PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr REVESTIVE®*

Teduglutide for injection

Powder for solution for injection
5 mg per vial

Alimentary tract and metabolism products
ATC Code: A16AX08

Shire Pharmaceuticals Ireland Limited
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Importer/Distributor:
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Pr REVESTIVE®

Teduglutide for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Powder for solution / 5mg/vial	none *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

REVESTIVE (teduglutide for injection) is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.

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

Treatment effect should be evaluated on an ongoing basis. Clinical assessment by the physician should consider individual treatment objectives and patient preferences. If no overall improvement is achieved after 12 months, the need for continued treatment should be assessed.

Treatment should not be initiated until the 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. For safety monitoring, patients should undergo initial laboratory assessments (see **Warnings and Precautions, Gallbladder and Biliary Tract Disease** and **Pancreatic Diseases**) prior to starting treatment with REVESTIVE.

Geriatrics (> 65 years of age)

No clinically significant differences in safety and efficacy were observed between subjects younger than 65 years and those older than 65 years. Experience in subjects 75 years and older is limited.

Pediatrics (< 18 years of age)

Safety and efficacy in pediatric patients have not been established.

Pregnant Women

There are no data from the use of REVESTIVE on pregnant women (see **Warnings and Precautions, Special Populations – Pregnant Women**).

Nursing Women

There are no data from the use of REVESTIVE on nursing women (see **Warnings and Precautions, Special Populations – Nursing Women**).

CONTRAINDICATIONS

REVESTIVE is contraindicated in patients who:

- are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph;
- have active gastrointestinal (GI) malignancy (GI tract, hepatobiliary, pancreatic);
- have a history of malignancies in the gastrointestinal tract and/or the hepatobiliary system including pancreas within the last 5 years.

WARNINGS AND PRECAUTIONS

General

Concomitant Medication

Based upon the pharmacodynamic effect of REVESTIVE, patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption. Patients may require dose adjustment of these medications while on REVESTIVE. Examples of such medications include but are not limited to benzodiazepines, opioids, digoxin, anti-hypertensives.

Discontinuation of Treatment

Discontinuation of treatment with REVESTIVE may result in fluid and electrolyte imbalance leading to potential dehydration. Therefore, patients' fluid and electrolyte status should be carefully monitored.

Cardiovascular

Fluid Overload

Fluid overload has been observed in clinical trials. Fluid overload adverse events occurred most

frequently during the first 4 weeks of therapy.

Patients should be advised to contact their physician in case of sudden weight gain, swollen ankles and/or dyspnoea. Due to increased fluid absorption, which may increase the risk of congestive heart failure, patients with and without a history of cardiovascular disease (such as cardiac insufficiency and hypertension) should be monitored with regard to fluid overload, especially during initiation of therapy. In general, fluid overload can be prevented by appropriate and timely assessment and adjustment of parenteral nutrition needs. This assessment should be conducted more frequently within the first months of treatment with close monitoring afterwards.

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

Heart Rate Increase

An increase in heart rate was reported with REVESTIVE in a clinical trial in healthy volunteers undergoing serial ECG monitoring (see **Action and Clinical Pharmacology, Pharmacodynamics – Cardiac Electrophysiology**). Because of limited clinical experience in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as ischemic heart disease or tachyarrhythmias, caution should be observed in these patients. (see **Drug Interactions, Drug-Drug Interactions – Drugs that Increase Heart Rate**).

Gastrointestinal

Gastrointestinal Neoplasia Including Hepatobiliary Tract

Based on the pharmacologic activity and findings in animals, REVESTIVE has the potential to cause hyperplastic changes including neoplasia in the small bowel and hepatobiliary tract. These observations were not confirmed in clinical studies of more than one year duration.

Patients should be monitored clinically for small bowel and hepatobiliary neoplasia. If a benign neoplasm is found, it should be removed. In patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic), REVESTIVE therapy should be discontinued. In patients with active non-gastrointestinal malignancy or who are at increased risk for malignancy, the clinical decision to continue REVESTIVE should be made based on risk-benefit considerations.

Colorectal Polyps

Colorectal polyps were identified during the clinical trials. Colonoscopy of the entire colon with removal of polyps should be done within 6 months prior to starting treatment with REVESTIVE. A follow-up colonoscopy (or alternate imaging) is recommended between 1 to 2 years after initiating REVESTIVE. Subsequent colonoscopies should be done every 5 years or more often as needed in high risk individuals. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of diagnosis of colorectal cancer, REVESTIVE therapy should be discontinued.

Intestinal Obstruction

Intestinal obstruction has been reported in clinical trials. In patients who develop intestinal or stomal obstruction, REVESTIVE should be temporarily discontinued while the patient is clinically managed. REVESTIVE may be restarted when the obstructive presentation resolves, if clinically indicated.

Hepatic/Biliary/Pancreatic

Gallbladder and Biliary Tract Disease

Cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies.

For identification of the onset or worsening of gallbladder/biliary disease, patients should undergo laboratory assessment of bilirubin and alkaline phosphatase prior to starting REVESTIVE, and while on REVESTIVE. If clinically meaningful changes are seen, further evaluation including imaging of the gallbladder and/or biliary tract is recommended; and 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.

For identification of onset or worsening of pancreatic disease, patients should undergo laboratory assessment of lipase and amylase prior to starting REVESTIVE, and while on REVESTIVE. If clinically meaningful changes are seen, further evaluation such as imaging of the pancreas is recommended, and the need for continued REVESTIVE treatment should be reassessed.

Special Populations

Pregnant Women

There are no data from the use of REVESTIVE in pregnant women.

In animal studies, no effects on embryo-fetal development were observed in pregnant rats given subcutaneous teduglutide at doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg) or pregnant rabbits given subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg). A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg).

Because animal reproductive studies are not always predictive of human response, REVESTIVE should be used during pregnancy only if clearly needed.

Nursing Women

It is not known whether teduglutide is present in human milk.

Teduglutide is excreted in the milk of lactating rats, and the highest concentration measured in milk was 2.9% of the plasma concentration following a single subcutaneous injection of 25 mg/kg (500 times the recommended daily human dose of 0.05 mg/kg).

Because of the potential for serious adverse reactions to nursing infants from REVESTIVE and because of the potential for tumorigenicity shown for teduglutide in mice and rats, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (<18 years of age)

The safety and efficacy of REVESTIVE in pediatric patients have not been established.

Geriatrics (>65 years of age)

Of the 595 subjects treated with REVESTIVE in clinical trials, 43 subjects were 65 years or older, whereas 6 subjects were 75 years of age or older. No clinically significant differences were observed between subjects younger than 65 years and those older than 65 years.

Renal Insufficiency

In patients with moderate or severe renal impairment, or end-stage renal disease the dose should be reduced by 50% (see **Dosage and Administration, Dosing Considerations – Patients with Renal Impairment; Action and Clinical Pharmacology, Pharmacokinetics – Renal Insufficiency**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Across all clinical studies, 595 subjects were exposed to at least one dose of REVESTIVE (249 patient-years of exposure; mean duration of exposure was 22 weeks). Of the 595 subjects, 173 subjects were treated in Phase 3 SBS studies (134/173 [77%] at the dose of 0.05 mg/kg/day and 39/173 [23%] at the dose of 0.10 mg/kg/day).

The most commonly reported (≥ 10%) adverse reactions in patients treated with REVESTIVE across all clinical studies (n=595) were: abdominal pain (31.3%), injection site reactions (21.8%), nausea (18.8%), headaches (16.3%), abdominal distension (14.8%), and upper respiratory tract infection (11.9%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The rates of adverse reactions in patients with SBS participating in 2 randomized, placebo-controlled, 24-week, double-blind clinical studies (Studies CL0600-020 and CL0600-004) are summarized in **Table 1**. Only those reactions with a rate of at least 5% in the REVESTIVE group and occurring greater than in the placebo group are summarized. The majority of these reactions were mild or moderate. Of subjects receiving REVESTIVE at the recommended dose of 0.05 mg/kg/day, 88.3% (n=68/77) experienced an adverse reaction, as compared to 83.1% (n=49/59) for placebo. Many of these adverse reactions have been reported in association with the underlying disease and/or parenteral nutrition.

