects were weaned off their parenteral support while on teduglutide.

Of the 12 subjects not randomised in the pivotal study, 6 completed 24 months of treatment with teduglutide. The mean reduction in parenteral nutrition was 4.0 l/week (39.4% reduction from baseline – the start of the extension study) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction in parenteral support. At the end of study, 3 (50%), 2 (33%) and 2 (33%) achieved a reduction of 1, 2, or 3 days per week in parenteral nutrition, respectively. One subject was weaned off their parenteral support while on teduglutide.
In another phase 3 double-blind, placebo-controlled study in patients with SBS, who required parenteral nutrition, patients received a 0.05 mg/kg/day dose (n=35), a 0.10 mg/kg/day dose (n=32) of teduglutide or placebo (n=16) for up to 24 weeks.

The primary efficacy analysis of the study results showed no statistically significant difference between the group on teduglutide 0.10 mg/kg/day and the placebo group, while the proportion of subjects receiving the recommended teduglutide dose of 0.05 mg/kg/day achieving at least a 20% reduction of parenteral nutrition at Week 20 and 24 was statistically significantly different *versus* placebo (46% *versus* 6.3%, $p<0.01$). Treatment with teduglutide resulted in a 2.5 l/week reduction in parenteral nutrition requirements (from a pre-treatment baseline of 9.6 litres) *versus* 0.9 l/week (from a pre-treatment baseline of 10.7 litres) for placebo at 24 weeks.

Teduglutide treatment induced expansion of the absorptive epithelium by significantly increasing villus height in the small intestine.

Sixty-five (65) patients entered a follow-up SBS study for up to an additional 28 weeks of treatment. Patients on teduglutide maintained their previous dose assignment throughout the extension phase, while placebo patients were randomised to active treatment, either 0.05 or 0.10 mg/kg/day.

Of the patients who achieved at least a 20% reduction of parenteral nutrition at Weeks 20 and 24 in the initial study, 75% sustained this response on teduglutide after up to 1 year of continuous treatment.

The mean reduction of weekly parenteral nutrition volume was 4.9 l/week (52% reduction from baseline) after one year of continuous teduglutide treatment.

Two (2) patients on the recommended teduglutide dose were weaned off parenteral nutrition by Week 24. One additional patient in the follow-up study was weaned off parenteral nutrition.

The European Medicines Agency has deferred the obligation to submit the results of studies with Revestive in one or more subsets of the paediatric population in the treatment of SBS (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Teduglutide was rapidly absorbed from subcutaneous injection sites with maximum plasma levels occurring approximately 3-5 hours after dose administration at all dose levels. The absolute bioavailability of subcutaneous teduglutide is high (88%). No accumulation of teduglutide was observed following repeated subcutaneous administration.

Distribution
Following subcutaneous administration, teduglutide has an apparent volume of distribution of 26 litres in patients with SBS.

Biotransformation
The metabolism of teduglutide is not fully known. Since teduglutide is a peptide it is likely that it follows the principal mechanism for peptide metabolism.

Elimination
Teduglutide has a terminal elimination half-life of approximately 2 hours. Following intravenous administration teduglutide plasma clearance was approximately 127 ml/hr/kg which is equivalent to the glomerular filtration rate (GFR). Renal elimination was confirmed in a study investigating pharmacokinetics in subjects with renal impairment. No accumulation of teduglutide was observed following repeated subcutaneous administrations.

Dose linearity
The rate and extent of absorption of teduglutide is dose-proportional at single and repeated subcutaneous doses up to 20 mg.

Pharmacokinetics in subpopulations
Paediatric population
Following subcutaneous administration, similar C_{max} of teduglutide across age groups was demonstrated by population pharmacokinetics modelling. However, lower exposure (AUC) and shorter half-life were seen in paediatric patients 1 to 17 years of age, as compared with adults. The pharmacokinetic profile of Revestive in this paediatric population, as evaluated by clearance and volume of distribution, was different from that observed in adults after correcting for body weights. Specifically, clearance decreases with increasing age from 1 year old to adults. No data are available for paediatric patients with moderate to severe renal impairment and end-stage renal disease (ESRD).

Gender
No clinically relevant gender differences were observed in clinical studies.

Elderly
In a phase 1 study no difference in pharmacokinetics of teduglutide could be detected between healthy subjects younger than 65 years *versus* older than 65 years. Experience in subjects 75 years and above is limited.

