ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revestive 5 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 5 mg of teduglutide*.
After reconstitution, each vial contains 5 mg teduglutide in 0.5 ml of solution, corresponding to a concentration of 10 mg/ml.

* A glucagon-like peptide-2 (GLP-2) analogue produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is white and the solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome. Patients should be stable following a period of intestinal adaptation after surgery.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a medical professional with experience in the treatment of Short Bowel Syndrome (SBS).

Treatment should not be initiated until it is reasonable to assume that no further intestinal adaptation will occur. Optimisation and stabilisation of intravenous fluid and nutrition support should be performed before initiation of treatment.

Treatment effect should be evaluated after 6 months. The assessment by the physician should consider individual treatment objectives and patient preferences. Treatment should be stopped if no overall improvement of the patient condition is achieved. Efficacy and safety in responding patients should be closely monitored on an ongoing basis according to clinical treatment guidelines.

Posology

Adults
The recommended dose of teduglutide is 0.05 mg/kg body weight once daily. A table with the injection volume per body weight is provided in section 6.6. Due to the heterogeneity of the SBS population, a carefully monitored down-titration of the daily dose may be considered for some patients to optimise tolerability of the treatment. If a dose is missed, that dose should be taken as soon as possible on that day.

Special populations

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

Renal impairment
No dose adjustment is necessary for patients with mild renal impairment. In patients with moderate and severe renal impairment (creatinine clearance less than 50 ml/min), and end-stage renal disease, the daily dose should be reduced by 50% (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects. Revestive has not been studied in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
Revestive should not be used in children below 18 years old because of safety concerns (vulnerability to fluid overload) (see section 5.1).

Method of administration

The reconstituted solution should be administered by subcutaneous injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen. In case the injection into the abdomen is hampered by pain, scarring or hardening of the tissue, the thigh can also be used. Revestive should not be administered intravenously or intramuscularly.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or trace residues of tetracycline.

Active or suspected malignancy.

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

4.4 Special warnings and precautions for use

Colo-rectal polyps

A colonoscopy with removal of polyps should be performed at the time of starting treatment with Revestive. Subsequent colonoscopies are recommended at a minimum of five year intervals. An individual assessment whether increased frequency of surveillance is necessary should be performed based on the patient characteristics (e.g. age, underlying disease). See also section 5.1. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of malignancy, Revestive therapy should be discontinued (see section 4.3).

Gastrointestinal neoplasia including hepatobiliary tract

In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. These observations were not confirmed in clinical studies of more than one year duration. If a neoplasia is detected, it should be removed. In case of malignancy, Revestive therapy should be discontinued (see sections 4.3 and 5.3).

Gallbladder and bile ducts

Cases of cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies. In case of gallbladder or bile duct-related symptoms, 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. In case of pancreatic adverse events, the need for continued Revestive treatment should be reassessed.

Monitoring of small bowel, gallbladder and bile ducts, and pancreas

SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of short bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques.

Intestinal obstruction

Cases of intestinal obstruction have been reported in clinical studies. In case of recurrent intestinal obstructions, the need for continued Revestive treatment should be reassessed.

Cardiovascular

Due to increased fluid absorption, patients with 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, swollen ankles and/or dyspnoea. In general, fluid overload can be prevented by appropriate and timely assessment of parenteral nutrition needs. This assessment should be conducted more frequently within the first months of treatment. In case of a significant deterioration of the cardiovascular disease, the need for continued Revestive treatment should be reassessed.

Concomitant treatment

Patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption (see section 4.5).

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 five years (see section 4.3). Caution should be exercised when prescribing Revestive.

Hepatic impairment

Revestive has not been studied in patients with severe hepatic impairment. The data from use in subjects with moderate hepatic impairment do not suggest a need for restricted use.

Discontinuation of treatment

Due to the risk of dehydration, discontinuation of treatment with Revestive should be managed carefully.

Excipients

Revestive contains less than 1 mmol sodium (23 mg) per dose. This means that it is essentially 'sodium-free'.

Caution is needed when administering Revestive to persons with a known hypersensitivity to tetracycline.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug-drug interaction studies have been performed. An *in vitro* study indicates that teduglutide does not inhibit cytochrome P450 drug metabolising enzymes. Based upon the pharmacodynamic effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Revestive in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Revestive during pregnancy.

Breast-feeding

It is unknown whether teduglutide is excreted in human milk. In rats, mean teduglutide concentration in milk was less than 3% of the maternal plasma concentration following a single subcutaneous injection of 25 mg/kg. A risk to the breastfed newborn/infant cannot be excluded. As a precautionary measure it is preferable to avoid the use of Revestive during breastfeeding.

Fertility

There are no data on the effects of teduglutide on human fertility. Animal data do not indicate any impairment of fertility.

