

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **REVESTIVE**[®]
Teduglutide for injection

Powder for Solution for injection, 5 mg per vial, Subcutaneous Injection

Alimentary tract and metabolism products
ATC Code: A16AX08

Takeda Canada Inc.
22 Adelaide Street West,
Suite 3800
Toronto Ontario M5H 4E3

Date of Initial Approval:
September 4, 2015

Date of Revision:
December 30, 2020

Submission Control No: 241622

REVESTIVE[®] is a registered trademark of Shire-NPS Pharmaceuticals, Inc., a Takeda company. Takeda[®] and the Takeda Logo are trademarks of Takeda Pharmaceutical Company Limited, used under license.

RECENT MAJOR LABEL CHANGES

N/A

TABLE OF CONTENTS

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics.....	4
1.2 Geriatrics.....	4
2 CONTRAINDICATIONS	4
4 DOSAGE AND ADMINISTRATION	5
4.1 Dosing Considerations.....	5
4.2 Recommended Dose and Dosage Adjustment.....	5
4.3 Administration.....	5
4.4 Reconstitution.....	6
4.5 Missed Dose.....	7
5 OVERDOSAGE	7
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	7
8 WARNINGS AND PRECAUTIONS	8
8.1 Special Populations	11
8.1.1 Pregnant Women	11
8.1.2 Breast-feeding.....	11
8.1.3 Pediatrics (≥1 year to <18 years of age).....	12
8.1.4 Geriatrics (>65 years of age).....	12
9 ADVERSE REACTIONS	12
9.1 Adverse Reaction Overview.....	12
9.2 Clinical Trial Adverse Reactions.....	13
9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.....	16
9.5 Clinical Trial Adverse Reactions (Pediatrics).....	16
9.6 Post-Market Adverse Reactions.....	17
10 DRUG INTERACTIONS	17
10.2 Overview.....	17
10.3 Drug-Drug Interactions.....	17
10.4 Drug-Food Interactions.....	17
10.5 Drug-Herb Interactions.....	17
10.6 Drug-Laboratory Test Interactions.....	17
11 ACTION AND CLINICAL PHARMACOLOGY	18
11.1 Mechanism of Action.....	18
11.2 Pharmacodynamics.....	18
11.3 Pharmacokinetics.....	19

12	STORAGE, STABILITY AND DISPOSAL.....	21
	PART II: SCIENTIFIC INFORMATION	22
14	PHARMACEUTICAL INFORMATION.....	22
15	CLINICAL TRIALS.....	23
15.1	Trial Design and Study Demographics	23
15.2	Study Results	25
16	NON-CLINICAL TOXICOLOGY	30
	PATIENT MEDICATION INFORMATION	32
	INSTRUCTIONS FOR PREPARING AND INJECTING REVESTIVE	37

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

REVESTIVE® (teduglutide for injection) is indicated for the treatment of adults and pediatric patients 1 year of age and above 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 in adults 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, Monitoring and Laboratory Tests**) prior to starting treatment with REVESTIVE.

1.1 Pediatrics

Pediatrics (≥1 year of age to <18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of REVESTIVE in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use (see **CLINICAL TRIALS**).

If no overall improvement is achieved after 6 months, the need for continued treatment should be assessed.

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that 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.

2 CONTRAINDICATIONS

REVESTIVE is contraindicated in patients who:

- are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**,
- 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Geriatrics (>65 years of age)

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

Patients with Renal Impairment

Reduce the dose by 50% in adult 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.

No pediatric patients with renal insufficiency were included in trials. Population pharmacokinetic modelling suggests response in pediatric patients with renal insufficiency would be consistent with that of adults with renal insufficiency.

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.

There are no data available from pediatric patients with active, severe, or unstable hepatic impairment.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of REVESTIVE for both adults and pediatric patients (aged 1 year and above) 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, upper arms, and the abdomen. REVESTIVE should not be administered intravenously or intramuscularly.

REVESTIVE should not be administered to pediatric patients weighing less than 10 kg.

4.3 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).

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

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

visit and inform the patient accordingly. The injection volume per body weight is provided in Table 1.

Body weight (kg)	Volume to be injected (mL)
10-11	0.05
12-13	0.06
14-17	0.08
18-21	0.10
22-25	0.12
26-29	0.14
30-33	0.16
34-37	0.18
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

4.4 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.

Table 2: Reconstitution

Vial Size	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, the solution should be used immediately. Microbial, chemical and physical stability have been demonstrated for up to 3 hours when stored below 25°C 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.

4.5 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.

5 OVERDOSAGE

The maximum dose of REVESTIVE studied during clinical development was 80 mg/day for 8 days in adult patients. No unexpected systemic adverse reactions were seen. Doses greater than 0.05 mg/kg were not assessed in pediatric patients. 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Powder for solution / • 5 mg/vial	dibasic sodium phosphate heptahydrate, L-histidine, mannitol, monobasic sodium phosphate monohydrate.

