VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of Disease Epidemiology

SBS is a serious, disabling, socially incapacitating and potentially life-threatening condition, which may result from surgical resection of a large portion of the bowel, congenital defect, or disease-associated loss of absorption. The body is unable to absorb the necessary carbohydrates, fats, proteins, fluids, and nutrients necessary to maintain normal health. Clinical manifestations include malnutrition, dehydration, diarrhoea and fatty stools. Currently the treatment is supportive and consists primarily of feeding the subjects intravenously (parenteral therapy).

VI.2.2 Summary of Treatment Benefits

The safety and effectiveness of REVESTIVE was studied in 190 patients with SBS who required at least 3 days of PN a week for 12 months. Effectiveness of the drug was determined by measuring the reduction in volume and days of IV feedings required to maintain health. The most significant reductions were for those patients who received 24 weeks of therapy and continued treatment for another 24 months. Of these patients, 33% completely weaned off of PN/IV feedings and 60% had a reduction in their PN/IV feedings of at least 3 days. Additional studies have shown that the beneficial effects are long-lasting with evidence of increased effectiveness occurring with REVESTIVE for up to 30 months. In an additional study 37 children, aged 1 year through 14 years with SBS dependent on parenteral support, were able to reduce PN by 39% and advance enteral feeds by 58%. In children with a teduglutide dose of 0.05 mg/kg/day, 3 out of 15 (20%) children experienced complete weaning by the end of the 12 weeks treatment, 1 child came off PN as early as week 4 and 4 out of 15 (27%) children had an additional 3 days per week off their parenteral support. On a per day basis, teduglutide was able to reduce infusion time by 4 hours. Overall the safety profile of REVESTIVE in children was similar to that in adults.

VI.2.3 Unknowns Relating to Treatment Benefits

Teduglutide has not been studied in children less below 1 year of age, pregnant women, and in patients with severe, unstable concomitant clinical conditions, including severe hepatic impairment. In addition, only 149 subjects received the drug for more than 1 year.

VI.2.4 Summary of Safety Concerns

Important Identified Risks		
Risk	**What is Known**	**Preventability**
Gall bladder and bile duct problems	Possible side effects include reduced flow of bile from the gallbladder and/or inflammation of the gallbladder. SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of short bowel	Contact your doctor or the emergency unit if you experience yellowing of the skin and the whites in the eyes, itching, dark urine and light-coloured stools or pain in the upper right side or middle of the stomach area. Your doctor will take special care and

Important Identified Risks		
Risk	**What is Known**	**Preventability**
	function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory and appropriate imaging tests. Cases of inflammation of the gall bladder, stones in the gallbladder and an infection of the common bile duct have been reported in clinical studies. In case of gallbladder or bile duct-related symptoms, the need for continued REVESTIVE treatment should be re-evaluated.	monitor your small bowel function and monitor for signs and symptoms indicating problems with your gallbladder, bile ducts and pancreas.
Pancreatic adverse events such as chronic and acute inflammation of the pancreas (pancreatitis), narrowing of the pancreatic duct, pancreas infection and increased blood amylase and lipase (tests that measure how well your pancreas is working)	SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of short bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory and appropriate imaging tests. Pancreatic AEs such as chronic and acute inflammation of the pancreas (pancreatitis), narrowing of the pancreatic duct, pancreas infection and increased blood amylase and lipase (tests that measure how well your pancreas is working) have been reported in clinical studies. In case of pancreatic AEs, the need for continued REVESTIVE treatment should be re-evaluated.	Seek immediate medical attention if you should develop inflammation of the pancreas (pancreatitis). Contact your doctor or the emergency unit if you experience severe stomach ache and fever.
Problems of the heart and blood vessels that are caused by fluid retention	Administration of REVESTIVE causes increased fluid absorption from the stomach and intestines. Inadequate or delayed adjustment of the volume of PN may lead to too much fluid in the blood.	Talk to your doctor before using REVESTIVE if you suffer from certain cardiovascular diseases (affecting the heart and/or blood vessels) such as high blood pressure (hypertension) or have a weak heart (cardiac insufficiency). The symptoms include sudden weight gain, swollen ankles and/or shortness of breath. Due to increased fluid absorption, patients with cardiovascular disease, such as a weak heart and high blood pressure, should be monitored with regard to fluid retention, especially during the beginning of therapy. Talk to your doctor in case of sudden weight gain, swollen ankles and/or shortness of breath. In general, fluid retention can be prevented by appropriate and timely evaluation of PN needs. This evaluation should be conducted more often within

