# Taiwan Food and Drug Administration

# Assessment Report

**Trade Name：利腸服 5 毫克注射劑 / Revestive injection 5mg**

**Active Ingredient：Teduglutide**

**License Number：衛部菌疫輸字第 001145 號**

**Applicant：台灣武田藥品工業股份有限公司**

**Approval Date：2020/11/16**

**Indication：**
**一歲以上患有短腸症且依賴靜脈營養的成人及兒童病人，病人須處於腸道手術適應期後之穩定狀態。**

**Revestive is indicated for the treatment of adult patients and patients aged 1 year and above with Short Bowel Syndrome (SBS) who are dependent on parenteral support. Patient should be stable following a period of intestinal adaptation after surgery.**

## Background Information

| | |
|---|---|
| **Trade Name** | 利腸服 5 毫克注射劑 /<br>Revestive injection 5mg |
| **Active Ingredient(s)** | Teduglutide |
| **Applicant** | 台灣武田藥品工業股份有限公司 |
| **Dosage Form & Strengths** | 5 mg powder and solvent for solution for injection. |
| **Indication** | 一歲以上患有短腸症且依賴靜脈營養的成人及兒童病人，病人須處於腸道手術適應期後之穩定狀態。<br>Revestive is indicated for the treatment of adult patients and patients aged 1 year and above with Short Bowel Syndrome (SBS) who are dependent on parenteral support. Patient should be stable following a period of intestinal adaptation after surgery. |
| **Posology** | 成人及兒童病人的建議劑量為每日一次 0.05 毫克/公斤體重(皮下注射)。<br>The recommended daily dose is 0.05 mg/kg body weight administered by subcutaneous injection once daily. |
| **Pharmacological Category**<br>**ATC Code** | A16AX08 |

# 2. Summary Report

### 2.1 Chemistry, Manufacturing and Controls Evaluation

#### 2.1.1 Drug substance

Teduglutide, the drug substance (DS) of brand name Revestive injection, is a novel recombinant analogue of native glucagon-like peptide-2 (GLP-2).

Teduglutide is manufactured in *E. coli* using recombinant technology. It is a 33 amino acid peptide that differs from GLP-2 in the substitution of alanine (in GLP-2) for glycine (in Teduglutide) at the second position at the N-terminus. The molecular weight of teduglutide is 3752 g/mol. Detailed description of the origin, history and preparations of cell banks including MCB, WCBs and EPC were provided. Adventitious agent safety testing, identity and genetic stability for cell banks were conducted based on the recommendations in ICH guidance. Raw materials of direct and indirect biological origin are also justified.

Characterization studies are presented including primary and higher-order structure, molecular mass, isoelectric point, purity, and biological activity of target binding, as well as process-related and product-related impurities. The exclusion for some process-related impurities from routine testing is appropriately justified. Manufacturing process with in-process controls, process development were minor changes, including scale-up and life-cycle process improvement. Comparability studies, process validation, specification, analytical methods and validation, batch analyses, and reference materials were provided abundantly to demonstrate the quality and consistency of teduglutide using commercial process.

Long-term (-20±5°C) stability studies have been carried out for teduglutide batches. The stability studies are derived from teduglutide batches produced with the commercial process.

**2.1.2 Drug product**

Revestive injection, 5 mg/vial teduglutide, is supplied in 3 mL single-use vials containing 5 mg teduglutide as a lyophilized powder. The lyophilized powder is intended for reconstitution with 0.5 mL sterile water for injection (sWFI) immediately before self-administration by subcutaneous injection. The reconstituted product is a nominal 10 mg/mL solution of teduglutide containing L-histidine (7.8 mg/mL), mannitol (30 mg/mL), and sodium phosphate (3.3 mg/mL as phosphate). The manufacturer for the drug product (DP) is Patheon Italia S.p.A., Italy.

The composition of DP is listed. The excipients for DP are complied with USP/Ph. Eur./JP. No novel excipients are used in the formulation. DP manufacturing process and formulation development were described appropriately. Adequate justifications for potential impurities and the container closure integrity were provided to support the suitability of the container closure system. The compatibility data was submitted adequately. Manufacturing process within process controls, process validation, specification and batch analyses were provided and showed that the manufactures are controlled properly and consistently.

The release specification and stability specification for Revestive injection include appearance, general characteristic properties, quantity, identity, purity/impurity, potency, and safety. The specifications of Revestive injection are generally acceptable.

