1 REVESTIVE 5 mg powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 5 mg of teduglutide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

REVESTIVE contains teduglutide powder and solvent for solution for injection. Each single-use vial contains 5 mg of teduglutide as a white lyophilised powder. The solvent is water for injections. After reconstitution, each vial contains 5 mg teduglutide in 0.5 mL of solution, corresponding to a concentration of 10 mg/mL with pH 6.9-7.9.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Patients should be stable at least to 4 weeks on their parenteral support regimen before initiating teduglutide therapy.

4.2 Dose and method of administration

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

Dose

The recommended daily dose of REVESTIVE is 0.05 mg/kg body weight administered by subcutaneous injection once daily.

After reconstitution with the solvent (0.5 mL water for injections), the prepared solution from each vial contains 10 mg/mL of teduglutide.

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

Continued treatment is recommended for patients who have weaned off parenteral nutrition.

Special populations

Elderly: No dose adjustment is necessary in patients above the age of 65 years.

Hepatic impairment: No dose adjustment is necessary for patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects. Teduglutide has not been formally studied in subjects with severe hepatic impairment.

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

Paediatric population: Safety and efficacy in paediatric patients have not been established.

Administration

Detailed instructions on the preparation (including assembly of the pre-filled syringe, dissolving the powder, preparing the injection syringe) and injection of REVESTIVE reconstituted solution are provided in the package leaflet.

The reconstituted solution must be injected subcutaneously into a cleaned area on the abdomen, or if this is not possible, on the thigh using a thin needle for subcutaneous injection. REVESTIVE should not be administered intravenously or intramuscularly.

Alternation of sites for subcutaneous injection is recommended. Sites of injection include the thighs, arms, and the quadrants of the abdomen.

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.

Determination of the number of vials needed for administration of one dose must be based on the individual patient's weight and the recommended dose of 0.05 mg/kg/day. The physician should at each visit weigh the patient, determine the daily dose to be administered until next visit and inform the patient accordingly. A table with the injection volume per body weight is provided below:

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

The powder in the vial must be dissolved by adding all the solvent from the pre-filled syringe. The vial should not be shaken, but can be rolled between the palms and gently turned upside-down once.

Reconstituted REVESTIVE is a sterile, clear, colourless to light straw-coloured solution, which should be free from particulates. The drug should be completely dissolved before the solution is withdrawn from the vial. Do not shake or freeze the reconstituted solution. The solution should not be used if it is cloudy or contains particulate matter. REVESTIVE does not contain any preservatives and should be used within 3 hours after reconstitution. The product is for single use in one patient only. Discard any residue.

Once the drug is completely dissolved, withdraw the prescribed dose 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 drawn up into the injection syringe containing the solution from the first vial. Any volume exceeding the prescribed dose in mL must be expelled and discarded.

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

4.3 Contraindications

Hypersensitivity to the active ingredient or to any of the excipients.

Active gastrointestinal malignancy (gastrointestinal tract, hepatobiliary, pancreatic).

Patients with a history of malignancies in the gastrointestinal tract including the hepatobiliary system within the last 5 years.

4.4 Special warnings and precautions for use

Colorectal polyps

Colorectal polyps were identified during the clinical trials. Colonoscopy of the entire colon with removal of polyps should be done within 6 months prior to starting treatment with teduglutide. A follow-up colonoscopy (or alternate imaging) is recommended between 1-2 years after initiating teduglutide. 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, teduglutide therapy should be discontinued.

Gastrointestinal neoplasia including hepatobiliary tract

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

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

Gallbladder and bile tract disease

Cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies. For identification of the onset or worsening of gallbladder/biliary disease, patients should undergo laboratory assessment of bilirubin and alkaline phosphatase prior to starting teduglutide, and while on teduglutide. If clinically meaningful changes are seen, further evaluation including imaging of the gallbladder and/or biliary tract is recommended and the need for continued teduglutide 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 teduglutide, and while on teduglutide. If clinically meaningful changes are seen, further evaluation such as imaging of the pancreas is recommended; and the need for continued teduglutide treatment should be reassessed.

Intestinal obstruction

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

Fluid and Electrolyte Balance

To avoid fluid overload or dehydration, careful adjustment of parenteral support is required in patients taking REVESTIVE. Electrolyte balance and fluid status should be carefully monitored throughout treatment, especially during initial therapeutic response and discontinuation of teduglutide treatment.