Table 1: Adverse reactions in ≥ 5% of REVESTIVE-Treated SBS Subjects and More Frequent than Placebo: CL0600-020 and CL0600-004

Adverse Reaction	REVESTIVE 0.05 mg/kg/day (N=77) n (%)	Placebo (N=59) n (%)
Gastrointestinal Disorders		
Abdominal Pain	29 (38)	16 (27)
Nausea	19 (25)	12 (20)
Abdominal Distension	15 (20)	1 (2)
Vomiting	9 (12)	6 (10)
Flatulence	7 (9)	4 (7)
Appetite Disorders	5 (7)	2 (3)
Infections and Infestations		
Upper Respiratory Tract Infection	20 (26)	8 (14)
Psychiatric Disorders		
Sleep Disturbances	4 (5)	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	4 (5)	0
Skin and Subcutaneous Tissue Disorders		
Hypersensitivity	6 (8)	3 (5)
Skin Hemorrhage	4 (5)	1 (2)
Vascular Disorders		
Fluid Overload	9 (12)	4 (7)
Subjects with Stoma		
Gastrointestinal Stoma Complication	13 (42)[a]	3 (14)[a]

[a]Percentage based on 53 subjects with a stoma (n=22 placebo; n=31 REVESTIVE 0.05 mg/kg/day).

No new safety signals have been identified in patients exposed to 0.05 mg/kg/day of REVESTIVE for up to 42 months in long-term open-label extension studies.

Adverse Reactions of Special Interest

Malignancy

Three subjects were diagnosed with malignancy in the clinical studies, all of whom were male and had received REVESTIVE 0.05 mg/kg/day in CL0600-021. One subject had a history of abdominal radiation for Hodgkin's disease two decades prior to receiving REVESTIVE and prior liver lesions on CT scan, and was diagnosed with metastatic adenocarcinoma of unconfirmed origin after 11 months of exposure to REVESTIVE. Two subjects had extensive smoking histories, and were diagnosed with lung cancers (squamous and non-small cell) after 12 months and 3 months of REVESTIVE exposure, respectively.

Colorectal Polyps

In the clinical studies, 14 subjects were diagnosed with polyps of the GI tract after initiation of study treatment. In the SBS placebo-controlled studies, 1/59 (1.7%) of subjects on placebo and 1/109 (0.9%) of subjects on REVESTIVE 0.05 mg/kg/day were diagnosed with intestinal polyps (inflammatory stomal and hyperplastic sigmoidal after 3 and 5 months, respectively). The remaining 12 polyp cases occurred in the extension studies – 2 colorectal villous adenomas (onset at 6 and 7 months in REVESTIVE 0.10 and 0.05 mg/kg/day dose groups, respectively), 2 hyperplastic polyp (onset 6 months in REVESTIVE 0.10 mg/kg/day dose group and 24 months in REVESTIVE 0.05 mg/kg/day dose group), 4 colorectal tubular adenomas (onset between 24 and 36 months in REVESTIVE 0.05 mg/kg/day dose group), 1 serrated adenoma (onset at 24 months in REVESTIVE 0.05 mg/kg/day dose group), 1 colorectal polyp biopsy not done (onset at 24 months in REVESTIVE 0.05 mg/kg/day dose group), 1 rectal inflammatory polyp (onset at 10 months in the REVESTIVE 0.05 mg/kg/day dose group), and 1 small duodenal polyp (onset at 3 months in REVESTIVE 0.05 mg/kg/day dose group).

Gastrointestinal Obstruction

Overall, 12 subjects experienced one or more episodes of intestinal obstruction/stenosis: 6 in the SBS placebo-controlled studies and 6 in the extension studies. The 6 subjects in the placebo-controlled trials were all on REVESTIVE: 3/77 (3.9%) on REVESTIVE 0.05 mg/kg/day and 3/32 (9.4%) on REVESTIVE 0.10 mg/kg/day. No cases of intestinal obstruction occurred in the placebo group. Onsets ranged from 1 day to 6 months. In the extension studies, 6 additional subjects (all on REVESTIVE 0.05 mg/kg/day) were diagnosed with intestinal obstruction/stenosis with onsets ranging from 6 days to 19 months. Two of the 6 subjects from the placebo-controlled trials experienced recurrence of obstruction in the extension studies. Of all 8 subjects with an episode of intestinal obstruction/stenosis in these extension studies, 2 subjects required endoscopic dilation and 1 required surgical intervention.

Gallbladder, Biliary and Pancreatic Disease

For gallbladder and biliary disease in the placebo-controlled studies, 3 subjects were diagnosed with cholecystitis, all of whom had a prior history of gallbladder disease and were in the REVESTIVE 0.05 mg/kg/day dose group. No cases were reported in the placebo group. One of these 3 cases had gallbladder perforation and underwent cholecystectomy the next day. The remaining 2 cases underwent elective cholecystectomy at a later date. In the extension studies, 4 subjects had an episode of acute cholecystitis; 4 subjects had new-onset cholelithiasis; and 1 subject experienced cholestasis secondary to an obstructed biliary stent. For pancreatic disease in the placebo-controlled studies, 1 subject (REVESTIVE 0.05 mg/kg/day dose group) had a pancreatic pseudocyst diagnosed after 4 months of REVESTIVE. In the extension studies, 1 subject was diagnosed with chronic pancreatitis; and 1 subject was diagnosed with acute pancreatitis.

Fluid Overload

In the placebo-controlled trials, fluid overload was reported in 4/59 (6.8%) of subjects on placebo and 9/77 (11.7%) subjects on REVESTIVE 0.05 mg/kg/day. Of the 9 cases in the REVESTIVE group, there were 2 cases of congestive heart failure (CHF, 2.6%), 1 of whom was reported as a serious adverse event and the other as non-serious. The serious case had onset at 6 months, and was possibly associated with previously undiagnosed hypothyroidism and/or cardiac dysfunction.

Concomitant Oral Medication

REVESTIVE can increase the absorption of concomitant oral medications such as benzodiazepines and psychotropic agents. One subject in the placebo-controlled trials in the REVESTIVE 0.05 mg/kg/day group (on prazepam) experienced dramatic deterioration in mental status progressing to coma during her first week of REVESTIVE therapy. She was admitted to the Intensive Care Unit where her benzodiazepine level was > 300 mcg/L. REVESTIVE and prazepam were discontinued, and the coma resolved 5 days later.

Immunogenicity

Based on integrated data from 2 trials in adults with SBS (a 6-month randomized 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/day teduglutide once daily was 3% (2/60) at Month 3, 18% (13/74) at Month 6, 25% (18/71) at Month 12, 31% (10/32) at Month 24 and 48% (14/29) at Month 30. The anti-teduglutide antibodies were cross-reactive to native glucagon-like peptide (GLP-2) in 5 of the 6 subjects (83%) who had anti-teduglutide antibodies. Anti-teduglutide antibodies appear to have no impact on efficacy and safety up to 2.5 years although the long-term impact is unknown.

In the same two trials, a total of 36 subjects were tested for neutralizing antibodies: 9 of these subjects had no neutralizing antibodies, and the remaining 27 subjects had no detectable neutralizing antibodies although, the presence of teduglutide at low levels in these study samples could have resulted in false negatives (no neutralizing antibody detected although present).

Injection Site Reactions

In the placebo-controlled trials CL0600-020 and CL0600-004, 12% of patients in each of the placebo and REVESTIVE 0.05 mg/kg/day treatment groups experienced an injection site reaction. The majority of reactions were moderate in severity and no occurrences led to drug discontinuation.

Abnormal Hematologic and Clinical Chemistry Findings

No clinically meaningful changes from baseline were seen for any of the hematology analytes, and no clinically meaningful shifts occurred.