Stability studies, conducted under long-term storage (30°C±2°C / 65%±5% RH) and accelerated (40°C±2°C / 75%±5% RH) conditions, and in-use stability studies could support the storage and on-site usage for Revestive injection, as well as the photostability studies. The data of long-term stability studies supports the shelf life of Revestive injection for 36 months for climatic zone IVa.

In conclusion, information on the drug substance and finished drug product is regarded as appropriate to support the quality of Revestive injection.

## 2.2 Preclinical Pharmacology/Toxicology Evaluation

### 2.2.1 Pharmacological Studies

Teduglutide is a drug for the treatment of short bowel syndrome (SBS) in patients aged 1 year and above. Teduglutide is a novel recombinant analogue of the human glucagon-like peptide-2 (GLP-2). It is a 33 amino acid peptide that differs from GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus.

The pharmacology studies indicated that subcutaneous administration of teduglutide increased small and large intestinal weight and villus height. Teduglutide improved small and large intestinal weight, villus height, and villus/crypt ratio, reduced by total parenteral nutrition. In the rodent model of SBS, teduglutide administration resulted in increased luminal diameter, increased total intestinal and mucosal wet weight, increased crypt/villus height and increased sucrase activity in both the remaining proximal jejunum and distal ileum. In the other enteritis model, teduglutide accelerated the reversal of increased intestinal permeability caused by inflammation. Teduglutide did not increase cAMP production in the cells expressing human GLP-1 receptor. Teduglutide did not affect somatostatin or insulin release from the pancreas.

The results of safety pharmacology studies indicated that teduglutide did not significantly affect CNS at the highest dose in the study. However, this highest dose was lower than the NOAEL in a repeated-dose toxicity study in the same species. In the cardiovascular safety pharmacology study in anesthetized dogs, some clinical signs presented in the low dose group rather than the higher dose groups, and were considered not related to teduglutide.

### 2.2.2 Toxicological Studies

Pivotal repeated-dose toxicity studies were conducted in mice, rats, and monkeys. Most of the clinical changes were due to the pharmacological effects of teduglutide. The major adverse finding was inflammation at the injection sites.

Both *in vitro* and *in vivo* genotoxicity studies presented negative results. The fertility and early embryonic development study showed that the NOAEL of teduglutide on fertility was the same as the NOAEL in the general toxicity study. Non-dose-dependent increases in the incidence of incomplete ossification of bones were noted in the offspring generation in rats after the parental generation received teduglutide, which was not identified as a maternal or direct embryo-fetal toxicity. The PPND study and the juvenile study indicated that juvenile animals exhibited a similar response to mature animals.

The carcinogenicity study in rats represented a statistically increased benign adenoma occurrence in the bile duct and jejunum in males. Teduglutide did not cause precipitation or coagulation in whole blood samples but produced local irritation and hemorrhage after a single perivenous or intra-arterial injection.

### 2.3 Clinical Pharmacology Evaluation

#### 2.3.1 General Pharmacodynamics and Pharmacokinetics

Teduglutide was absorbed with a peak concentration at 3-5 hours following subcutaneous (SC) administration. The $C_{max}$ and AUC of teduglutide were dose proportional over the dose range of 0.05 to 0.4 mg/kg. No accumulation of teduglutide was observed following repeated daily SC administration. Teduglutide had an absolute bioavailability of 88% after SC administration. The exposure ($AUC_{0-t}$ and $AUC_{inf}$) of teduglutide was similar after SC injection at the thigh, the arm, and the abdomen. Following IV administration, teduglutide had a mean Vss of about 103 mL/kg. Teduglutide is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as the endogenous GLP-2. Following IV administration, teduglutide plasma clearance was approximately 123 mL/hr/kg which is roughly equivalent to the GFR suggesting that teduglutide is primarily cleared by the kidneys. After SC administration, mean terminal half-life of teduglutide was approximately 2 hours in healthy subjects and 1.3 hours in SBS subjects. Following SC administration, similar $C_{max}$ of teduglutide across age groups was demonstrated by population PK analysis. However, lower AUC and shorter half-life were seen in pediatric patients aged 1-17 years, as compared with adults.