Important Identified Risks		
Risk	**What is Known**	**Preventability**
		the first months of treatment. In case of worsening cardiovascular disease, the need for continued REVESTIVE treatment should be reassessed.
Narrowing and blockage of the ducts of the stomach and intestines	Rapid cell growth and increased blood flow in the lining of the intestines can cause blockage of the bowel with REVESTIVE treatment. Cases of intestinal blockage have been reported in clinical studies. In case of recurrent intestinal blockages, the need for continued REVESTIVE treatment should be re-evaluated.	SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of short bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory and appropriate imaging tests. Contact your doctor or the emergency unit if you experience severe stomach ache, vomiting and constipation. *Children and adolescents* Medical check-ups before and during treatment with REVESTIVE Before you start treatment with this medicine, you will also need to have undergone a recent (i.e. within 6 months) abdominal ultrasound (a procedure used to examine organs in your abdomen) to check for any issues with your gallbladder and an upper GI tract radiography (a procedure using radiation to take a picture [X-ray]) to see if you have any abnormal narrowing of your GI tract.
Stoma (an artificial opening for waste removal) complications	Patients with SBS had multiple or extensive intestinal surgeries, which partially lead to the construction of GI stoma.	Ongoing monitoring for signs and symptoms of GI complications should be practiced by patients and their physicians.

Important Identified Risks		
Risk	**What is Known**	**Preventability**
Growth of small, abnormal growths (polyps) in the intestine that were present before starting treatment with REVESTIVE	REVESTIVE may cause the growth of intestinal cells including abnormal growths that were present before starting treatment. Those growths are limited to the stomach, intestines, liver, gall bladder and bile ducts. This was not seen during clinical trials.	Before you start treatment with this medicine, your doctor will need to perform a colonoscopy (a procedure to see inside your colon and rectum) to check for the presence of polyps (small abnormal growths) and remove them. It is recommended that your doctor performs these examinations once a year during the first 2 years after starting treatment, and then at a minimum of 5-year intervals. If polyps are found either before or during your treatment with REVESTIVE, your doctor will decide whether you should continue using this medicine. REVESTIVE should not be used if a cancer is detected during your colonoscopy. *Children and adolescents* Medical check-ups before and during treatment with REVESTIVE Before you start treatment with this medicine, if you are at least 12 years of age, you will need to have undergone a recent (i.e. within 1 year) colonoscopy (a procedure to see inside your colon and rectum) to check for the presence of polyps (small abnormal growths) and remove them. This procedure will also be performed if you are under 12 years of age and have unexplained blood in your bowel movements (stools). If polyps are found before your treatment with REVESTIVE, your doctor will decide whether you should use this medicine. REVESTIVE should not be used if a cancer is detected during your colonoscopy.
Non-cancerous growths of the stomach, intestines, liver, gall bladder and bile ducts	REVESTIVE may cause the growth of intestinal cells including abnormal growths that were present before starting treatment. Those growths are limited to the stomach, intestines, liver, gall bladder and bile ducts. This was not seen during clinical trials.	Patients are not to use REVESTIVE if they have or are suspected to have cancer and if they have had cancer in the stomach, intestines, liver, gallbladder or bile ducts, in the last 5 years.

Important Identified Risks		
Risk	**What is Known**	**Preventability**
Potential to cause tumours	REVESTIVE may cause the growth of intestinal cells including abnormal growths that were present before starting treatment. Those growths are limited to the stomach, intestines, liver, gall bladder and bile ducts. This was not seen during clinical trials.	Patients are not to use REVESTIVE if they have or are suspected to have cancer and if they have had cancer in the stomach, intestines, liver, gallbladder or bile ducts, in the last 5 years.
Immune response to REVESTIVE (Occurrence of anti-teduglutide antibodies, cross reactivity with GLP-2, and occurrence of anti-ECP antibodies (and associated clinical immunogenicity reactions))	Antibodies are proteins created by the body's immune system to help protect it against bacteria, viruses and other harmful substances. You may develop antibodies to REVESTIVE. Decreased effectiveness of REVESTIVE due to these antibodies was not observed in clinical trials. The occurrence of anti-ECP antibodies may be an indication that the immune system in general responds to impurities of the medicinal product. There is, however, no indication, that the natural tolerance against endogenous peptides is affected. It is theoretically possible that an immune reaction towards ECP or teduglutide, which occurs in a subject, may clinically manifest as a hypersensitivity reaction. The occurrence of anti-ECP antibodies may be a direct indication that the immune system responds specifically to impurities of the medicinal product.	It cannot be prevented. In Phase 3 studies with SBS patients who received REVESTIVE for ≥ 2 years, 39% of patients developed anti-teduglutide antibodies and 21% of patients developed antibodies against ECP (residual host cell protein from the manufacture). The antibody formation has not been associated with clinically relevant safety findings, reduced efficacy or changed PK of REVESTIVE. Antibodies were not measured in these subjects as there is no commercially available assay
Anxiety	The potential effect of REVESTIVE on anxiety is not known.	Anxiety is listed as an undesirable effect of the drug. Ongoing evaluation for signs and symptoms of anxiety should be practiced by patients and their physicians.