Abnormal clinical chemistry is a common manifestation of SBS and a significant proportion of subjects in the SBS placebo-controlled trials had abnormal chemistry at baseline. The most common markedly abnormal clinical chemistry analyte post-baseline in REVESTIVE 0.05 mg/kg/day patients vs. placebo was C-Reactive Protein (CRP) ≥ 21 mg/L, (25% vs. 8.6%). Higher changes from baseline in CRP values were found in REVESTIVE-treated subjects (1.74 g/m^3) vs. placebo-treated subjects (-1.15 g/m^3) at Week 24. For the remainder of the analytes, the change from baseline was similar or greater in placebo-treated subjects.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of REVESTIVE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders: Cardiac arrest, cardiac failure
Gastrointestinal Disorders: Pancreatitis acute
Nervous System Disorders: Cerebral hemorrhage

DRUG INTERACTIONS

Overview

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 oral medications, such as benzodiazepines, opioids, digoxin and anti-hypertensives, which should be considered if these drugs require titration or have a narrow therapeutic index.

Among the patients on benzodiazepines, one patient in the 0.05 mg/kg/day REVESTIVE group in Study CL0600-004 was taking prazepam and experienced dramatic deterioration in mental status progressing to coma during the first week of REVESTIVE therapy. The patient was admitted to the ICU where the benzodiazepine level was > 300 mcg/L; REVESTIVE and prazepam were discontinued, and the coma resolved 5 days later.

Drug-Drug Interactions

No clinical drug-drug interaction studies have been performed.

Drugs that Increase Heart Rate

REVESTIVE caused an increase in heart rate in a clinical trial in healthy volunteers (see **Warnings and Precautions, Cardiovascular – Heart Rate Increase**; **Action and Clinical Pharmacology, Pharmacodynamics – Cardiac Electrophysiology**). The impact on heart rate of co-administration of REVESTIVE with other drugs that increase heart rate, such as sympathomimetic drugs, has not been evaluated in drug-drug interaction studies. As a result, caution should be observed with co-administration of REVESTIVE with these drugs.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Geriatrics (>65 years of age)

Evidence from clinical trials studies and post-marketing experience suggests that no dose adjustment is necessary in patients above the age of 65 years.

Patients with Renal Impairment

Reduce the dose by 50% in patients with moderate and severe renal impairment (creatinine clearance less than 50 mL/min), and end-stage renal disease. No dose adjustment is necessary for patients with mild renal impairment.

Patients with Hepatic Impairment

No dosage 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 subjects with severe hepatic impairment.

Recommended Dose and Dosage Adjustment

The recommended daily dose of REVESTIVE is 0.05 mg/kg body weight administered by subcutaneous injection once daily. Alternation of sites for subcutaneous injection is recommended, and can include the thighs, arms, and the 4 quadrants of the abdomen. REVESTIVE should not be administered intravenously or intramuscularly.

Missed Dose

If a dose is missed, that dose should be taken as soon as possible on that day. Do not take 2 doses on the same day.

Administration

Each single-use vial of REVESTIVE contains 5 mg of teduglutide as a white lyophilized powder for solution for subcutaneous injection. At the time of administration the lyophilized powder is reconstituted with 0.5 mL of Sterile Water for Injection, which is provided in a pre-filled syringe. A 10 mg/mL sterile solution is obtained after reconstitution (see **Reconstitution** below).

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 (see injection volumes in the table below). The physician should at each visit weigh the patient, determine the daily dose to be administered until next visit and inform the patient accordingly.

Table 2: REVESTIVE Injection Volume Per Body Weight

Body weight (kg)	Volume to be injected (mL)
38-41	0.20
42-45	0.22
46-49	0.24
50-53	0.26
54-57	0.28
58-61	0.30
62-65	0.32
66-69	0.34
70-73	0.36
74-77	0.38
78-81	0.40
82-85	0.42
86-89	0.44
90-93	0.46

The prepared solution must be injected subcutaneously into a cleaned area on the abdomen, arm,

or thigh using a thin needle for subcutaneous injection.

Detailed instructions on the preparation and injection of REVESTIVE are provided in the Patient Medication Information.

Reconstitution

Reconstitute each vial of REVESTIVE by slowly injecting the 0.5 mL of preservative-free Sterile Water for Injection provided in the pre-filled syringe. Allow the vial containing REVESTIVE and water to stand for approximately 30 seconds and then gently roll the vial between your palms for about 15 seconds. Do not shake the vial. Allow the mixed contents to stand for about 2 minutes. Inspect the vial for any undissolved powder.

If undissolved powder is observed, gently roll the vial again until all material is dissolved. Do not shake the vial. The solution should be clear and colorless to light straw colored and free from visible particles. Do not use if the product remains undissolved or is discolored.

Once the drug is completely dissolved, remove the empty syringe and replace with an injection syringe. Withdraw the prescribed dose of solution into an injection syringe (up to 1 mL with scale intervals of 0.02 mL or lower).

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

Reconstitution

Vial Strength	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
5 mg	0.5 mL Sterile Water for Injection	0.38 mL	10 mg/mL (up to 3.8 mg teduglutide can be withdrawn)

Vials of REVESTIVE and pre-filled syringes of Sterile Water for Injection do not contain any preservatives and are for single-use only. After reconstitution, from a microbiological point of view, the solution should be used immediately. However, chemical and physical stability have been demonstrated for up to 3 hours below 25ºC after reconstitution. Any unused product or waste material should be disposed of in accordance with local requirements.

In the absence of compatibility studies, REVESTIVE should not be mixed with other medicinal products.

OVERDOSAGE

The maximum dose of REVESTIVE studied during clinical development was 80 mg/day for 8 days. No unexpected systemic adverse reactions were seen. In the event of overdose, the patient should be carefully monitored by the medical professional.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Teduglutide is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cells of the distal intestine. 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 binds to the glucagon-like peptide-2 receptors located in intestinal subpopulations of enteroendocrine cells, subepithelial myofibroblasts and enteric neurons of the submucosal and myenteric plexus. Activation of these receptors results in the local release of multiple mediators including insulin-like growth factor (IGF)-1, vasoactive intestinal polypeptide (VIP), nitric oxide and keratinocyte growth factor (KGF). GLP-2 is mainly responsible for the maintenance and expansion of the gastrointestinal mucosal surface area through the regulation of proliferation and apoptosis of the intestinal epithelium. GLP-2 also promotes energy absorption through a number of mechanisms including enhanced capacity for carbohydrate, amino acid, and lipid absorption, increased activity and expression of brush border digestive enzymes, and increased mucosal nutrient transport. Exogenous GLP-2 increases intestinal and portal blood flow, decreases gastrointestinal motility and inhibits gastric acid secretion. 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.

Pharmacodynamics

The ability of REVESTIVE to improve intestinal absorption of fluids and nutrients was studied in 17 adult subjects with Short Bowel Syndrome using daily doses of 0.03, 0.10, 0.15 mg/kg (n=2-3 per dose group) in a 21-day, open-label, multi-center, dose-ranging study. All subcutaneous (abdomen) doses studied, except 0.03 mg/kg once daily, decreased stomal output or fecal fluid and macronutrient excretion, resulted in enhanced gastrointestinal fluid (wet weight) absorption of approximately 750-1000 mL/day, and increased villus height and crypt depth of the intestinal mucosa.

Cardiac Electrophysiology

A randomised, double-blind, placebo- and active-controlled, four period crossover study was performed to investigate the electrocardiographic effects of single subcutaneous doses of REVESTIVE 5 mg and 20 mg in healthy subjects (N=70).

REVESTIVE was associated with increases in heart rate. Following single dose treatment with REVESTIVE 5 mg, statistically significant positive mean differences from placebo were observed from 1 to 16 h post-dosing, inclusive, with a maximum mean difference from placebo of 9.3 bpm (90% CI 8.0, 10.6) at 1 h post-dosing. Following treatment with a supra-therapeutic 20 mg dose, statistically significant positive mean differences from placebo were observed from 1 to 24 h post-dosing, inclusive, with a maximum mean difference from placebo of 9.8 bpm (90% CI 8.0, 11.5) at 6 h post-dosing (see **Warnings and Precautions, Cardiovascular – Heart Rate Increase**; **Drug Interactions, Drug-Drug Interactions – Drugs that Increase Heart Rate**).

There was no evidence of a treatment-related effect of REVESTIVE on the QTcF interval, the QRS duration, or the PRc interval.