REVESTIVE is intended for subcutaneous injection and is supplied as a sterile, preservative free, white lyophilized powder for reconstitution with sterile Water for Injection. The REVESTIVE pack is supplied with the following:

REVESTIVE 5 mg (for adults and pediatrics ≥ 10 kg body weight)

- 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.

Other materials needed for administration but not included in the pack are:

Adults

- 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

Pediatrics

- Reconstitution needles (size 22G, length 1½" [0.7 x 40 mm])
- 1 mL injection syringes (with scale intervals of 0.02 mL or smaller)
- Injection needles for subcutaneous injection (e.g. size 30G, length ½" [0.31 x 12.7 mm])
- Alcohol swabs
- A puncture-proof container for safe disposal of the used syringes and needles

8 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 studies. 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.

Parents, caregivers, and healthcare professionals should be alert to signs of fluid overload and congestive heart failure in pediatric patients, particularly younger patients. Immediate assessment should be sought if symptoms such as sudden weight gain, peripheral edema, dyspnea, or signs such as tachypnea, tachycardia, or hepatomegaly are observed.

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 studies. 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 study 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**).

Fluid and Electrolyte Balance

To avoid fluid overload or dehydration, careful adjustment of parenteral support is required in patients taking REVESTIVE (see Cardiovascular, Fluid Overload and Fluid and Electrolyte Balance, Dehydration). Electrolyte balance and fluid status should be carefully monitored throughout treatment, especially during initial therapeutic response and discontinuation of teduglutide treatment (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Dehydration: Patients with SBS are susceptible to dehydration that may lead to acute renal failure. Fluid and electrolyte imbalance leading to dehydration and acute renal impairment/failure was similarly observed between patients with SBS receiving teduglutide and patients not receiving teduglutide. In general, dehydration can be prevented by appropriate and timely monitoring for fluid and electrolyte imbalance, and subsequent adjustment of parenteral fluid and electrolytes. This assessment should be conducted more frequently within the first few months after treatment response, at discontinuation of treatment, and during times of dehydration and acute metabolic stress such as intercurrent infection, intestinal obstruction, and during the post operative period.

Gastrointestinal

Gastrointestinal Neoplasia Including Hepatobiliary Tract: Based on the pharmacologic activity and findings in animals, including juvenile animals, REVESTIVE has the potential to cause hyperplastic changes in the small bowel and hepatobiliary tract. In carcinogenicity studies, neoplasia was observed in the small bowel and hepatobiliary tract in mice and rats. These observations were not confirmed in adult and pediatric patients in clinical studies.

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:

Adults: Colorectal polyps were identified during the clinical studies. 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.

Pediatrics: Prior to initiating treatment with REVESTIVE, fecal occult blood testing should be done for all children and adolescents. Colonoscopy/sigmoidoscopy is required if there is unexplained blood in the stool. Subsequent fecal occult blood testing should be done annually in children and adolescents while they are receiving REVESTIVE.

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

Monitoring and Laboratory Tests

For safety monitoring, patients should undergo the following within 6 months prior to starting treatment with REVESTIVE:

- Adults: Perform a colonoscopy of the entire colon with removal of polyps (see **WARNINGS AND PRECAUTIONS, Colorectal Polyps**).
- Pediatric patients: Perform fecal occult blood testing; if there is unexplained blood in the stool, perform colonoscopy/sigmoidoscopy (see **WARNINGS AND PRECAUTIONS, Colorectal Polyps**).
- Obtain baseline laboratory assessments (bilirubin, alkaline phosphatase, lipase and

amylase).

Colonoscopy/sigmoidoscopy is recommended for all children and adolescents after 1 year of treatment, every 5 years thereafter while on continuous treatment with REVESTIVE, and if they have new or unexplained gastrointestinal bleeding.

Electrolyte balance and fluid status should be carefully monitored throughout treatment, especially during initial therapeutic response and discontinuation of teduglutide treatment (see **WARNINGS AND PRECAUTIONS, Fluid and Electrolyte Balance**).

Laboratory assessments (bilirubin, alkaline phosphatase, lipase and amylase) are recommended every 6 months while on REVESTIVE. If any clinically meaningful changes are seen, further evaluation is recommended as clinically indicated (i.e., imaging of the biliary tract, liver or pancreas).

Renal

Renal Insufficiency: In adult 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**).

No pediatric patients with renal insufficiency were included in trials. Population pharmacokinetic modelling suggests response in pediatric patients with renal insufficiency would be consistent with that of adults with renal insufficiency.

8.1 Special Populations

8.1.1 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.

8.1.2 Breast-feeding

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.

8.1.3 Pediatrics (≥1 year to <18 years of age)

Safety and efficacy in pediatric patients under 1 year of age have not been established.

The safety and efficacy of REVESTIVE in the treatment of SBS have been established in pediatric patients 1 through 17 years of age. Use in this population is supported by adequate and well controlled studies in adults, as well as safety, pharmacokinetic and pharmacodynamic data from 2 studies in pediatric patients up to 24 weeks duration. These studies included 87 pediatric patients treated with REVESTIVE in the following groups: 5 infants (1 year to less than 2 years), 75 children (2 years to less than 12 years) and 7 adolescents (12 years to less than 18 years). The results from pharmacokinetic modeling support the recommended dose of 0.05 mg/kg daily.