Fluid overload

Fluid overload and congestive heart failure have been observed in clinical trials. Fluid overload adverse events occurred most frequently during the first 4 weeks of therapy and decreased over time. There is a theoretical rationale that, during the initial several weeks of teduglutide treatment, subjects may become volume expanded if their PN/IV volumes are not appropriately down titrated.

Due to increased fluid absorption, 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. Patients should be advised to contact their physician in case of sudden weight gain, face swelling, swollen ankles and/or dyspnoea. 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. In case of a significant deterioration of cardiovascular disease, the need for continued teduglutide treatment should be reassessed.

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.

Concomitant medication

Patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption and may require dose adjustment of these medications while on teduglutide. Examples of such medications include benzodiazepines, opioids, digoxin, anti-hypertensives.

Special clinical conditions

REVESTIVE has not been studied in patients with severe, clinically unstable concomitant diseases (e.g. cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS), or in patients with malignancies within the last 5 years (also see section 4.3).

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.

Paediatric use

The safety and efficacy of teduglutide in the paediatric population has not been established.

Use in the elderly

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

4.5 Interaction with other medicines and other forms of interaction

Based upon the pharmacodynamic effects of teduglutide, there is a potential for increased absorption of concomitant oral medications, which should be considered if these drugs require titration or have a narrow therapeutic index.

Clinical interaction studies were not performed. No inhibition or induction of the cytochrome P450 enzyme system (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [10HMDZ and 6βT]) has been observed based on *in vitro* studies, although the relevance of *in vitro* studies to an *in vivo* setting is unknown. Teduglutide treatment is unlikely to result in P-glycoprotein-mediated drug interactions.

4.6 Fertility, pregnancy and lactation

Effects on fertility

There are no data on the effects of teduglutide on human fertility. There were no effects on fertility in rats administered with teduglutide at subcutaneous doses up to 50 mg/kg/day (about 180 times the recommended human dose of 0.05 mg/kg/day, based on body surface area).

Use in pregnancy (Category B1)

There are limited data from the use of teduglutide in pregnant women. Available data from case reports with teduglutide use in pregnant women have not identified a drug associated risk of major birth defects, miscarriage, or adverse maternal or foetal outcomes. A risk to the pregnant woman or developing foetus cannot be excluded. A decision should be made whether to initiate or discontinue treatment with teduglutide, taking into account the risk/benefit of therapy.

In animal studies, no adverse effects on embryofoetal development were observed in rats or rabbits given teduglutide during the period of organogenesis at subcutaneous doses up to 50 mg/kg/day (plasma AUC exposure more than 400 times clinical exposure at the recommended human dose of 0.05 mg/kg/day). There were no adverse effects on pre- and postnatal development in rats given teduglutide from early gestation to weaning at subcutaneous doses up to 50 mg/kg/day (about 180 times the recommended human dose of 0.05 mg/kg/day, based on body surface area). Pharmacokinetic data demonstrated that the teduglutide exposure of foetal rabbits and suckling rat pups was low. Because animal reproductive studies are not always predictive of human response, REVESTIVE should be used during pregnancy only if clearly needed.

Use in lactation

It is not known whether teduglutide is excreted in human milk. Teduglutide was excreted in the noncolostral milk of lactating rats (highest concentration 2.9% of the plasma concentration) following a single subcutaneous injection of 25 mg/kg (about 90 times the recommended human dose, based on body surface area). Because many drugs are excreted in human milk, because of the potential for serious adverse reactions to nursing infants from teduglutide 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.

4.7 Effects on ability to drive and use machines

Teduglutide has minor influence on the ability to drive and use machines. However, cases of syncope have been reported in clinical studies. Such events might impact the ability to drive and use machines.

4.8 Undesirable effects

Adverse events in REVESTIVE-treated patients with SBS participating in 2 randomised, placebo-controlled, 24-week, double-blind clinical studies (Studies CL0600-020 and CL0600-004, involving in total 109 patients treated with REVESTIVE) are listed in the Table 1 below. The most

commonly reported adverse events were abdominal pain (28%) and abdominal distension (17%), nausea (26%), injection site reactions (26%), headache (16%), vomiting (14%), urinary tract infection (13%), and nasopharyngitis (13%). Approximately 38% of the treated patients with a stoma experienced gastrointestinal stoma complications. The majority of these events were mild or moderate.