Pharmacokinetics

Table 3: Summary of REVESTIVE Pharmacokinetic Parameters in Patients with SBS

	C_{max} (ng/mL)*	$t_{½}$ (h)	AUC (ng·hr/mL)*	Clearance (L/h)	Volume of distribution (L)
Single dose mean (0.05 mg/kg)	38.4	1.5	247	13.1	27.2

C_{max} and AUC are measured under steady state conditions

The C_{max} and AUC of teduglutide was dose proportional over the dose range of 0.05 to 0.4 mg/kg teduglutide.

Absorption

In healthy subjects, REVESTIVE when administered subcutaneously in the thigh/abdomen had an absolute bioavailability of 88% and reached maximum plasma teduglutide concentrations at 3-5 hours after administration. Following a 0.05 mg/kg subcutaneous dose in SBS subjects, the median peak teduglutide concentration (C_{max}) was 36 ng/mL and the median area under the curve ($AUC_{0\text{-}inf}$) was 0.15 µg•hr/mL. No accumulation of teduglutide was observed following repeated subcutaneous administrations.

Distribution

In healthy subjects, teduglutide had a volume of distribution of 103 mL/kg, similar to blood volume.

Metabolism

The metabolic pathway of teduglutide was not investigated in humans. However, teduglutide is expected to be degraded into small peptides and amino acids via catabolic pathways, similar to the catabolism of endogenous GLP-2.

Excretion

In healthy subjects, teduglutide plasma clearance was approximately 123 mL/hr/kg which is similar to the GFR suggesting that teduglutide is primarily cleared by the kidney. Teduglutide has a mean terminal half-life ($t_{1/2}$) of approximately 2 hours in healthy subjects and 1.3 hours in SBS subjects.

Special Populations and Conditions

Pediatrics

There are no pharmacokinetic (PK) data in children.

Geriatrics

No differences in PK were observed between healthy subjects younger than 65 years and those older than 65 years. Experience in subjects 75 years and older is limited.

Gender

No clinically relevant gender differences were observed.

Hepatic Insufficiency

Subjects with moderate hepatic impairment had lower teduglutide C_{max} and AUC (10 ~15%) compared to healthy matched control subjects after a single subcutaneous dose of 20 mg REVESTIVE. Teduglutide PK was not assessed in subjects with severe hepatic impairment.

Renal Insufficiency

In subjects with moderate to severe renal impairment or end stage renal disease (ESRD), teduglutide C_{max} and $AUC_{0\text{-}inf}$ increased with the degree of renal impairment following a single subcutaneous administration of 10 mg teduglutide. Teduglutide exposure increased by a factor of 2.1 (C_{max}) and 2.6 ($AUC_{0\text{-}inf}$) in ESRD subjects compared to healthy subjects.

STORAGE AND STABILITY

Store below 25°C. Do not freeze.

Keep in a safe place out of the reach and sight of children.

Reconstituted solution: Store below 25°C. Do not freeze. The product should be used within 3 hours after reconstitution.

DOSAGE FORMS, COMPOSITION AND PACKAGING

REVESTIVE is intended for subcutaneous injection and is supplied as a sterile, white lyophilized powder for reconstitution that should be reconstituted with Sterile Water for Injection. The REVESTIVE pack is supplied with the following:

- 5 mg teduglutide powder in glass vial with rubber stopper (bromobutyl)
- 0.5 mL of diluent sterile Water for Injection in pre-filled syringe (glass) assembled with plungers (plastic)
- Pack size of 28 vials of powder and 28 pre-filled syringes

Each single-use vial of REVESTIVE contains 5 mg of teduglutide and the following non-medicinal ingredients: dibasic sodium phosphate heptahydrate, L-histidine, mannitol, monobasic sodium phosphate monohydrate. No preservatives are present.

Other materials needed for administration but not included in the pack are:
- Reconstitution needles (size 22G, length 1½" [0.7 x 40 mm])
- 1 mL injection syringes (with scale intervals of 0.02 mL or smaller)
- Thin injection needles for subcutaneous injection (e.g. size 26G, length 5/8" [0.45 x 16 mm])
- Alcohol swabs
- A puncture-proof container for safe disposal of the used syringes and needles

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

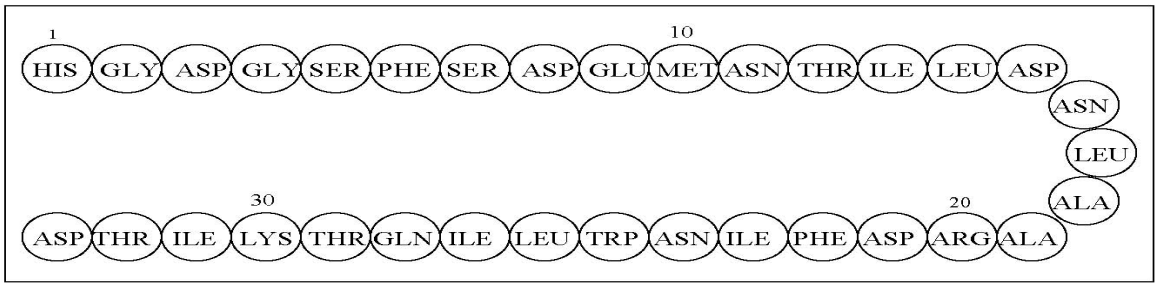
Drug Substance

Proper name: teduglutide

Chemical name: 2-glycine-1-33-glucagon-like peptide 2 (human); [gly2]-hGLP-2

Molecular formula and molecular mass: $C_{164}H_{252}N_{44}O_{55}S$, 3752 Daltons

Structural formula: L-histidyl-L-glycyl-L-aspartyl-L-glycyl-L-seryl-L-phenylalanyl-L-seryl-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-isoleucyl-L-glutaminyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid



Physicochemical properties: Teduglutide is a 33 amino acid glucagon-like peptide-2 (GLP-2) analog. Teduglutide is a clear, colorless to light straw colored liquid in aqueous buffer.

Solubility Properties: Teduglutide is soluble to at least 18 mg/mL in 17.5 mM, pH 7.4 phosphate buffer and at least 50 mg/mL in 60 mM, pH 7.8 phosphate buffer.

Product Characteristics:
Teduglutide is a 33 amino acid glucagon-like peptide-2 analog manufactured using a strain of Escherichia coli modified by recombinant DNA technology.

CLINICAL TRIALS

Study Demographics and Trial Design

Table 4: Summary of Patient Demographics for Clinical Trials in Patients with Short Bowel Syndrome (SBS)

Study #	Trial design	Dosage, route of administration and duration	Study subjects enrolled (n = number)	Mean age (range [years])	Gender
Placebo-controlled Studies					
CL0600-020	Phase 3, multicenter, randomized, double-blind, placebo-controlled study To evaluate the efficacy, safety, tolerability, and pharmacodynamics of REVESTIVE compared with placebo in subjects with PN/I.V. dependent SBS	A: REVESTIVE 0.05 mg/kg/day SC B: Dose-matching placebo SC 24 weeks	A: 42 B: 43	51.3 (22 – 78) 49.7 (18 – 82)	M = 20 F = 22 M = 19 F = 24
CL0600-004	Phase 3, multicenter, randomized, double-blind, placebo-controlled study To evaluate the efficacy, safety, tolerability and pharmacokinetics of REVESTIVE compared with placebo in subjects with PN/I.V. dependent SBS.	A: REVESTIVE 0.05 mg/kg/day SC B: REVESTIVE 0.10 mg/kg/day SC C: Dose-matching placebo SC 24 weeks	A: 35 B: 32 C: 16	47.1 (20 – 68) 50.3 (19 – 79) 49.4 (20 – 72)	M = 17 F = 18 M = 13 F = 19 M = 7 F = 9

Table 4: Summary of Patient Demographics for Clinical Trials in Patients with Short Bowel Syndrome (SBS)