In these 2 studies and the corresponding open-label extension studies, 89 pediatric patients were administered REVESTIVE prospectively for up to 69 weeks. The total extent of exposure was ≤12 weeks for 10 (11.2%) patients, 12 to ≤24 weeks for 18 (20.2%) patients, 24 to ≤48 weeks for 37 (41.6%) patients, and 48 to ≤96 weeks for 24 (27.0%) patients. Adverse reactions observed in these studies were similar in pediatric patients who received REVESTIVE to those seen in the adult population (See **ADVERSE REACTIONS, Clinical Trial Adverse Reactions (Pediatrics)**).

8.1.4 Geriatrics (>65 years of age)

Of the 595 subjects treated with REVESTIVE in clinical studies, 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.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

Across all clinical studies in adults, 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 adult 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%).

In the core pediatric studies, 87 patients aged 1-17 years were exposed to teduglutide. Of these, 8 received 0.0125 mg/kg/day, 38 received 0.025 mg/kg/day, and 41 received 0.05 mg/kg/day. In these studies, 98.9% of teduglutide-treated patients experienced treatment-emergent adverse events, 29.9% experienced severe events, 62.1% experienced serious

events, and 31.0% experienced drug-related adverse reactions.

9.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The rates of adverse reactions in adult 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 4. 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.

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

^aPercentage 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 Interests

Concomitant Oral Medication: REVESTIVE can increase the absorption of concomitant oral medications such as benzodiazepines and psychotropic agents. One subject in the adult placebo-controlled studies 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.

In the pediatric clinical studies (up to 69 weeks of exposure), there were no adverse events associated with increased absorption of oral medications.

Fluid Overload: In the adult placebo-controlled studies, 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.

In the pediatric clinical studies (up to 69 weeks of exposure), there was 1 subject who had a non-serious related adverse event of peripheral edema in the 0.025 mg/kg/day group.

Gallbladder, Biliary and Pancreatic Disease: For gallbladder and biliary disease in the adult 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 adult 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 adult 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 adult extension studies, 1 subject was diagnosed with chronic pancreatitis; and 1 subject was diagnosed with acute pancreatitis.

In the pediatric studies, 2 patients treated with teduglutide experienced 4 biliary events, of which one event of cholestasis in a patient with pre-existing liver disease was serious. In case of gallbladder or bile duct-related symptoms, the need for continued treatment with REVESTIVE should be reassessed.

Immunogenicity: Based on integrated data from 2 studies in adults with SBS (a 6-month randomized placebo-controlled study, followed by a 24-month open-label study), the development of anti-teduglutide antibodies in subjects who received subcutaneous administration of 0.05 mg/kg teduglutide once daily was 3% (2/60) at Month 3, 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 studies, 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).

In pediatric patients who received subcutaneous administration of 0.05 mg/kg REVESTIVE once daily for 24 weeks, the rate of anti-teduglutide antibody formation at Month 6 was 19% (5/26) and was similar to the rate of antibody formation in adult patients (18%). Of the 5 pediatric patients who had developed antibodies to teduglutide at Month 6, 2 patients had neutralizing antibodies. However, with a longer duration of treatment, the rate of anti-teduglutide formation at Month 12 was higher in pediatric patients at 54% (14/26), compared to that of adults (24%). Of the 14 pediatric patients who had developed antibodies to teduglutide at Month 12, 1 patient had neutralizing antibodies. In the relatively small population of pediatric patients that developed anti-teduglutide antibodies, there did not appear to be an association with adverse events of hypersensitivity.

Injection Site Reactions: In the placebo-controlled studies 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.

In the pediatric clinical studies TED-C14-006 and TED-C13-003, 20% (17/87) of subjects that received REVESTIVE experienced an injection site reaction. All of the events were mild in severity, non-serious, and none led to drug discontinuation.

Intestinal Obstruction: Overall, in the adult clinical studies, 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 studies 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 adult 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 studies 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.

In the 24-week pediatric clinical study, there was 1 serious event of intestinal obstruction and 1 serious event of ileus that were assessed as related to teduglutide. Teduglutide was temporarily withheld and there were no recurrences once teduglutide was restarted.

Intestinal Polyps: In the adult 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).

In the pediatric clinical studies (up to 69 weeks of exposure), there were no confirmed cases of polyps.

Malignancy: Three subjects were diagnosed with malignancy in the adult 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.

In the pediatric clinical studies (up to 69 weeks of exposure), there were no events of malignancy.

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 studies had abnormal chemistry at baseline. The most common markedly abnormal clinical chemistry analyte post-baseline in adult 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 adult 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.

In the pediatric clinical studies, no clinically meaningful changes in laboratory values were observed in association with teduglutide treatment.

9.5 Clinical Trial Adverse Reactions (Pediatrics)

In two completed clinical studies and the corresponding open-label extension studies, there were 89 pediatric subjects (aged 1 through 17 years) treated with REVESTIVE prospectively for up to 69 weeks. Overall, the safety profile of REVESTIVE (including type and frequency of adverse reactions, and immunogenicity) in children and adolescents was similar to that in adults.