Table 1. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Reported in ≥5% of Subjects in All Teduglutide) - Safety Population - SBS Placebo Studies

	Placebo (N=59)	**Teduglutide (N=109)**
	n (%)	**n (%)**
Gastrointestinal Disorders		
Abdominal pain	12 (20.3)	31 (28.4)
Nausea	12 (20.3)	28 (25.7)
Abdominal distension	1 (1.7)	18 (16.5)
Vomiting	6 (10.2)	15 (13.8)
Flatulence	4 (6.8)	9 (8.3)
Diarrhoea	6 (10.2)	7 (6.4)
Abdominal pain upper	1 (1.7)	6 (5.5)
General Disorders and Administration Site Conditions		
Injection site haematoma	3 (5.1)	12 (11.0)
Fatigue	5 (8.5)	10 (9.2)
Pyrexia	5 (8.5)	10 (9.2)
Oedema peripheral	2 (3.4)	9 (8.3)
Injection site erythema	0	8 (7.3)
Infections and Infestations		
Nasopharyngitis	2 (3.4)	14 (12.8)
Urinary tract infection	7 (11.9)	14 (12.8)
Catheter sepsis	2 (3.4)	9 (8.3)
Influenza	1 (1.7)	8 (7.3)
Catheter related infection	1 (1.7)	6 (5.5)
Injury, Poisoning and Procedural Complications		
Gastrointestinal stoma complication	3 (5.1)	17 (15.6)
Metabolism and Nutrition Disorders		
Decreased appetite	2 (3.4)	8 (7.3)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3 (5.1)	7 (6.4)
Nervous System Disorders		
Headache	8 (13.6)	17 (15.6)

Adverse reactions are listed by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Adverse reactions from postmarketing experience are *italicised*.

Infections and infestations

Very common: Nasopharyngitis

Common: Influenza; *Influenza-like illness*

Immune system disorders

Not known: *Hypersensitivity*

Metabolism and nutrition disorders
Common: Decreased appetite
Uncommon: Fluid overload

Psychiatric disorders
Common: Insomnia

Nervous system disorders
Very common: Headache

Cardiac disorders
Common: Cardiac failure congestive

Respiratory, thoracic and mediastinal disorders
Common: Cough; Dyspnoea

Gastrointestinal disorders
Very common: Abdominal distension; Abdominal pain; Flatulence; Nausea; Vomiting
Common: Colonic polyp; Intestinal obstruction; Pancreatitis*; Small intestinal stenosis
Uncommon: Duodenal polyp; Colonic stenosis; Pancreatic duct stenosis

Hepatobiliary disorders
Common: Cholecystitis; Cholecystitis acute

General disorders and administration site conditions
Very common: Injection site reaction**; Oedema peripheral
Not known: *Fluid retention*

Injury, poisoning and procedural complications
Very common: Gastrointestinal stoma complication

*Includes the following preferred terms: Pancreatitis, *Pancreatitis acute*, and Pancreatitis chronic.
**Includes the following preferred terms: Injection site haematoma, Injection site erythema, Injection site pain, Injection site swelling and Injection site haemorrhage.

Immunogenicity

Based on data from a trial and its extension in adults with SBS (a 6-month randomised placebo-controlled trial, followed by a 24-month open-label extension), the development of anti-teduglutide antibodies in subjects who received subcutaneous administration of 0.05 mg/kg teduglutide once daily was 3% (2/60) at Month 3, 17% (13/77) at Month 6, 24% (16/67) at Month 12, 33% (11/33) at Month 24 and 48% (14/29) at Month 30.

The antibody formation has not been associated with clinically relevant safety findings, reduced efficacy or changed pharmacokinetics of REVESTIVE.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

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

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766) .

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Teduglutide is an analogue of naturally occurring human 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. GLP-2 is known to increase intestinal and portal blood flow, decrease intestinal motility and inhibit gastric acid secretion. Teduglutide binds to the GLP-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, nitric oxide and keratinocyte growth factor (KGF). Teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth.