Study #	Trial design	Dosage, route of administration and duration	Study subjects enrolled (n = number)	Mean age (range [years])	Gender
Extension Studies					
CL0600-021	Phase 3, multicenter, open label, extension study of CL0600-020 To further study long-term safety and efficacy in subjects who completed, participated in or qualified for Study CL0600-020. Key secondary efficacy variables focused on reductions in PN/I.V. volume.	REVESTIVE 0.05 mg/kg/day SC 2 years	88 (37 on REVESTIVE 0.05 mg/kg and 51 on placebo or not treated in Study -020)	50.9 (18 – 82)	M = 41 F = 47
CL0600-005	Phase 3, multicenter, randomized, double-blind extension study of CL0600-004 To evaluate the long-term safety and tolerability of daily REVESTIVE dosing for up to 12 months in adult subjects with SBS who were dependent on PN/I.V. Key secondary efficacy variables focused on reductions in PN/I.V. volume.	A: REVESTIVE 0.05 mg/kg/day SC B: REVESTIVE 0.10 mg/kg/day SC C: REVESTIVE 0.05 mg/kg/day SC D: REVESTIVE 0.10 mg/kg/day SC 28 weeks	A: 6 B: 7 C: 25 D: 27	42.2 (21 – 59) 56.6 (41 – 73) 46.7 (21 – 67) 49.4 (20 – 80)	M = 2 F = 4 M = 3 F = 4 M = 15 F = 10 M = 13 F = 14

PN/I.V. = parenteral nutrition/intravenous fluid; SC = subcutaneous

Study Results

Study CL0600-020

The efficacy, safety, and tolerability of REVESTIVE (teduglutide for injection) was evaluated in a randomized, double-blind, placebo-controlled, parallel-group, multi-national, multi-center clinical trial in adults with SBS who were dependent on parenteral nutrition/intravenous (PN/I.V.) support for at least 12 months and required PN at least 3 times per week.

The mean age was similar across all treatment groups, with most participating subjects less than 65 years of age. Medical and surgical histories, prior medications, and concomitant medications were consistent with SBS and were generally well balanced between treatment groups and studies.

For 8 weeks (or less) prior to randomization, investigators optimized the PN/I.V. volume of all subjects. Optimization was followed by a 4-week to 8-week period of fluid stabilization. Subjects then were randomized (1:1) to placebo (n=43) or REVESTIVE 0.05 mg/kg/day (n=43). Study treatment was administered subcutaneously once daily for 24 weeks. PN/I.V. volume adjustments (up to 30% decrease) and clinical assessments were made at 2, 4, 8, 12, 20, and 24 weeks.

The primary efficacy endpoint was based on a clinical response, defined as a subject achieving at least 20% reduction in weekly PN/I.V. volume from baseline (immediately before randomization) to both Weeks 20 and 24.

The mean age of subjects was 50.3 years. Mean duration of PN/I.V. dependency prior to enrollment was 6.25 years (range 1-25.8 years). The most common reasons for intestinal resection leading to SBS were vascular disease (34.1%, 29/85), Crohn's Disease (21.2%, 18/85), and "other" (21.2%, 18/85). Stoma was present in 44.7% (38/85) of subjects, and the most common type was jejunostomy/ileostomy (81.6%, 31/38). The mean length of remaining small intestine was 77.3±64.4 cm (range: 5 to 343 cm). The colon was not in continuity in 43.5% (37/85) subjects. At baseline, the mean (± SD) prescribed days per week for PN/I.V. infusion was 5.73 (±1.59) days.

The percentages of treatment group responders were compared in the intent-to-treat population of this study which was defined as all randomized patients. 63% (27/43) of the REVESTIVE group were considered responders compared to 30% (13/43) in the placebo group (p=0.002). At all visits, change from baseline in actual PN/I.V. volume was greater in the REVESTIVE group compared to the placebo group: at Week 24, the actual mean reduction in weekly PN/I.V. volume was 4.4 L (SD=3.81) for the REVESTIVE group (from pre-treatment baseline of 12.9 L) versus 2.3 L (SD=2.74) for the placebo group (from pre-treatment baseline of 13.2 L/week) ($p<0.001$). The difference in the corresponding percent change from baseline between the treatment groups was statistically significant at Week 24 (reduction of 32.1% [SD=18.71] in the REVESTIVE group vs 21.0% in the placebo group [SD=24.35]) (p=0.025).

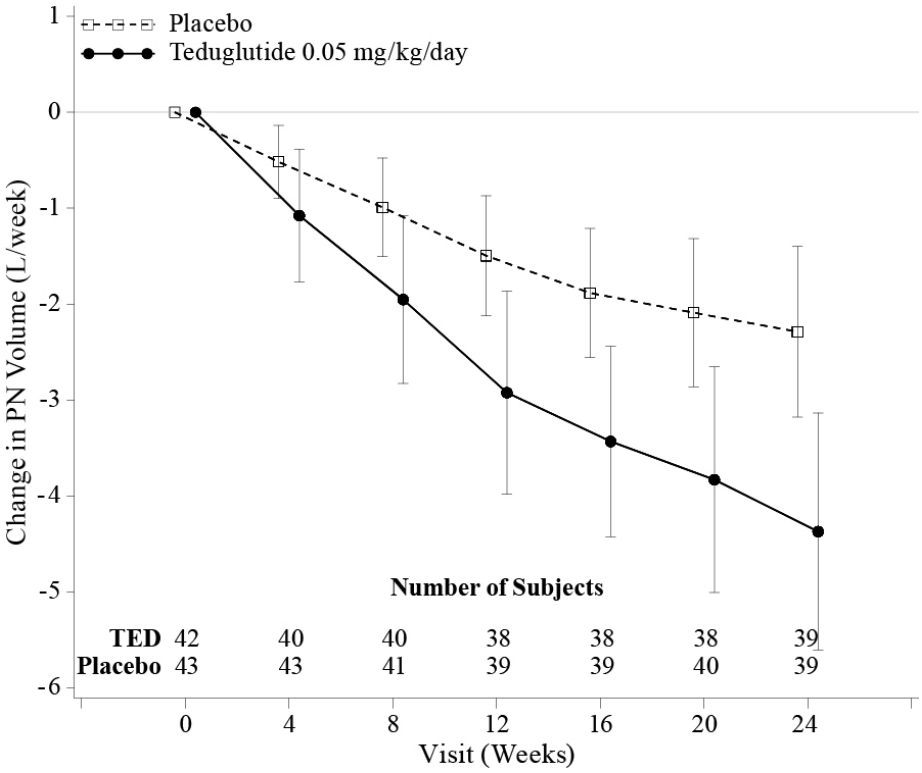
The percentage of subjects with a duration of response for ≥ 3 consecutive visits was higher in the REVESTIVE group (24/43 subjects, 55.8%) than in the placebo group (12/43 subjects, 27.9%). The distribution of duration of response was statistically significant (p=0.005).

The proportion of subjects with a 20 to 100% reduction or a 2 L reduction in PN/I.V. volume from baseline at Weeks 20 and 24 was higher in the REVESTIVE group (30/43 subjects, 69.8%) than the placebo group (16/43 subjects, 37.2%). The difference was statistically significant (p=0.002).

Twenty-one subjects on REVESTIVE (53.8%) versus 9 on placebo (23.1%) achieved at least a one-day reduction in PN/I.V. support at week 24 (p=0.005).

The mean changes from baseline in PN/I.V. volume by visit are shown in Figure 1.

Figure 1 - Change (+95% CI) in PN/I.V. volume (L/week)



PN/I.V. = parenteral nutrition/intravenous fluid; SD = standard deviation TED = teduglutide

Treatment with REVESTIVE at a dose of 0.05 mg/kg/day in double-blind study CL0600-020 demonstrated a benefit for patients with SBS who are dependent on parenteral support. REVESTIVE treatment, resulted in reductions in PN/I.V. support, including reductions in PN/I.V. volume, and at least one day reduction on PN/I.V. in some patients.

Study CL0600-021

CL0600-021 was a 2-year open-label extension of CL0600-020 in which 88 subjects received REVESTIVE 0.05 mg/kg/day. Ninety-seven percent (76/78) of subjects who completed CL0600-020 elected to enroll in CL0600-021 (37 received REVESTIVE; 39 received placebo). An additional 12 subjects entered CL0600-021 who had been optimized and stabilized but not randomized in CL0600-020 because of closed enrollment.

<u>24-month Exposure</u>

Of the 39 placebo subjects from CL0600-020 entering CL0600-021, 29 completed 24 months of treatment with REVESTIVE. The mean reduction in PN/I.V. was 3.11 L/week (an additional

28.3% reduction) from the start of CL0600-021. Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. At the end of study, 14 (48.3%), 7 (24.1%) and 5 (17.2%) achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively. Two subjects were weaned off their PN/I.V. support while on REVESTIVE. Of the 12 subjects entering CL0600-021 directly, 6 completed 24 months of treatment with REVESTIVE. Similar effects were seen. One of the six subjects was weaned off their PN/I.V. support while on REVESTIVE.