The most common adverse events experienced by pediatric patients treated with 0.05 mg/kg REVESTIVE were pyrexia (43.9%), cough (34.1%), abdominal pain (24.4%), device-related infection (19.5%), headache (17.1%), nausea (12.2%), fatigue (12.2%), and rhinitis (12.2%).

No data are available for children under 1 year of age.

9.6 Post-Market Adverse 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

10 DRUG INTERACTIONS

10.2 Overview

No clinical pharmacokinetic 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.

10.3 Drug-Drug Interactions

Interactions with other drugs have not been established.

Drugs that Increase Heart Rate

REVESTIVE caused an increase in heart rate in a clinical study in healthy volunteers (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Heart Rate Increase; ACTION AND 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.

10.4 Drug-Food Interactions

Interactions with food have not been established.

10.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 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.

11.2 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.

Based on preclinical pharmacology studies, 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 increased in normal animals and was restored in animals following small bowel resection or total parenteral nutrition (TPN)-induced intestinal atrophy.

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. The intestinotrophic effect follows a sigmoidal dose-response curve with an ED50 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.

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.

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).

11.3 Pharmacokinetics

Table 5: Summary of REVESTIVE Pharmacokinetic Parameters in Adult 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-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.

Elimination: 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: Following subcutaneous administration of 0.05 mg/kg daily dose, similar C_{max} of teduglutide across age groups was demonstrated by population pharmacokinetics modeling. However, lower exposure (AUC) and shorter half-life were seen in pediatric patients 1 to 17 years of age, as compared with adults. The pharmacokinetic profile of teduglutide in this pediatric population, as evaluated by clearance and volume of distribution, was different from that observed in adults after correcting for body weights. Specifically, body weight corrected clearance decreases with increasing age from 1 year old to adults.

Table 6 contains the steady state data derived from population pharmacokinetic modeling in pediatric patients after dosing with 0.05 mg/kg/day.

Table 6: Teduglutide pharmacokinetic parameters following subcutaneous dosing of REVESTIVE 0.05 mg/kg/day				
	C_{max} (ng/mL)*	$t_{1/2}$ (h)	AUC (ng-hr/mL)*	Clearance (L/h)
Aged 1-11 years (n=37)	33.5±11.5	0.7±0.2	128±56.7	7.45±2.1
Ages 12-17 years (n=3)	29.7±8.4	1.0±0.01	154±17.6	13.0±2.3

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

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.

Sex: No clinically relevant differences were observed based on sex.

Hepatic Insufficiency: Adult 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 adult subjects with moderate to severe renal impairment or end stage renal disease (ESRD), teduglutide C_{max} and AUC_{0-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-inf}) in ESRD subjects compared to healthy subjects.

12 STORAGE, STABILITY AND DISPOSAL

Store REVESTIVE 5 mg below 25°C. Do not freeze.

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

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

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

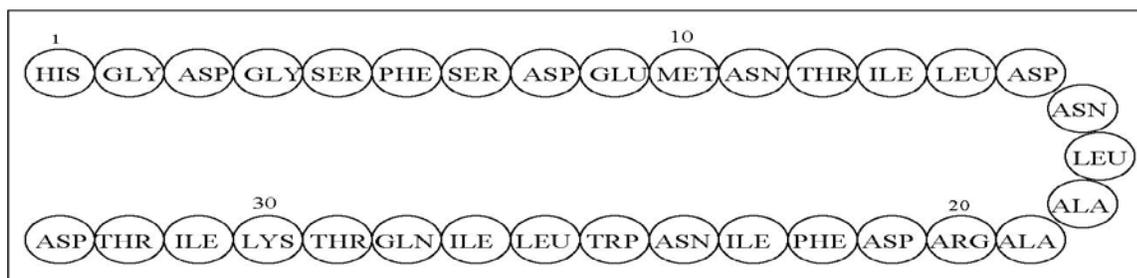
Drug Substance

Proper name: teduglutide

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

Molecular formula and molecular mass: C₁₆₄H₂₅₂N₄₄O₅₅S, 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-iso-leucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-iso-leucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-iso-leucyl-L-glutamyl-L-threonyl-L-lysyl-L-iso-leucyl-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.

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.

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

Table 7: Summary of Patient Demographics for Clinical Studies 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])	Sex
Placebo-controlled Studies					
CL0600-020	<u>Phase 3, multicenter, randomized, double-blind, placebo-controlled study</u> 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	<u>Phase 3, multicenter, randomized, double-blind, placebo-controlled study</u> 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 7: Summary of Patient Demographics for Clinical Studies 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])	Sex
Pediatric Study					
TED-C14-006	<u>Phase 3, multicenter, study</u> To evaluate safety, efficacy, and pharmacodynamic study investigating two arms; a teduglutide treatment arm and a SOC. The treatment arm were blinded and randomized to either strength.	A: REVESTIVE 0.025 mg/kg/day SC	A: 24	6.6 (1-14)	M/F = 16/8
		B: REVESTIVE 0.05 mg/kg/day SC	B: 26	6.2 (2-15)	M/F = 19/7
		C: SOC 24 week	C: 9	5.7 (2-17)	M/F = 6/3
Extension Studies					
CL0600-021	<u>Phase 3, multicenter, open label, extension study of CL0600-020</u> 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