Pharmacodynamic effects

The ability of teduglutide to improve intestinal absorption of fluid and nutrients was studied in 17 adult subjects with Short Bowel Syndrome (SBS) using daily doses of 0.03, 0.10, and 0.15 mg/kg (n=2-3 per dose group) in a 21-day, open-label, multi-centre, dose-ranging study. All subcutaneous (abdomen) doses studied, except 0.03 mg/kg once daily, decreased stomal output or faecal 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.

At a dose 5 times the maximum recommended dose, teduglutide did not prolong the QTc interval to any clinically relevant extent.

Clinical trials

The safety and clinical evidence of efficacy of REVESTIVE in adult patients with SBS is derived from 2 randomised placebo-controlled trials and 2 extension trials. In these studies, 173 patients received REVESTIVE at doses of 0.05 mg/kg (n=134) or 0.10 mg/kg (n=39) via subcutaneous injection.

Study CL0600-020

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

For 8 weeks (or less) prior to randomisation, investigators optimised the PN/IV volume of all subjects. Optimisation was followed by a 4-week to 8-week period of fluid stabilisation. Subjects then were randomised (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/IV volume adjustments (up to 30% decrease) and clinical assessments were made at 2, 4, 8, 12, 16, 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/IV volume from baseline (immediately before randomisation) to both weeks 20 and 24.

The mean age of subjects was 50.3 years. Mean duration of PN/IV dependency prior to enrolment was 6.25 years (range 1-25.8 years). The most common reasons for intestinal resection leading to

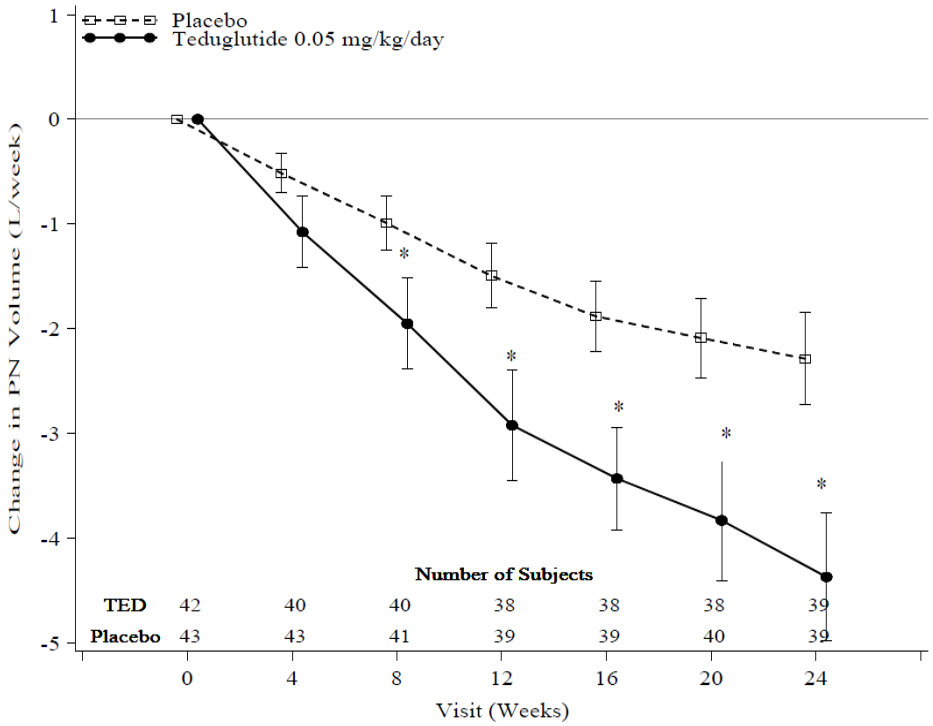
SBS were vascular disease (34.1%, 29/85), Crohn's Disease (21.2%, 18/85), and "other" (21.2%, 18/85). Stoma was present in 44.7% (38/85) of subjects, and the most common type was jejunostomy/ileostomy (81.6%, 31/38). The mean length of remaining small intestine was 77.3±64.4 cm (range: 5 to 343 cm). The colon was not in continuity in 43.5% (37/85) of subjects. At baseline, the mean (±SD) prescribed days per week for PN/IV 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 randomised patients. Sixty-three percent (27/43) of subjects treated with REVESTIVE versus 30% (13/43) of placebo-treated subjects were considered responders (p=0.002).