30-month Exposure

Thirty REVESTIVE-treated subjects completed a total duration of 30 months (CL0600-020 followed by CL0600-021 treatment). Of these, 28 subjects (93%) achieved a 20% or greater reduction of parenteral support. Of responders in CL0600-020 who had completed 2 additional years of continuous treatment with REVESTIVE, 96% (21/22) sustained their response to REVESTIVE. The mean reduction in PN/I.V. (n=30) was 7.55 L/week (a 65.6% reduction from baseline). Ten subjects were weaned off their PN/I.V. support while on REVESTIVE treatment for 30 months. Subjects were maintained on REVESTIVE even if no longer requiring PN/I.V. support. These 10 subjects had required PN/I.V. support for 1.2 to 15.5 years, and prior to REVESTIVE had required between 3.5 L/week and 13.4 L/week of PN/I.V. support. At the end of study, 21 (70%), 18 (60%) and 18 (60%) of the 30 completers achieved a reduction of at least 1, 2, or 3 days per week in PN/I.V. support, respectively.

Results of the long-term extension study, CL0600-021, demonstrated the reproducibility as well as the durability of the beneficial effects of REVESTIVE 0.05 mg/kg/day, without evidence for the development of tolerance for up to 30 months of treatment. PN/I.V. volume reductions in subjects who previously received REVESTIVE translated to additional days off PN/I.V. and, in a subset of subjects, complete weaning from PN/I.V. support. Newly treated subjects also achieved and maintained the similar clinical benefits from 24 months of REVESTIVE treatment.

Study CL0600-004

CL0600-004 was a randomized, double-blind, placebo-controlled, three parallel-group, multinational study in adults with Short Bowel Syndrome who were dependent on parenteral nutrition/intravenous (PN/I.V.) support for at least 12 months and required PN at least 3 times per week. After a period of optimization and stabilization similar to CL0600-020, subjects were randomized to receive 24 weeks of one of the following treatment regimens: REVESTIVE 0.05 mg/kg/day (n=35), REVESTIVE 0.10 mg/kg/day dose (n=32), or placebo (n=16). The primary efficacy endpoint was a graded categorical score that did not achieve statistical significance for the high dose. Further evaluation of PN/I.V. volume reduction using the endpoint of response (defined as at least 20% reduction in PN/I.V. fluid from baseline to Weeks 20 and 24) showed that 46% of subjects on REVESTIVE 0.05 mg/kg/day responded versus 6% on placebo (p=0.010).

The mean age was similar across all treatment groups, with most participating subjects less than 65 years of age. Medical and surgical histories, prior medications, and concomitant medications were consistent with SBS and were generally well balanced between treatment groups and studies.

Treatment with REVESTIVE at a dose of 0.05 mg/kg/day in double-blind study CL0600-004 demonstrated a clinically meaningful benefit for patients with SBS who are dependent on parenteral support. REVESTIVE treatment resulted in reductions in PN/I.V. fluid needed.

Study CL0600-005

CL0600-005 was a blinded, uncontrolled extension of CL0600-004, in which 65 subjects from CL0600-004 received REVESTIVE for up to an additional 28 weeks of treatment. Of responders in CL0600-004 who entered CL0600-005, 75% sustained their response on REVESTIVE after one year of treatment. In the REVESTIVE 0.05 mg/kg/day dose group, a 20% or greater reduction of parenteral support was achieved in 68% (17/25) of subjects. The mean reduction of weekly PN/I.V. volume was 4.9 L/week (52% reduction from baseline) after one year of continuous REVESTIVE treatment. The subjects who had been completely weaned off PN/I.V. support in CL0600-004 (n=2) remained off parenteral support through CL0600-005. During CL0600-005, an additional subject from CL0600-005 was weaned off parenteral support.

Results of the long-term extension study, CL0600-005, demonstrated the reproducibility as well as the durability of the clinical benefits of REVESTIVE 0.05 mg/kg/day, without evidence for the development of tolerance for up to an additional 28 weeks of treatment.

DETAILED PHARMACOLOGY

Teduglutide is a novel recombinant analog of the human glucagon-like peptide-2 (GLP-2), that differs from GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus.

Teduglutide binds to the human and rat GLP-2 receptor (GLP-2R) with similar affinity compared to native GLP-2. Receptor binding results in intracellular cyclic adenosine 3'-5'- monophosphate (cAMP) levels and activation of several downstream signaling pathways such as protein kinase A (PKA), cAMP response element-binding protein (CREB), and activator protein-1(AP-1). The potency of teduglutide is equivalent to native GLP-2 for the GLP-2R with enhanced biological activity due to resistance to DPP-IV cleavage, resulting in a longer half-life in the circulation.

Most pharmacology studies assessed the intestinotrophic activity of teduglutide in healthy animals through measures of intestinal weight, morphological analysis and in some cases protein and DNA content, barrier function and D-xylose absorption. The intestinotrophic effect was used to elaborate a full pharmacological profile of teduglutide, including an assessment of dose response, optimal treatment regimen, maximum effect and reversibility. Teduglutide showed intestinotrophic activity in mice, rats, ferrets, minipigs, dogs, and monkeys. The intestinotrophic effect follows a sigmoidal dose-response curve with an ED_{50} of 0.98 mcg/day (equivalent to 0.05 mg/kg/day) in mice. Depending on dose and duration of treatment, the intestinotrophic effect reaches a plateau, and reverses if administration is discontinued. The intestinotrophic effect in mice was independent of a once or twice daily treatment regimen.

Pharmacology studies on the intestinotrophic activity of teduglutide in healthy animals were complemented by studies in various animal models of intestinal disease including total parenteral nutrition (TPN)-induced intestinal hypoplasia, short bowel resection, and various models of induced and spontaneous gastrointestinal damage. Teduglutide has demonstrated the ability to protect the intestinal epithelium from TPN -induced intestinal hypoplasia and enhance intestinal functionality by increasing nutrient absorption and expanding mucosal surface area in models of short bowel resection.

A cardiovascular and respiratory safety pharmacology study was conducted in beagle dogs administered 0.1, 1 and 10 mg/kg doses of teduglutide intravenously and no treatment-related effects were observed that were attributed to teduglutide. No effect of teduglutide was noted on the human ether-à-go-go-related gene (hERG) channel or canine cardiac Purkinje fibers. In addition no central nervous system effects were observed in rodents receiving teduglutide at doses well above the targeted clinical therapeutic dose (500 times the recommended daily human dose of 0.05 mg/kg).

The effect of teduglutide is specific to the gastrointestinal tract. Intestinal mucosal absorptive surface area increased as assessed by intestinal weight, mucosal architecture, DNA and protein content. The functional absorptive capacity is increased in normal animals and restored in animals following small bowel resection or TPN-induced intestinal atrophy.

TOXICOLOGY

Subchronic and Chronic Toxicity

Hyperplasia in the gallbladder and hepatic biliary ducts of mouse, juvenile minipig and monkey species as well as in the stomach and pancreatic ducts of monkey species were observed in subchronic and chronic toxicology studies at doses ranging from 0.2 to 50 mg/kg/day. These observations were potentially related to the expected intended pharmacology of teduglutide and were to a varying degree reversible within an 8- to 13-week recovery period following chronic administration.

Injection site reactions

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

Carcinogenesis and Mutagenesis

Carcinogenic potential of teduglutide was assessed in 2-year subcutaneous carcinogenicity studies in rats and mice. In a 2-year carcinogenicity study in Wistar Han rats at subcutaneous doses of 3, 10 and 35 mg/kg/day (60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences

of adenomas in the bile duct and jejunum of male rats. No malignant tumors were observed.

In a 2-year carcinogenicity study in Crl:CD1(ICR) mice at subcutaneous doses of 1, 3.5 and 12.5 mg/kg/day (20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gallbladder; it also caused adenocarcinomas in the jejunum in male mice at the high dose of 12.5 mg/kg/day (about 250 times the recommended human dose).