#### 2.3.2 Interaction Studies

Based on *in vitro* studies, significant inhibition or induction on tested CYP450 isozymes was not observed at 2000 ng/mL teduglutide, a 55-fold concentration greater than the median $C_{max}$ at the clinical dose of 0.05 mg/kg. Additionally, teduglutide was neither a substrate nor an inhibitor of P-gp at concentrations above 2000 ng/mL. No *in vivo* DDI studies were conducted based on the results from *in vitro* studies. On the other hand, there appears to be a potential for DDIs following the PD activity of teduglutide, which might result in enhanced absorption of concomitant medication. This needs to be considered when it is co-administered with drugs requiring titration or having a narrow therapeutic index.

#### 2.3.3 Special Populations

The population PK analysis showed that there are no clinically relevant effects of age, gender, and hepatic impairment on the PK of teduglutide. In hepatic impairment study (CL0600-017), teduglutide $C_{max}$ and AUC in subjects with moderate hepatic impairment were 10 ~15% lower compared to those in healthy subjects after a single SC administration of 20 mg teduglutide. Teduglutide was not assessed in subjects with severe hepatic impairment. In renal impairment

study (CL0600-018), the PK parameters of teduglutide increased in the following ranges for $AUC_{inf}$ ($C_{max}$): 1.5 (1.6) fold for moderate renal impairment, 1.7 (1.4) fold for severe renal impairment and 2.6 (2.1) fold for end stage renal impairment when compared to normal renal function.

## 2.4 Clinical Efficacy and Safety Evaluation

### 2.4.1 Efficacy Results

In this submission, two Phase III, randomized, double-blind, multi-national, multi-center, placebo-controlled studies (Studies [CL0600-004] and [CL0600-020]) were provided to support the efficacy of Revestive (teduglutide) 0.05 mg/kg/day for adult patients with Short Bowel Syndrome (SBS). In addition, two open-label studies ([TED-C13-003] and [TED-C14-006]) were conducted to investigate the efficacy of two doses of Revestive (0.025 mg/kg/day and 0.05 mg/kg/day) in pediatric patients with SBS. The key efficacy findings are summarized below.

- **Study [CL0600-004]**

Study [CL0600-004] was a Phase III, randomized, double-blind, multi-national, multi-center, placebo-controlled study to evaluate the efficacy of two teduglutide doses (0.05 mg/kg/day and 0.10 mg/kg/day) compared with placebo in patients with parenteral nutrition dependent SBS.

The primary efficacy endpoint of the study was a graded response score. Per the protocol, the comparison between 0.10 mg/kg/day dose and placebo was performed first, followed by the comparison between 0.05 mg/kg/day and placebo. For this study, the 0.10 mg/kg/day teduglutide dose did not show a difference from placebo (p-value = 0.161). The subsequent comparison, although deemed as exploratory, showed a difference between the 0.05 mg/kg/day teduglutide dose and placebo (nominal p-value = 0.007).

- **Study [CL0600-020]**

Study [CL0600-020] was a Phase III, randomized, double-blind, multi-national, multi-center, placebo-controlled study to evaluate the efficacy of 0.05 mg/kg/day teduglutide compared with placebo in patients with parenteral nutrition dependent SBS.

The primary efficacy endpoint was the proportion of subjects who demonstrated at least a 20% reduction in PN volume at Week 20 and sustained through Week 24. The responder rate was statistically significantly higher in the teduglutide 0.05 mg/kg/day group than in the placebo group (62.8% vs. 30.2%, CMH test p-value = 0.002, Table 2.4.1-1).

Although, 0.05 mg/kg/day teduglutide dose group is significantly better than placebo in overall population. However, the exploratory test for homogeneity across the two randomization strata

is rejected (p = 0.022, Table 2.4.1-1). It is clear from these subgroup analyses, albeit exploratory, that there is heterogeneity across the two randomization strata. The overall results were mainly driven by the patients whose baseline PN/I.V. weekly volumes that are greater than 6 Liters (Table 2.4.1-1).

**Table 2.4.1-1 Number and Percent of patients by graded response (Study [CL-0600-020], ITT)**

| Response status (overall) | Placebo (N = 43) | Teduglutide 0.05 mg/kg/day (N = 43) | p-value |
|---|---|---|---|
| Non-responder | 30 (69.8%) | 16 (37.2%) | 0.002 |
| Responder | 13 (30.2%) | 27 (62.8%) | |
| **p-value for test for homogeneity across randomization strata : 0.022** | | | |
| Baseline PN volume > 6 L | Placebo (N = 36) | Teduglutide 0.05 mg/kg/day (N = 35) | p-value |
| Non-responder | 26 (72.2%) | 10 (28.6%) | 0.0003 |
| Responder | 10 (27.8%) | 25 (71.4%) | |
| Baseline PN volume ≦ 6 L | Placebo (N = 7) | Teduglutide 0.05 mg/kg/day (N = 8) | p-value |
| Non-responder | 4 (57.1%) | 6 (75.0%) | 0.608 |
| Responder | 3 (42.9%) | 2 (25.0%) | |

Six key secondary efficacy endpoints were pre-specified and the results are summarized in Table 2.4.1-2. Tests for all key secondary endpoints until stopping PN usage were significant.