4.7 Effects on ability to drive and use machines

Revestive has minor influence on the ability to drive and use machines. However, cases of syncope have been reported in clinical studies (see section 4.8). Such events might impact the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions were retrieved from two placebo-controlled clinical studies with Revestive in 109 patients with SBS treated with doses of 0.05 mg/kg/day and 0.10 mg/kg/day for up to 24 weeks. Approximately 52% of the patients treated with Revestive experienced adverse reactions (*versus* 36% of the patients given placebo). The most commonly reported adverse reactions were abdominal pain and distension (49%), respiratory tract infections (28%), nausea (27%), injection site reactions (21%), headache (17%), vomiting (14%) and oedema peripheral (10%). Approximately 38% of the treated patients with a stoma experienced gastrointestinal stoma complications. The majority of these reactions were mild or moderate.

Tabulated list of adverse reactions

Adverse reactions are listed below 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); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequency **System Organ Class**	**Very common**	**Common**	**Uncommon**
Infections and infestations	Respiratory tract infection	Influenza	
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders		Anxiety Sleep disorder	
Nervous system disorders	Headache	Paraesthesia	
Cardiac disorders		Cardiac failure congestive	
Vascular disorders		Flushing	Syncope
Respiratory, thoracic and mediastinal disorders		Dyspnoea Cough	
Gastrointestinal disorders	Abdominal pain and distension Vomiting Nausea Gastrointestinal stoma complication*	Pancreatitis Intestinal obstruction	
Hepatobiliary disorders		Cholestasis and cholecystitis	
Skin and subcutaneous tissue disorders		Dermatitis allergic	
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders		Renal colic Costovertebral angle tenderness	
General disorders and administration site conditions	Oedema peripheral Injection site reaction	Chest pain Night sweats	
Investigations		C-reactive protein increased	

* Gastrointestinal stoma complication (swelling of the stoma and associated complications) is considered to be rather a sign of efficacy than an adverse reaction.

Description of selected adverse reactions

Immunogenicity
Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of Revestive may potentially trigger the development of antibodies. In phase 3 studies with SBS patients who received Revestive for up to one year, 30% of patients developed anti-teduglutide antibodies and 40% of patients developed antibodies against *E.coli* protein (residual host cell protein from the manufacture). The antibody formation has not been associated with clinically relevant safety findings, reduced efficacy or changed pharmacokinetics of Revestive.

Injection site reactions
Injection site reactions occurred in 21% of patients treated with teduglutide. The reactions appeared to be dose dependent and occurred with the same frequency in patients given the recommended dose of 0.05 mg/kg/day teduglutide and in patients given placebo (injection site reactions were experienced by 12% of the placebo-treated patients, by 12% of the patients who received 0.05 mg/kg/day teduglutide and by 41% of the patients who received 0.10 mg/kg/day teduglutide). The reactions included injection site erythema, injection site haematoma and injection site pain (see also section 5.3).

C-reactive protein
Modest increases of C-reactive protein of approximately 25 mg/l have been observed within the first seven days of Revestive treatment, which decreased continuously under ongoing daily injections. After 24 weeks of Revestive treatment, patients showed small overall increase in C-reactive protein of approximately 1.5 mg/l on average. These changes were neither associated with any changes in other laboratory parameters nor with any reported clinical symptoms.

4.9 Overdose

The maximum dose of teduglutide studied during clinical development was 86 mg/day for 8 days. No unexpected systemic adverse reactions were seen (see section 4.8).

In the event of an overdose, the patient should be carefully monitored by the medical professional.

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

The naturally occurring human glucagon-like peptide-2 (GLP-2) is a peptide secreted by L cells of the intestine which is known to increase intestinal and portal blood flow, inhibit gastric acid secretion, and decrease intestinal motility. Teduglutide is an analogue of GLP-2. In several nonclinical studies, 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

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 increases villus height and crypt depth of the intestinal epithelium.

Based on the concerns derived from pre-clinical studies (see section 5.3) and the proposed mechanism of action with the trophic effects on intestinal mucosa, there appears to be a risk for the promotion of small intestinal and/or colonic neoplasia. The clinical studies conducted could neither exclude nor confirm such an increased risk. Several cases of benign colonic polyps occurred during the course of the trials, however, the frequency was not increased compared to placebo-treated patients. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment (see section 4.4.), every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g. age and underlying disease, previous occurrence of polyps etc.).

Clinical efficacy

Revestive was studied in 17 patients with SBS allocated to five treatment groups using doses of 0.03, 0.10 or 0.15 mg/kg teduglutide once daily, or 0.05 or 0.075 mg/kg bid in a 21-day open-label, multicenter, dose-ranging study. Treatment resulted in enhanced gastrointestinal fluid absorption of approximately 750-1000 ml/day with improvements in the absorption of macronutrients and electrolytes; decreased stomal or faecal fluid and macronutrients excretion, and enhanced key structural and functional adaptations in the intestinal mucosa. Structural adaptations were transient in nature and returned to baseline levels within three weeks of discontinuing the treatment.

In the pivotal phase 3 double-blind, placebo-controlled study in patients with SBS, who required parenteral nutrition, 43 patients were randomised to a 0.05 mg/kg/day dose of teduglutide and 43 patients to placebo for up to 24 weeks.