AE=adverse event; ECP=E. coli protein; GI=gastrointestinal; GLP-2=glucagon-like peptide; PK=pharmacokinetics; PN=parenteral nutrition; SBS=short bowel syndrome

Important Potential Risks	
Risk	**What is Known (Including reason why it is considered a potential risk)**
Undesirable experiences associated with increased absorption of oral medications taken in conjunction with REVESTIVE	REVESTIVE may improve intestinal absorption, which potentially increases the effects of other medications taken in conjunction with REVESTIVE (concomitant medication). This may result in effects that can be dangerous or toxic to the patient. Per the SmPC: Concomitant medication: Patients receiving oral concomitant medication requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption. 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 CYP450 drug metabolising enzymes. Based upon the PD effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products. Patient might be asked or speak to their physician whether his concomitant medications or doses need to be changed over time.
Increased C-Reactive Protein	As noted in studies in healthy volunteers, REVESTIVE treatment resulted in a transient increase in CRP during the first days of treatment. During daily administration of REVESTIVE CRP levels were highest on Day 3 and returned to baseline levels within a week after stopping treatment.
Local skin reactions	The mechanism is unknown. However, REVESTIVE is a peptide drug, which may contain impurities from the production process. SC injection of such drug may lead to activation of the immune system which may cause symptoms such as injection site erythema, injection site haematoma and injection site pain. The patient should choose alternating injection sites in order to avoid repeated and permanent trigger of the same area of the skin.
Potential off-label use in patients with active Crohn's disease	Results from clinical studies with teduglutide in subjects with active Crohn's disease were published including a claim for a potential effect of teduglutide (Buchman et al., 2010). Although teduglutide may be used off-label to treat Crohn's disease, the risk profile for SBS subjects and active Crohn's disease subjects as determined in clinical trials is believed to be comparable, i.e. no increased clinical risk is expected in case of off-label use of teduglutide in active Crohn's disease. Per the current SmPC: REVESTIVE is indicated for the treatment of patients aged 1 year and above with SBS. Patients should be stable following a period of intestinal adaptation. *Adults* Treatment should be initiated under the supervision of a medical professional with experience in the treatment of SBS. *Paediatrics* Treatment should be initiated under the supervision of a medical professional with experience in the treatment of paediatric SBS. This medicine should not be used in children under 1 year of age. This is because there is no experience with REVESTIVE in this age group
Medication errors	Medication errors can never be fully excluded. No AEs were reported in cases of overdose. Per the Package Leaflet: **Dose**

	The recommended daily dose is 0.05 mg per kg body weight. The dose will be given in mL of solution. Your doctor will choose the dose that is right for you depending on your body weight. Your doctor will tell you which dose to inject. If you are not sure, ask your doctor, pharmacist or nurse. **If you use more REVESTIVE than you should** If you inject more REVESTIVE than you are told to by your doctor, you should contact your doctor, pharmacist or nurse. **If you forget to use REVESTIVE** If you forget to inject this medicine (or cannot inject it at your usual time), use it as soon as possible on that day. Never use more than one injection in the same day. Do not inject a double dose to make up for a forgotten dose.
Compromised nutritional status	REVESTIVE may improve intestinal absorption, which may require adjustment of the volume of your parenteral (IV) nutrition. This change may imbalance your need of vitamins, minerals and micronutrients. The SmPC recommends optimising nutrition before starting therapy and evaluating treatment effects after 6 months. This includes nutritional status. Your doctor will monitor the nutritional status on a regular basis including macronutrients, micronutrients, vitamins and minerals and correct your nutrition and PN to prevent energy malnutrition and nutrient deficiencies.