**Table 2.4.1-2**

| Endpoint | Placebo (N = 43) | Teduglutide 0.05 mg/kg/day (N = 43) | p-value | Significant or not |
|---|---|---|---|---|
| Percent change from baseline to last dosing visit in weekly PN volume | -21.27 | -32.26 | 0.023 | Yes |
| Change from baseline to last dosing visit in weekly PN volume | -2.35 | -4.42 | < 0.001 | Yes |
| Duration of response | 27.9% | 55.8% | 0.005 | Yes |
| Proportion of patients with 20% or 2L reduction in PN volume at Week 20, maintained to Week 24 | 37.2% | 69.8% | 0.002 | Yes |
| Proportion of patients who stopped PN usage | 2.3% | 0 | > 0.999 | No |
| Graded response | | | 0.004 | NA |

- **Study [TED-C13-003]**

This was a 4-cohort, non-randomized, open-label, PK/PD study in pediatric patients with SBS who were dependent on PN. This study included three teduglutide doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks and an observational standard of care (SOC) cohort. The baseline demographics were not balanced among treatment groups in this non-randomized study.

There was no pre-specified primary endpoint for this study. The percentage of patients who achieved greater than or equal to 20% reduction in PN volume was higher in two teduglutide

dose groups (71.4% in the 0.025 mg/kg/day arm and 53.3% in the 0.05 mg/kg/day arm) compared to the 0.0125 mg/kg/day arm (12.5%) and SOC (0%). Although this was an open-label, non-randomized study, the two doses of teduglutide (0.025 and 0.05 mg/kg/day) were selected for further study.

- **Study [TED-C14-006]**

This was a multi-national, multi-center study to evaluate the safety, PK, and efficacy/PD effects of teduglutide in pediatric subjects through 17 years of age with SBS and who are dependent on parenteral support. During the screening period, subjects were chosen between SOC and teduglutide treatment, and only subjects in the teduglutide treatment arm were randomized to either 0.025 or 0.05 mg/kg subcutaneously once daily in a double-blind manner.

The primary efficacy endpoint was a percentage of subjects weighted-normalized reduction in PN/IV volume of at least 20% at EOT compared to baseline. In the ITT analysis based on the subject diary data, 13 (54.2%) subjects in the 0.025 mg/kg group, 18 (69.2%) subjects in the 0.05 mg/kg group, and 1 (11.1%) subjects in the SOC arm achieved the primary endpoint. In addition, teduglutide treatment resulted in increases in enteral nutrition (EN) volume and caloric intake as well as plasma citrulline. Although the differences in efficacy between the 0.025 and 0.05 mg/kg dose groups were small, a consistently greater effect was seen in the 0.05 mg/kg dose in all efficacy parameters.

In summary, the efficacy of Revestive (teduglutide) 0.05 mg/kg/day was demonstrated in Study [CL-0600-020] for the treatment of Short Bowel Syndrome (SBS) in adult subjects. Efficacy of Revestive (teduglutide) 0.05 mg/kg/day in pediatric patients with SBS was supported by two open-label studies with greater effect seen in the 0.05 mg/kg dose group as compared to the 0.025 mg/kg dose group.

### 2.4.2 Safety Results

Adult Safety Data

In the two core adult trials (CL-0600-004 and CL0600-020), the most common AE with teduglutide were abdominal pain, nausea, upper respiratory tract infection, injection site reaction, fluid overload, hypersensitivity. The incidence of SAE was higher in the teduglutide 0.05mg/kg group than the placebo group (36.4% vs. 28.8%). Significant SAEs included bowel obstruction, biliary disorder, infection and congestive cardiac failure. With the longer exposure to teduglutide for up to 2.5 years in the extension studies CL0600-005 and CL0600-021, the incidence of overall AE, SAE and AE leading to treatment discontinuation increased. There were three deaths reported in the extension Study CL0600-021. Two were malignancies, and one case with generalized intestinal metastatic adenocarcinoma without known primary site was considered related to study drug.