Table 7: Summary of Patient Demographics for Clinical Studies 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])	Sex
CL0600-005	<p><u>Phase 3, multicenter, randomized, double-blind extension study of CL0600-004</u></p> <p>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.</p>	<p>A: REVESTIVE 0.05 mg/kg/day SC</p> <p>B: REVESTIVE 0.10 mg/kg/day SC</p> <p>C: REVESTIVE 0.05 mg/kg/day SC</p> <p>D: REVESTIVE 0.10 mg/kg/day SC</p> <p>28 weeks</p>	<p>A: 6</p> <p>B: 7</p> <p>C: 25</p> <p>D: 27</p>	<p>42.2 (21 – 59)</p> <p>56.6 (41 – 73)</p> <p>46.7 (21 – 67)</p> <p>49.4 (20 – 80)</p>	<p>M = 2 F = 4</p> <p>M = 3 F = 4</p> <p>M = 15 F = 10</p> <p>M = 13 F = 14</p>

PN/I.V. = parenteral nutrition/intravenous fluid; SC = subcutaneous; TED = teduglutide; NTT= no teduglutide treatment

15.2 Study Results

Clinical Studies in Adults

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 study 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).

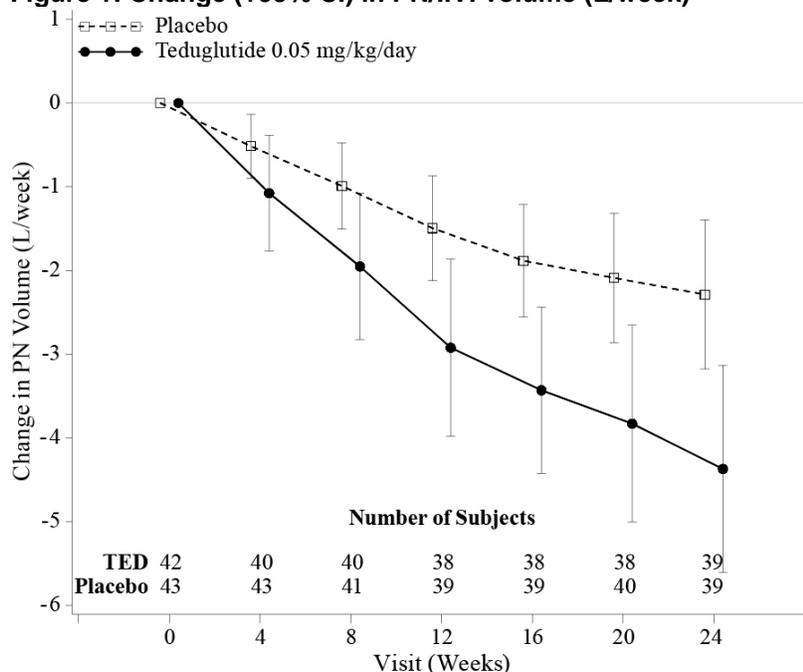
The percentage of subjects with a duration of response for ≥3 consecutive visits was higher in the REVESTIVE group (24/43 subjects, 55.8%) than in the placebo group (12/43 subjects, 27.9%). The distribution of duration of response was statistically significant (p=0.005).

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)



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.

24-month Exposure

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.

Clinical Study in Pediatric Patients

Study TED-C14-006

TED-C14-006 was a 24 week, multicenter study conducted in 59 pediatric subjects aged 1 year through 17 years who were dependent on PS. The objective was to evaluate safety/tolerability, pharmacokinetics and efficacy of REVESTIVE. Subjects chose whether to receive REVESTIVE or standard of care (SOC). Subjects in the REVESTIVE treatment arm were randomized in a double blind manner to 0.025 mg/kg/day (n=24) or 0.05 mg/kg/day (n=26), while 9 subjects enrolled in the SOC arm. Randomization to REVESTIVE dose group was stratified by age. Results described below correspond to subject diary data in the ITT population at the recommended dose of 0.05 mg/kg SC once daily.