Hepatic impairment
In a phase 1 study the effect of hepatic impairment on the pharmacokinetics of teduglutide following subcutaneous administration of 20 mg teduglutide was investigated. The maximum exposure and the overall extent of exposure to teduglutide following single 20 mg subcutaneous doses were lower (10-15%) in subjects with moderate hepatic impairment relative to those in healthy matched controls.

Renal impairment
In a phase 1 study, the effect of renal impairment on the pharmacokinetics of teduglutide following subcutaneous administration of 10 mg teduglutide was investigated. With progressive renal impairment up to and including end-stage renal disease the primary pharmacokinetic parameters of teduglutide increased up to a factor of 2.6 (AUC_{inf}) and 2.1 (C_{max}) compared to healthy subjects.

5.3 Preclinical safety data

Hyperplasia in the gall bladder, hepatic biliary ducts, and pancreatic ducts were observed in subchronic and chronic toxicology studies. These observations were potentially associated with the expected intended pharmacology of teduglutide and were to a varying degree reversible within an 8-13 week recovery period following chronic administration.

Injection site reactions
In pre-clinical studies, severe granulomatous inflammations were found associated with the injection sites.

Carcinogenicity / mutagenicity
Teduglutide was negative when tested in the standard battery of tests for genotoxicity.

In a rat carcinogenicity study, treatment related benign neoplasms included tumours of the bile duct epithelium in males exposed to teduglutide plasma levels approximately 32- and 155-fold higher than obtained in patients administered the recommended daily dose (incidence of 1 out of 44 and 4 out of 48, respectively). Adenomas of the jejunal mucosa were observed in 1 out of 50 males and 5 out of 50 males exposed to teduglutide plasma levels approximately 10- and 155-fold higher than obtained in patients administered the recommended daily dose. In addition, a jejunal adenocarcinoma was observed in a male rat administered the lowest dose tested (animal:human plasma exposure margin of approximately 10-fold).

Reproductive and developmental toxicity
Reproductive and developmental toxicity studies evaluating teduglutide have been carried out in rats and rabbits at doses of 0, 2, 10 and 50 mg/kg/day subcutaneously. Teduglutide was not associated with effects on reproductive performance, *in utero* or developmental parameters measured in studies to investigate fertility, embryo-foetal development and pre- and post-natal development. Pharmacokinetic data demonstrated that the teduglutide exposure of foetal rabbits and suckling rat pups was very low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
L-histidine
Mannitol
Sodium phosphate monohydrate
Disodium phosphate heptahydrate

Solvent
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials
4 years.

Reconstituted product
Chemical and physical in-use stablility has been demonstrated for 24 hours up to 25°C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder
3 ml vial (glass) with rubber stopper (bromobutyl) containing 1.25 mg teduglutide.

Solvent
Pre-filled syringe (glass) with plungers (bromobutyl) containing 0.5 ml of solvent.

Pack size of 28 vials of powder with 28 pre-filled syringes.

6.6 Special precautions for disposal and other handling

Determination of the number of vials needed for administration of one dose must be based on the individual patient's weight and the recommended dose of 0.05 mg/kg/day. The physician should at each visit weigh the patient, determine the daily dose to be administered until next visit and inform the patient accordingly.

A table with the injection volumes based on the recommended dose per body weight for paediatric patients is provided in section 4.2.

The pre-filled syringe must be assembled with a reconstitution needle.

The powder in the vial must then be dissolved by adding all the solvent from the pre-filled syringe.

The vial should not be shaken, but can be rolled between the palms and gently turned upside-down once. Once a clear colourless solution is formed in the vial, the solution should be sucked up into a 1 ml injection syringe (or 0.5 ml or smaller injection syringe for paediatric use) with scale intervals of 0.02 ml or smaller (not included in the pack).

If two vials are needed, the procedure for the second vial must be repeated and the additional solution sucked up into the injection syringe containing the solution from the first vial. Any volume exceeding the prescribed dose in ml must be expelled and discarded.

The solution must be injected subcutaneously into a cleaned area on the abdomen, or if this is not possible, on the thigh (see section 4.2 Method of administration) using a thin needle for subcutaneous injection suitable for paediatric use.

Detailed instructions on the preparation and injection of Revestive are provided in the package leaflet.

The solution must not be used if it is cloudy or contains particulate matter.

For single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

All needles and syringes should be disposed of in a sharps disposal container.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited
Block 2 & 3 Miesian Plaza
50 – 58 Baggot Street Lower
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/787/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 August 2012
Date of latest renewal: 23 June 2017

10. DATE OF REVISION OF THE TEXT

January 2019

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.