At week 24, the mean reduction in weekly PN/IV volume was 4.4 L for subjects treated with REVESTIVE (from pre-treatment baseline of 12.9 L) versus 2.3 L for placebo-treated subjects (from pre-treatment baseline of 13.2 L/week) (p<0.001).

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

Figure 1: Change (±SE) in PN/IV volume (L/week)



L=liter; SE=standard error, TED=teduglutide
* p < 0.05

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 enrol in CL0600-021 (37 received REVESTIVE; 39 received placebo). An additional 12 subjects whom entered CL0600-021 had been optimised and stabilised but not randomised in CL0600-020 because of closed enrolment.

24 months 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/IV 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 in parenteral support. At the end of the study, 14 (48.3%), 7 (24.1%) and 5 (17.2%) subjects achieved a reduction of 1, 2, or 3 days per week in PN/IV support, respectively. Two subjects were weaned off their PN/IV 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/IV support while on REVESTIVE.

30 months exposure

Thirty subjects on REVESTIVE 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 the responders in CL0600-020 who had completed 2 additional years of continuous treatment with REVESTIVE, 96% (21/22) demonstrated durability in the effect of REVESTIVE.

The mean reduction in PN/IV (n=30) was 7.55 L/week (a 65.6% reduction from baseline). Ten subjects were weaned off their PN/IV support while on treatment with REVESTIVE for 30 months. Subjects were maintained on REVESTIVE even if no longer requiring PN/IV support. These 10 subjects had required PN/IV 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/IV support. At 24 months, 21 (70%), 18 (60%) and 18 (60%) of the 30 completers achieved a reduction of 1, 2, or 3 days per week in PN/IV support, respectively.

Study CL0600-004

CL0600-004 was a randomised, double-blind, placebo-controlled, three-arm parallel-group, multinational study in adults with SBS who were dependent on PN/IV support for at least 12 months and required PN at least 3 times per week. After a period of optimisation and stabilisation similar to CL0600-020, subjects were randomised 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=33), or placebo (n=16). The primary efficacy endpoint was a graded categorical score that did not achieve statistical significance for the high dose (0.10 mg/kg/day).

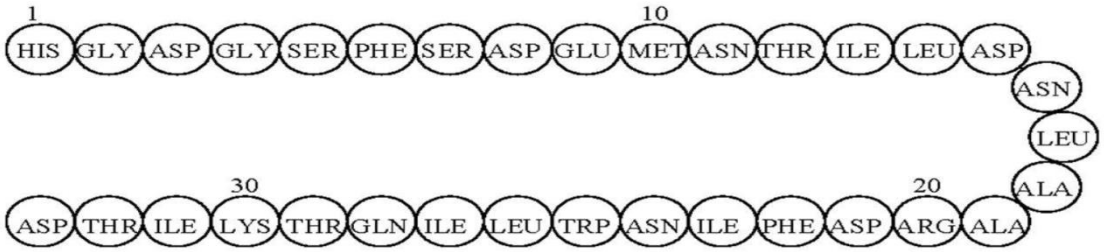
Study CL0600-005

CL0600-005 was a randomised, double-blinded, parallel-group, extension of CL0600-004, in which 65 subjects from CL0600-004 received REVESTIVE for up to an additional 28 weeks of treatment. Of the responders in CL0600-004 who entered CL0600-005, 75% (12/16) demonstrated durability in the effect of 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/IV volume was 4.9 L/week (52% reduction from baseline) after one year of continuous treatment with REVESTIVE. The subjects who had been completely weaned off PN/IV support in CL0600-004 remained off parenteral support through CL0600-005. During CL0600-005, an additional subject from CL0600-005 was weaned off parenteral support.

Active ingredient

The active ingredient teduglutide (rDNA origin) is a 33 amino acid glucagon-like peptide-2 (GLP-2) analogue manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. The chemical composition of teduglutide is L-histidyl-L-glycyl-L-aspartyl-L-glycyl-L-seryl-L-phenylalanyl-L-seryl-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-isoleucyl-L-glutaminyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid.

Structural formula:



Molecular formula: $C_{164}H_{252}N_{44}O_{55}S$
Molecular weight: 3752 Daltons
CAS registry number: 197922-42-2

5.2 Pharmacokinetic properties

Absorption

In healthy subjects, teduglutide 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 mean peak teduglutide concentration (C_{max}) was 36.4 ng/mL and the mean area under the curve ($AUC_{0-\tau}$) was 235 ng○h/mL. No accumulation of teduglutide was observed following repeated subcutaneous administrations.