AE=adverse event; CRP=C-reactive protein; CYP450=cytochrome P450; IV=intravenous; PD=pharmacodynamic; PN=parenteral nutrition; SBS=short bowel syndrome; SC=subcutaneous; SmPC=Summary of Product Characteristics

Missing Information

Risk	What is Known
Lack of experience in subjects with other several, unstable medical conditions	The SmPC states that 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 5 years. The SmPC advises that caution should be exercised when prescribing REVESTIVE.
Lack of experience in pregnant or lactating women	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. As a precautionary measure, it is preferable to avoid the use of REVESTIVE during pregnancy.
Lack of experience in the paediatric population	The safety and efficacy of REVESTIVE in children below 1 year of age has not been established. In one completed clinical study, there were 37 paediatric subjects (aged 1 to 14 years) enrolled and exposed to REVESTIVE for a duration of 12 weeks. No significant hepatobiliary events or events related to intestinal obstruction or fluid overload occurred. No subject discontinued the study due to an AE. Overall, the safety profile of REVESTIVE in children and adolescents was similar to that in adults.
Long-term safety in the paediatric population	Long-term safety data are not yet available for this paediatric population. No data are available for children under 1 year of age.
Limited longer-term safety data over one year exposure	Data for Registry protocol TED-R13-002 are not yet available. A total of 106 individuals were exposed to teduglutide for 1 year and 43 individuals were exposed to teduglutide at least 2 years or longer. In Study TED-C11-001, 14 subjects in this long-term study were enrolled following up to 30 months of treatment with teduglutide (24 weeks of exposure in the in the placebo-controlled study, CL0600-020, and 24 months of exposure in the

	open label extension study, CL0600-021). Preliminary safety and efficacy data from this study indicated that long-term treatment with teduglutide continues to be safe and well tolerated while efficacy is maintained or further enhanced. Given the small number of subjects in this study, only descriptive statistics were employed. The SAE profile for the subjects with this exposure is similar to the SAE profile seen with shorter exposures. No safety signals were identified with long-term use. All of the potential risks of REVESTIVE use are considered acceptable and manageable in view of the high unmet need in the orphan disease of SBS with intestinal failure. The results from long-term extension studies demonstrate that the benefits of teduglutide persist and are durable.
Lack of data in subjects with pre-existing severe hepatic impairment	No dose adjustment is necessary for patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects. REVESTIVE has not been studied in patients with severe hepatic impairment. Additional safety data will be available through the NIS (TED-R13-002).

AE=adverse event; CNS=central nervous system; NIS=non-interventional study; PBRER=Periodic Benefit-Risk Evaluation Report; PIP=Paediatric Investigation Plan; SAE=serious adverse event; SBS=short bowel syndrome; SmPC=Summary of Product Characteristics

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the PIL. The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PIL for REVESTIVE can be found in the REVESTIVE EPAR page: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002345/human_med_001583.jsp&mid=WC0b01ac058001d124.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned Post-Authorisation Development Plan

List of Studies in Post-authorisation Development Plan

Study/Activity (including study number)	Objectives	Safety Concerns/Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and) Final Results
Clinical study TED-C14-006: A 24-week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age with Short Bowel Syndrome	To evaluate the safety, tolerability, pharmacokinetics, and efficacy/pharmacodynamics of teduglutide in pediatric subjects through 17 years of age with short bowel syndrome (SBS) and who are dependent on parenteral support	Lack of experience in the paediatric population Long-term safety in the paediatric population	Planned	Final study report: December 2017

List of Studies in Post-authorisation Development Plan				
Study/Activity (including study number)	**Objectives**	**Safety Concerns/Efficacy Issue Addressed**	**Status**	**Planned Date for Submission of (Interim and) Final Results**
who are Dependent on Parenteral Support (Category 3)				
Registry protocol TED-R13-002: A Prospective, Multicentre Registry for Patients with Short Bowel Syndrome	Primary: To evaluate the long-term safety profile for subjects (adults and children) with SBS who are treated with teduglutide in a routine clinical setting. Secondary: To evaluate long term clinical outcome in subjects with SBS.	The primary safety outcome is the occurrence of colorectal cancer in SBS subjects with a remnant colon taking teduglutide.	Started. Five years of enrolment with at least 10 years of follow-up per subject. The goal is to enrol at least 655 SBS subjects of whom 393 will have any remnant colon treated with teduglutide who are at risk for colorectal cancer.	Four interim reports will be provided within six months after the data lock points (i.e., Q4 2016, Q4 2018, Q4 2020, and Q4 2022) Final report Q3/2031

SBS=short bowel syndrome

VI.2.6.1 Studies which are a Condition of the Marketing Authorisation.

Registry protocol TED-R13-002 is a condition of the Marketing Authorisation.