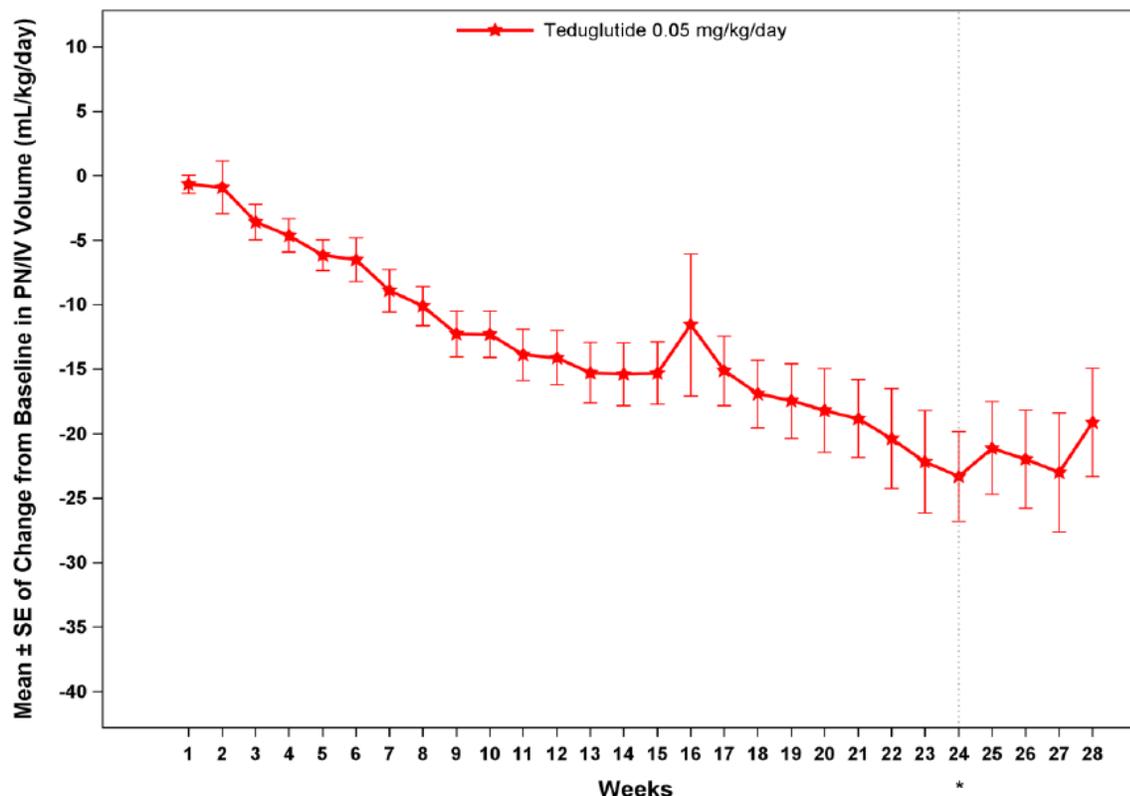
The primary endpoint was a reduction in PS volume of at least 20% from baseline to the end of treatment. Intake diaries were used to collect and evaluate each subject's nutritional support. The subject/parent/guardian completed the appropriate fields of the PN/I.V. and enteral nutrition (EN) sections of the intake diary. The PN/I.V. volume and infusion duration and EN volume were provided in the intake diaries, which were completed every day of the study from screening through Week 28/end of study. Site personnel determined the actual PN/I.V. and EN daily calories based on diary entries. PS prescription data were also collected to assess accuracy of the diary data.

The mean age of subjects at baseline was 6.2 years. The most common reasons for intestinal resection leading to SBS were gastroschisis (54%, 14/26), midgut volvulus (23%, 6/26), and necrotizing enterocolitis (12%, 3/26). Stoma was present in 19% (5/26) of subjects, and the most common type was jejunostomy (80%, 4/5). The mean length of remaining small intestine was 46.75 (\pm 27.90) cm (range: 9 to 120 cm). Among the 96.2% (25/26) of subjects who had remaining colon, the colon was in continuity in 88% (22/25) of subjects. At baseline, the mean PS volume was 60.09 (\pm 29.19) mL/kg/day (range: 23.6 to 132.9 mL/kg/day) and mean PS infusion time was 6.6 (\pm 0.79) days/week (range: 5 to 7 days/week) and 11.2 (\pm 2.99) hours/day (range: 7 to 20 hours/day).

Table 8: Summary of efficacy endpoints at Week 24 for Study TED-C14-006—Pediatric patients treated with REVESTIVE 0.05 mg/kg/day (n=26) [Patient diary-derived results]

Reduction in PS volume of at least 20% n (%)	18 (69%)
Achieved enteral autonomy n (%)	3 (12%)
Change from baseline PS volume (mL/kg/day) (mean [range])	-23 [-61.40, 1.89]
Change from baseline in daily time spent for infusion (hours/day) (mean [range])	-3.03 [-14.0, 4.2]

Figure 2: Absolute Change from Baseline in PN/IV Volume (mL/kg/day) by Week based on Diary Data



PN/IV = parenteral nutrition/intravenous fluids.

*Week 24 is the end of treatment visit.

Average daily value is calculated as [(sum of non-missing daily values in the diary/number of days with non-missing values)]/last available body weight prior to the visit.

16 NON-CLINICAL TOXICOLOGY

Subchronic and Chronic Toxicity

Hyperplasia in the small and large intestines across species (mice, rats, juvenile minipigs and cynomolgus monkeys) and 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, injection site effects (inflammation/fibrosis/degeneration/severe granulomatous cellulitis) were noted across species, including juvenile animals. The effects were partially reversible.

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.