Distribution

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

Metabolism

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

Excretion

In healthy subjects, teduglutide plasma clearance was approximately 123 mL/h/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 1.1 hours in SBS subjects.

Dose Linearity

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

Special populations

Gender: No clinically relevant gender differences were observed.

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

Hepatic impairment: 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 teduglutide. The pharmacokinetics of teduglutide was not assessed in subjects with severe hepatic impairment.

Renal impairment: In subjects with moderate to severe renal impairment or end-stage renal disease (ESRD), teduglutide C_{max} and $AUC_{0\text{-}inf}$ increased with the degree of renal impairment following a single subcutaneous administration of 10 mg teduglutide. Teduglutide exposure increased by a factor of 2.1 (C_{max}) and 2.6 ($AUC_{0\text{-}inf}$) in ESRD subjects compared to healthy subjects. The AUC and C_{max} values of subjects with mild renal impairment were 50% higher than in subjects without renal impairment.

5.3 Preclinical safety data

Carcinogenicity

In a 2-year rat carcinogenicity study with subcutaneous doses of 3, 10 and 35 mg/kg/day, treatment related benign neoplasms included tumours of the bile duct epithelium in 1 out of 44 males at 10 mg/kg and 4 out of 48 males and 1 out of 48 females at 35 mg/kg, associated with respective exposures (plasma AUC) approximately 32-fold and 155-fold clinical exposure at the recommended dose. Adenomas of the jejunal mucosa were observed in 5 out of 50 males at 155-fold clinical exposure, and jejunal adenocarcinoma and jejunal adenoma were observed in 1 out of 50 males at 3 mg/kg (approximately 10-fold clinical exposure). These tumours were not observed in females at exposures up to 97-fold clinical exposure.

In a 2-year mouse subcutaneous carcinogenicity study, treatment related benign neoplasms of the gallbladder developed in 5 out of 71, 2 out of 70 and 6 out of 70 males dosed at 1, 3.5 and 12.5 mg/kg/day respectively, associated with respective exposures (plasma AUC) approximately 12-, 45- and 186-fold clinical exposure at the recommended dose. Four out of 68 males and 1 out of 69 females dosed at 12.5 mg/kg developed a jejunal adenocarcinoma.

There is limited evidence that sub-therapeutic doses of teduglutide may accelerate tumour growth in rodent models of chemically-induced intestinal neoplasia. The human clinical relevance of rodent models of chemically-induced intestinal neoplasia is uncertain.

Genotoxicity

Teduglutide was negative in the Ames test, chromosomal aberration test in Chinese hamster ovary cells, and in an *in vivo* mouse micronucleus assay. The genotoxic potential of teduglutide is considered to be low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Histidine
Mannitol
Monobasic sodium phosphate monohydrate
Dibasic sodium phosphate heptahydrate

Solvent
Water for injections

pH adjuster
Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

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

6.3 Shelf life

4 years.

REVESTIVE does not contain any preservatives and should be used within 3 hours after reconstitution.

6.4 Special precautions for storage

Store below 25°C. (Do not freeze.)

Please refer to section 6.3 for storage conditions for reconstituted product.

6.5 Nature and contents of container

Each pack of REVESTIVE contains:

- **5 mg teduglutide powder** in glass vial with rubber stopper
- **0.5 mL of solvent of sterile water for injections** in pre-filled glass syringe.

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

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. All needles and syringes should be disposed of in a sharps disposal container.

Information on the preparation of the drug product

Please refer to section 4.2. Detailed instructions on the preparation are provided in the package leaflet. The final solution should be clear. Do not use if the solution is cloudy or contains particular matter.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Takeda New Zealand Limited
Level 10, 21 Queen Street
Auckland 1010
New Zealand
Telephone: 0508 169 077

www.takeda.com/en-nz

9 DATE OF FIRST APPROVAL

19 December 2019

10 DATE OF REVISION OF THE TEXT

26 March 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6, 4.9, 5.1, 8 and end of document	Update to Trademark statement at end of document, removal of reference to Australian Poisons Information Centre, and correction to Sponsor website and address. Minor spelling changes.