Teduglutide was negative in the Ames test, chromosomal aberration test in Chinese hamster ovary cells, and in an in vivo mouse micronucleus assay.

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 (1000 times the recommended daily human dose of 0.05 mg/kg). Teduglutide was not associated with effects on reproductive performance, in utero or developmental parameters measured in studies to investigate fertility, and embryo-fetal development and pre- and post-natal development. Pharmacokinetic data demonstrated that the teduglutide exposure of fetal rabbits and suckling rat pups was very low.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrREVESTIVE®*
Teduglutide for injection

Read this carefully before you start taking **REVESTIVE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **REVESTIVE**.

What is REVESTIVE used for?
REVESTIVE is used to treat adults with Short Bowel Syndrome. Short Bowel Syndrome is a disorder arising from an inability to absorb food nutrients and fluid across the gastrointestinal tract (gut) due to not enough surface area. It is often caused by surgical removal of all or part of the small intestine.

How does REVESTIVE work?
REVESTIVE improves the absorption of fluids from your remaining gut by increasing the surface area and function of your remaining gut.

What are the ingredients in REVESTIVE?
Medicinal ingredients: teduglutide
One vial of powder contains 5 mg of teduglutide. After reconstitution, each vial contains 5 mg teduglutide in 0.5 mL of solution, corresponding to a concentration of 10 mg/mL.

Non-medicinal ingredients: dibasic sodium phosphate heptahydrate, L-histidine, mannitol, monobasic sodium phosphate monohydrate. The diluent contains sterile water for injection.

REVESTIVE comes in the following dosage forms:
REVESTIVE is a powder and diluent for solution for injection (5 mg powder in vial, 0.5 mL diluent in pre-filled syringe). Pack size of 28 each.

The powder is white and the diluent is clear and colorless.

Do not use REVESTIVE if:
- you are allergic to teduglutide or any of the other ingredients of this medicine;
- you have or are suspected to have cancer in the gastrointestinal tract, including liver, gallbladder, bile ducts or pancreas;
- you have had cancer in the gastrointestinal tract, including liver, gallbladder, bile ducts or pancreas, within the last five years.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REVESTIVE. Talk about any health conditions or problems you may have, including if you:

- have a history of bowel obstruction. Your doctor will consider this when prescribing this medicine.
- 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. This may require closer monitoring and more frequent changes to the amount of parenteral nutrition/IV fluid that you receive.
- have decreased kidney function. Your doctor may need to give you a lower dose of this medicine.
- have severely decreased liver function. Your doctor will consider this when prescribing this medicine.

Medical check-ups before and during treatment with REVESTIVE

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 growths that may be normal or abnormal) and remove them. It is recommended that your doctor performs a follow-up colonoscopy between 1 to 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.

Your doctor will take special care and monitor your small bowel function and monitor for signs and symptoms indicating problems with your gallbladder, bile ducts and pancreas.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

REVESTIVE may affect how other medicines are absorbed from the gut and therefore how well they work. Your doctor may have to change your dose of other medicines.

How to take REVESTIVE:

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

REVESTIVE is injected under the skin (subcutaneously) once daily. The injection can be self-administered or given by another person, for example your doctor, his/her assistant or your home nurse. If you are injecting the medicine yourself, you must receive adequate training by your doctor or nurse. Do not use the same area each day for each injection. Rotate the site of injection between the upper, lower, left and right side of your belly, either arm or either thigh.

You will find detailed instructions for the preparation, reconstitution and administration of REVESTIVE at the end of this leaflet.

Usual 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.

Overdose:

If you think you have taken too much REVESTIVE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
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.

Keep using this medicine for as long as your doctor prescribes it for you. Do not stop using this medicine without consulting your doctor, as a sudden stop can cause changes in your fluid balance.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

What are possible side effects from using REVESTIVE?
These are not all the possible side effects you may feel when taking REVESTIVE. If you experience any side effects not listed here, contact your healthcare professional.

Very common (may affect more than 1 in 10 people):
- Stomach pain
- Feeling sick (nausea)
- Bloated stomach
- Vomiting
- Respiratory tract infection (any infection of the sinuses, throat, airways or lungs)
- Swelling of hands and/or feet
- Reddening, pain or swelling at the site of the injection
- Swelling of stoma (an artificial opening for waste removal)

Common (may affect up to 1 in 10 people):
- Passing gas (flatulence)
- Decreased appetite
- Problems sleeping
- Rash (hypersensitivity)
- Bleeding of the skin
- Cough

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional in all cases**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Reduced flow of bile from the gallbladder and/or inflammation of the gallbladder: 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		√	
Congestive heart failure: Tiredness, shortness of breath or swelling of ankles or legs, sudden weight gain		√	
Intestinal obstruction (blockage of the bowel): Stomach ache, vomiting and constipation		√	
Inflammation of the pancreas (pancreatitis): Stomach ache and fever		√	
UNCOMMON			
Fainting: If heart rate and breathing are not normal and you don't awaken fast, seek help as soon as possible		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

Note: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

The unopened vials may be stored below 25ºC.

Do not freeze.

The product should be used within 3 hours after reconstitution.

Do not use this medicine if you notice that the solution is cloudy or contains particulate matter.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Dispose of all needles and syringes in a sharps disposal container.

Keep out of reach and sight of children.

If you want more information about REVESTIVE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or by calling 1-844-633-6713.

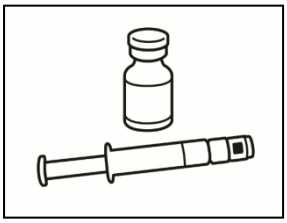
This leaflet was prepared by Shire Pharmaceuticals Ireland Limited.

*REVESTIVE is a registered trade-mark of Shire-NPS Pharmaceuticals, Inc.

Last Revised October 30, 2018

Instructions for preparing and injecting REVESTIVE

Important information:
- Read the Patient Medication Information before using REVESTIVE.
- REVESTIVE is for injection under the skin (subcutaneous injection).
- Do not inject REVESTIVE into a vein (intravenously) or muscle (intramuscularly).
- Keep REVESTIVE out of the sight and reach of children.
- Do not use REVESTIVE after the expiry date which is stated on the carton, the vial and the pre-filled syringe. The expiry date refers to the last day of that month.
- Store below 25°C.
- Do not freeze.
- The product should be used within 3 hours after reconstitution.
- Do not use REVESTIVE if you notice that the solution is cloudy or contains particulate matter.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.
- Dispose of all needles and syringes in a sharps disposal container.



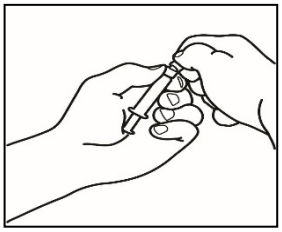
Materials in the REVESTIVE pack:
- 28 vials with 5 mg teduglutide as a powder
- 28 pre-filled syringes with diluent

Materials needed but not included in the pack:
- Reconstitution needles (size 22G, length 1½" (0.7 x 40 mm))
- 1 mL injection syringes (with scale intervals of 0.02 mL or smaller)
- Thin injection needles for subcutaneous injection (e.g. size 26G, length 5/8" (0.45 x 16 mm))
- Alcohol swabs
- A puncture-proof container for safe disposal of the used syringes and needles

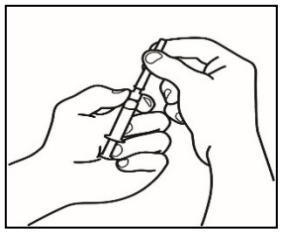
NOTE: Before you start, make sure you have a clean work surface and that you have washed your hands before proceeding.

1. Assemble the pre-filled syringe

Once you have all the materials ready, you need to assemble the pre-filled syringe. The following procedure shows how you do this.



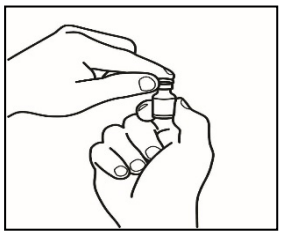
1.1 Take the pre filled syringe with diluent and flip off the top part of the white plastic cap so that it is ready for the reconstitution needle to be attached.