Pediatric Safety Data

In the two core pediatric trials (TED-C13-003 and TED-C14-006), the overall percentage of any AE was similar between teduglutide and SOC groups. The most common AEs with teduglutide were similar to those seen in adults. The most frequently reported SAEs were central line infection and pyrexia. Two SAEs, fecaloma and ileus, were assessed related to teduglutide treatment. In the two pediatric extension studies (SHP-633-303 and 304), according to the 6-month interim reports, the overall safety profile with teduglutide treatment was similar to those observed in the core studies. There was one subject died but was assessed not related to study drug.

Post-marketing Safety Data

The post-marketing Study TED-R13-002 was a prospective, observation, multi-center registry for SBS initiated in 2014. The primary safety outcome of Study TED-R13-002 was the occurrence of colorectal cancer. Until 2019, there were a total of 947 adult patients enrolled. Overall, 811 adult patients met the inclusion and exclusion criteria of the protocol: 391 teduglutide ever-treated (288 of whom were currently treated) and 420 teduglutide never-treated patients. There were no occurrences of colorectal cancer from the start of the study until the data cutoff date in 2019. The other safety signal identified in this study included benign neoplasia of the GI track, colorectal polyps, intestinal obstruction, pancreatic disease (other than neoplasia), biliary disease (other than neoplasia), volume overload, other gastrointestinal surgery, and central line infection.

The Immunogenicity

The occurrence of anti-teduglutide antibody increased with the longer treatment period. However, in study CL0600-021, no clear differences could be seen in the occurrence, seriousness and severity between subjects with and without specific anti-teduglutide antibodies. There was no neutralizing antibody detected in study CL0600-021.

Safety Summary

In summary, the safety profile of teduglutide was acceptable. The significant risk associated with teduglutide treatment included fluid overload, cardiovascular events, intestinal neoplasia, biliary and pancreatic events, intestinal obstruction, and increased absorption of oral medications.

**2.5 Bridging Study Evaluation**

The impact of ethnic factor on teduglutide PK was assessed by cross study comparison and population PK analysis. Exposure parameters of teduglutide in East Asian (TED-C14-004, n=8, Japanese) and non-East Asian (CL0600-004, n=33) patients with SBS at a dose level of

0.05 mg/kg were compared. For adult patients with SBS, mean $C_{max,ss}$ in East Asian patients was 17% higher than those observed in non-East Asian patients, and mean $AUC_{ss}$ was similar between East Asian and non-East patients. Population PK analysis also demonstrated that the mean CL/F of teduglutide in East-Asian patients was comparable to non-East Asian patients. Overall, race is not a sensitive factor on teduglutide PK.

Ethnic sensitivity of teduglutide in adult patients with short bowel syndrome (SBS) has been evaluated by comparing the results between the global pivotal studies (CL0600-004 + CL0600-020) and the Japanese study (TED-C14-004). The efficacy results of the East Asian adults (Japanese) receiving teduglutide were similar to that of the Western population. In terms of safety, although the rate of serious adverse events in East Asian adults was higher than that of the Western population, most of the events were not related to study drug, but related to the complications of parenteral nutrition. In the global package, the efficacy and safety data of children were similar to those of adults. Therefore, it is appropriate to extrapolate the data from global subjects to East Asian subjects both in adult and pediatric population.

In conclusion, the bridging study of teduglutide for pediatric and adult patients with SBS could be waived.

**2.6 Conclusion**

Overall, the submitted NDA package for CMC , PT, PK and Clinical section were considered adequate and acceptable. The benefit/risk ratio is positive in the treatment of adult and pediatric patients with Short Bowel Syndrome (SBS). A risk management plan (RMP) is required to ensure that the benefits of the drug outweigh the risks.

This new drug application of Revestive (Teduglutide) is suggested to be approved.
The approved indication is “for the treatment of patients aged 1 year and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.”

## 3. Post-Marketing Requirements

(1) Risk management plan (RMP) is required for the potential risk of colorectal polyps, neoplastic growth, intestinal obstruction, biliary tract and pancreatic disease, fluid overload, and increased absorption of oral medications.
(2) The sponsor should provide the final report of study SHP-633-303 andSHP-633-304 after its completion.
(3) The sponsor should provide the annual report of study TED-R13-002 every two years until its completion.