Juvenile Animal Toxicity Data

In a juvenile toxicity study, teduglutide was administered twice daily to juvenile Göttingen minipigs at subcutaneous doses of 1, 5, and 25 mg/kg/day from post-natal day 7 and continuing for 90 days. Exposures (AUC) at these doses were 24-, 50-, and 340-fold the pediatric clinical exposure for ages 1 to 11 years at 0.05 mg/kg, respectively, and 20-, 42-, and 283-fold the pediatric clinical exposure for ages 12 to 17 years at 0.05 mg/kg, respectively.

In juvenile animals, teduglutide had the same pharmacological effect and toxicological target organ findings (intestintrophic effects, gall bladder mucosal hyperplasia, bile duct mucosal hyperplasia, injection site reactions) as those observed in normal healthy adult animals of other species used in toxicity studies.

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 and pediatric patients 1 year of age and above 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 with 0.5 mL of sterile water for injection, a 10 mg/mL sterile solution is obtained.

Non-medicinal ingredients: dibasic sodium phosphate heptahydrate, L-histidine, mannitol, monobasic sodium phosphate monohydrate. The diluent contains sterile water for injection that is provided in a pre-filled syringe.

REVESTIVE comes in the following dosage forms:

REVESTIVE is a powder and diluent for solution for under the skin (subcutaneous) injection (5 mg powder in a vial and 0.5 mL diluent in a 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

Colonoscopy Schedule in Adults

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.

Colonoscopy Schedule in Children (ages 1 through 17 years)

Before your child starts treatment with this medicine, your doctor will need to test for any hidden blood in the stool. If there is sign of unexplained blood in the stool, a colonoscopy will be required (a procedure to see inside your child's colon, rectum and the large intestine). It is recommended that your child's doctor tests for hidden blood in the stool every year while your child is receiving REVESTIVE.

Colonoscopy is recommended for all children after 1 year of treatment, every 5 years thereafter while on continuous treatment with REVESTIVE, and if they have new or unexplained blood in the stool.

Laboratory Testing

Your doctor will take special care and monitor your small bowel function and monitor for signs and symptoms indicating problems with your gallbladder, liver and pancreas by conducting initial laboratory tests (bilirubin, alkaline phosphatase, lipase and amylase) within 6 months before starting treatment with REVESTIVE and every 6 months while you are using REVESTIVE. If there is significant increase in test results, more tests may be needed (for example, imaging of the biliary tract, liver, or 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 upper 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.

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

Side effects were similar in adults and children. Other common events seen in children (ages 1 through 17 years) during clinical studies were; fever, infections related to the central line, headache, feeling tired, and runny nose.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		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.

Store REVESTIVE 5 mg below 25°C. Do not freeze.

Reconstituted solution: Store below 25°C. 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](#); the manufacturer's website www.takeda.com/en-ca, or by calling 1-800-268-2772.

This leaflet was prepared by Takeda Canada Inc.

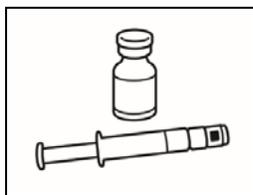
Last Revised December 30, 2020

REVESTIVE® is a registered trademark of Shire-NPS Pharmaceuticals, Inc., a Takeda company. Takeda® and the Takeda Logo are trademarks of Takeda Pharmaceutical Company Limited, used under license.

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:

Adults

- 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

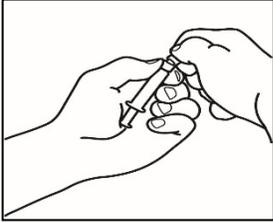
Pediatrics

- Reconstitution needles (size 22G, length 1½" [0.7 x 40 mm])
- 1 mL injection syringes (with scale intervals of 0.02 mL or smaller)
- Injection needles for subcutaneous injection (e.g. size 30G, length ½" [0.31 x 12.7 mm])
- Alcohol swabs
- A puncture-proof container for safe disposal of the used syringes and needles

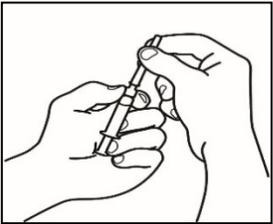
NOTE: Before you start, make sure you have a clean work surface and that you have washed your hands before proceeding.

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.



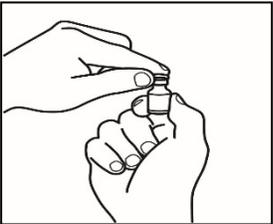
- 1.1 Take the pre filled syringe with diluent and flip off the top part of the white plastic cap so that it is ready for the reconstitution needle to be attached.



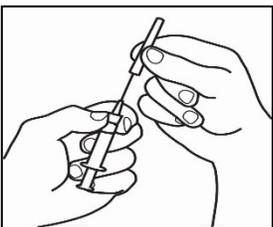
- 1.2 Attach the reconstitution needle (22G, 1½" (0.7 x 40 mm)) to the assembled pre-filled syringe by screwing it on in a clockwise direction.

2. Dissolve the powder

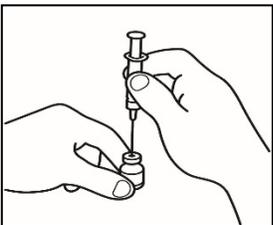
Now you are ready to dissolve the powder with the diluent.