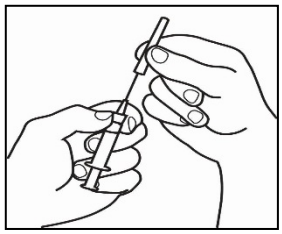
1.2 Attach the reconstitution needle (22G, 1½" (0.7 x 40 mm)) to the assembled pre-filled syringe by screwing it on in a clockwise direction.

2. Dissolve the powder

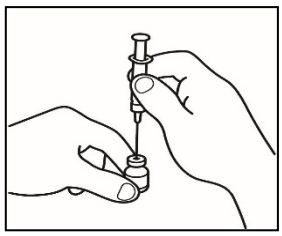
Now you are ready to dissolve the powder with the diluent.



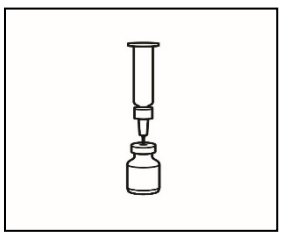
2.1 Remove the green flip-off button from the powder vial, wipe the top with an alcohol wipe and allow to dry. Do not touch the top of the vial.



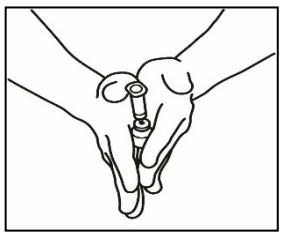
2.2 Uncap the reconstitution needle on the assembled pre-filled syringe with diluent without touching the tip of the needle.



2.3 Taking the powder vial, insert the reconstitution needle attached to the assembled pre-filled syringe into the centre of the rubber stopper and gently push the plunger all the way down to inject all the diluent into the vial.

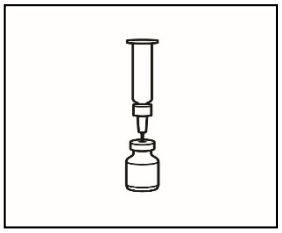


2.4 Leave the reconstitution needle and empty syringe in the vial. Let the vial rest for approximately 30 seconds.



2.5 Gently roll the vial between your palms for about 15 seconds. Then gently turn the vial upside-down once with the reconstitution needle and empty syringe still in the vial.

NOTE: Do not shake the vial. Shaking the vial may produce foam, which makes it difficult to extract the solution from the vial.



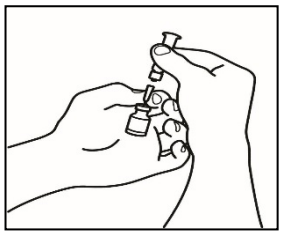
2.6 Let the vial rest for about two minutes.

2.7 Observe the vial for any undissolved powder. If any powder remains, repeat steps 2.5 and 2.6. Do not shake the vial. If there is still some undissolved powder, discard the vial and start the preparation again from the beginning with a new vial.

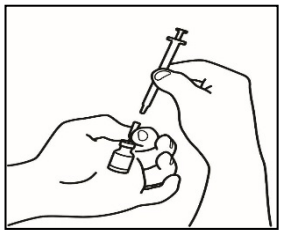
NOTE: The final solution should be clear. If the solution is cloudy or contains particulate matter, do not inject it.

NOTE: The product should be used within 3 hours after reconstitution.

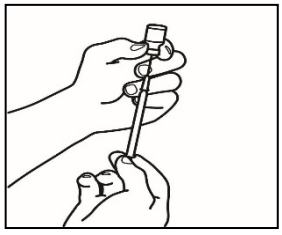
3. Prepare the injection syringe



3.1 Remove the reconstitution syringe from the reconstitution needle which is still in the vial and discard the reconstitution syringe.

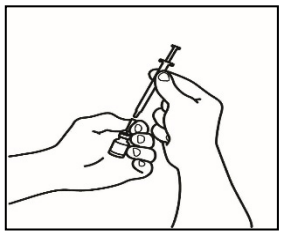


3.2 Take the injection syringe and attach it to the reconstitution needle which is still in the vial.

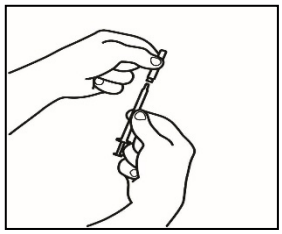


3.3 Turn the vial upside down, slide the tip of the reconstitution needle close to the stopper and allow all the medicine to fill the syringe by pulling the plunger back gently.

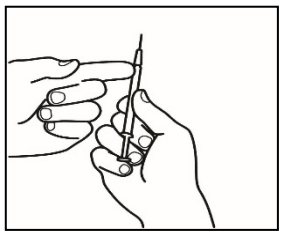
NOTE: If your doctor has told you that you need two vials, prepare a second pre-filled syringe with diluent and a second powder vial as shown in the main steps 1 and 2. Withdraw the solution from the second vial into the same injection syringe by repeating step 3.



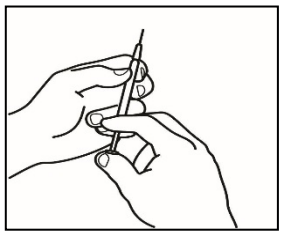
3.4 Remove the injection syringe from reconstitution needle leaving the needle in the vial. Discard the vial and reconstitution needle together into the sharps disposal container.



3.5 Take the injection needle (26G, 5/8" [0.45 x 16 mm]), but do not remove the plastic needle cap. Attach the needle to the injection syringe containing the medicine.

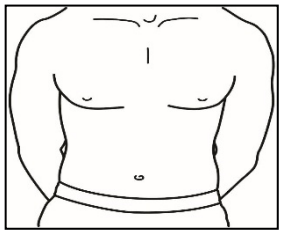


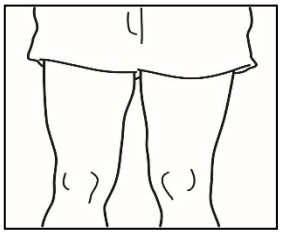
3.6 Check for air bubbles. If air bubbles are present, gently tap the syringe until they rise to the top. Then gently push up the plunger to expel the air.



3.7 Your dose in mL has been calculated by your doctor. Expel any excessive volume from the syringe with the needle cap still on until your dose is reached.

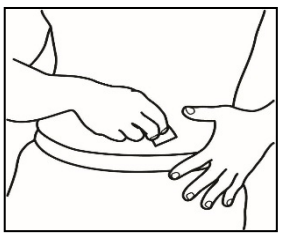
4. Inject the solution



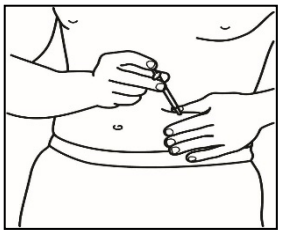


4.1 Find an area on your belly, upper arm, or on your thigh where it is easy for you to give the injection (see the diagram).

NOTE: Do not use the same area each day for each injection - rotate sites (use upper, lower, and left and right side of your belly, or either arm or thigh) to avoid discomfort. Avoid areas that are inflamed, swollen, scarred or covered by a mole, birthmark or other lesion.



4.2 Clean the intended site of injection on your skin with an alcohol swab, using a circular motion, working outwards. Allow the area to air-dry.



4.3 Remove the plastic cap from the needle of the prepared injection syringe. Gently grasp the cleaned skin at the injection site with one hand. With the other hand, hold the syringe as you would with a pencil. Bend your wrist back and quickly insert the needle at a 45° angle.

4.4 Pull back the plunger slightly. If you see any blood in the syringe, withdraw the needle and replace the needle on the injection syringe with a clean one of the same size. You can still use the medicine that is already in the syringe. Try to inject in another place in the cleaned skin area.

4.5 Inject the medicine slowly by pushing steadily on the plunger until all the medicine is injected and the syringe is empty.

4.6 Pull the needle straight out of the skin and discard the needle and syringe together into the sharps disposal container. A small amount of bleeding may occur. If necessary, press gently on the injection site with an alcohol swab or 2x2 gauze until any bleeding has stopped.

Dispose all needles and syringes in a sharps disposal container or hard-walled container (for example, a detergent bottle with a lid). This container must be puncture proof (top and sides). If you need a sharps disposal container, please contact your doctor.