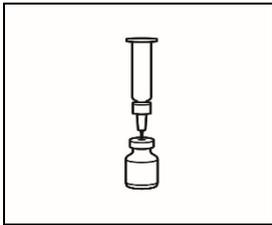
- 2.1 Remove the green flip-off button from the powder vial, wipe the top with an alcohol wipe and allow to dry. Do not touch the top of the vial.



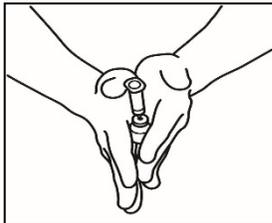
- 2.2 Uncap the reconstitution needle on the assembled pre-filled syringe with diluent without touching the tip of the needle.



- 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.

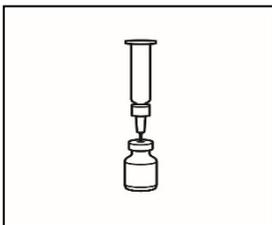


2.4 Leave the reconstitution needle and empty syringe in the vial. Let the vial rest for approximately 30 seconds.



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.



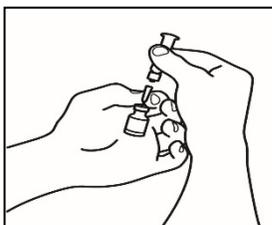
2.6 Let the vial rest for about two minutes.

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.

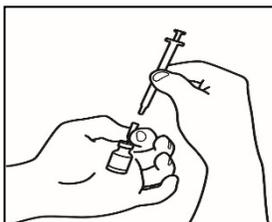
NOTE: The final solution should be clear. If the solution is cloudy or contains particulate matter, do not inject it.

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

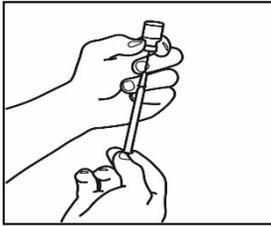
3. Prepare the injection syringe



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

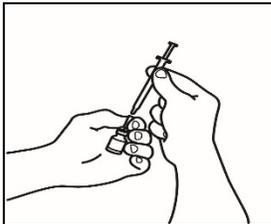


3.2 Take the injection syringe and attach it to the reconstitution needle which is still in the vial.

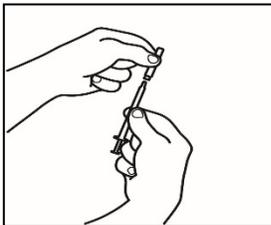


- 3.3 Turn the vial upside down, slide the tip of the reconstitution needle close to the stopper and allow **ALL** the medicine to fill the syringe by pulling the plunger back gently.

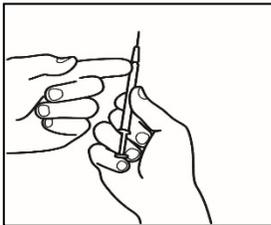
NOTE: If your doctor has told you that you need two vials, prepare a second pre-filled syringe with diluent and a second powder vial as shown in the main steps 1 and 2. Withdraw the solution from the second vial into the same injection syringe by repeating step 3.



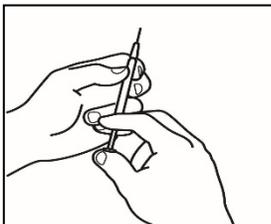
- 3.4 Remove the injection syringe from reconstitution needle leaving the needle in the vial. Discard the vial and reconstitution needle together into the sharps disposal container.



- 3.5 Take the injection needle (Adults: 26G, 5/8" [0.45 x 16 mm]) or (Pediatrics: 30G, 1/2" [0.31 x 12.7 mm]), but do not remove the plastic needle cap. Attach the needle to the injection syringe containing the medicine.

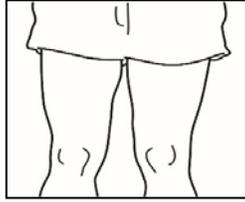
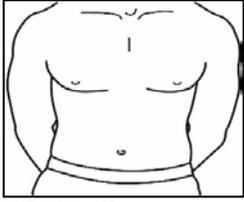


- 3.6 Check for air bubbles. If air bubbles are present, gently tap the syringe until they rise to the top. Then gently push up the plunger to expel the air.



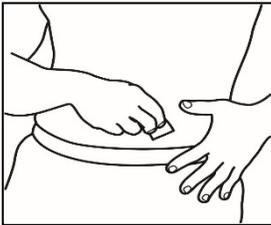
- 3.7 Your dose in mL has been calculated by your doctor. Expel any excessive volume from the syringe with the needle cap still on until your dose is reached.

4. Inject the solution

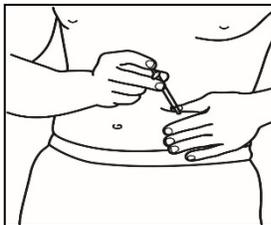


4.1 Find an area on your belly, upper arm, or on your thigh where it is easy for you to give the injection (see the diagram).

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 upper 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.