The proportion of teduglutide treated subjects achieving a 20% to 100% reduction of parenteral nutrition at Week 20 and 24 was statistically significantly different from placebo (27 out of 43 subjects, 62.8% *versus* 13 out of 43 patients, 30.2%, p=0.002). Treatment with teduglutide resulted in a 4.4 l/week reduction in parenteral nutrition requirements (from a pre-treatment baseline of 12.9 litres) *versus* 2.3 l/week (from a pre-treatment baseline of 13.2 litres) for placebo at 24 weeks. Twenty-one patients treated with teduglutide (48.8%) *versus* 9 on placebo (20.9%) achieved at least a one day reduction in parenteral nutrition administration (p=0.008).

Ninety-seven percent of patients (37 out of 39 patients treated with teduglutide) that completed the placebo-controlled study entered a follow-up study where all patients received 0.05 mg/kg of teduglutide daily for up to an additional two years. In total 88 patients participated in this follow-up study, thereof 39 treated with placebo and 12 enrolled, but not randomised, in the previous study.

At an interim assessment after six months of the follow-up study, continued reductions in parenteral nutrition have been achieved. Three subjects were completely weaned off parenteral nutrition at the time of the interim report.

In another phase 3 double-blind, placebo-controlled study in patients with SBS, who required parenteral nutrition, patients received a 0.05 mg/kg/day dose (n = 35), a 0.10 mg/kg/day dose (n = 32) of teduglutide or placebo (n = 16) for up to 24 weeks.

The primary efficacy analysis of the study results showed no statistically significant difference between the group on teduglutide 0.10 mg/kg/day and the placebo group, while the proportion of subjects receiving the recommended teduglutide dose of 0.05 mg/kg/day achieving at least a 20% reduction of parenteral nutrition at Week 20 and 24 was statistically significantly different *versus* placebo (46% *versus* 6.3%, p<0.01). Treatment with Revestive resulted in a 2.5 l/week reduction in parenteral nutrition requirements (from a pre-treatment baseline of 9.6 litres) *versus* 0.9 l/week (from a pre-treatment baseline of 10.7 litres) for placebo at 24 weeks.

Revestive treatment induced expansion of the absorptive epithelium by significantly increasing villus height in the small intestine.

Sixty-five patients entered a follow-up SBS study for up to an additional 28 weeks of treatment. Patients on Revestive maintained their previous dose assignment throughout the extension phase, while placebo patients were randomised to active treatment, either 0.05 or 0.10 mg/kg/day.

Of the patients who achieved at least a 20% reduction of parenteral nutrition at Week 20 and 24 in the initial study, 75% sustained this response on Revestive after up to one year of continuous treatment.

The mean reduction of weekly parenteral nutrition volume was 4.9 l/week (52% reduction from baseline) after one year of continuous teduglutide treatment.

Two patients on the recommended teduglutide dose were able to be totally weaned off parenteral nutrition by Week 24. One additional patient in the follow-up study was weaned off parenteral nutrition.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Revestive in one or more subsets of the paediatric population in the treatment of SBS (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Teduglutide was rapidly absorbed from subcutaneous injection sites with maximum plasma levels occurring approximately 3-5 hours after dose administration at all dose levels. The absolute bioavailability of subcutaneous teduglutide is high (88%). No accumulation of teduglutide was observed following repeated subcutaneous administration.

Distribution

Following subcutaneous administration, teduglutide has an apparent volume of distribution of 26 litres in patients with SBS.

Biotransformation

The metabolism of teduglutide is not fully known. Since teduglutide is a peptide it is likely that it follows the principal mechanism for peptide metabolism.

Elimination

Teduglutide has a terminal elimination half-life of approximately two hours. Following intravenous administration teduglutide plasma clearance was approximately 127 ml/hr/kg which is equivalent to the glomerular filtration rate (GFR). Renal elimination was confirmed in a study investigating pharmacokinetics in subjects with renal impairment. No accumulation of teduglutide was observed following repeated subcutaneous administrations.

Dose linearity

The rate and extent of absorption of teduglutide is dose-proportional at single and repeated subcutaneous doses up to 20 mg.

Pharmacokinetics in subpopulations

Gender
No clinically relevant gender differences were observed in clinical studies.

Elderly
In a phase 1 study no difference in pharmacokinetics of teduglutide could be detected between healthy subjects younger than 65 years *versus* older than 65 years. Experience in subjects 75 years and above is limited.

Hepatic impairment
In a phase 1 study the effect of hepatic impairment on the pharmacokinetics of teduglutide following subcutaneous administration of 20 mg teduglutide was investigated. The maximum exposure and the overall extent of exposure to teduglutide following single 20 mg subcutaneous doses were lower (10-15%) in subjects with moderate hepatic impairment relative to those in healthy matched controls.

Renal impairment
In a phase 1 study, the effect of renal impairment on the pharmacokinetics of teduglutide following subcutaneous administration of 10 mg teduglutide was investigated. With progressive renal impairment up to and including end stage renal disease the primary pharmacokinetic parameters of teduglutide increased up to a factor of 2.6 (AUC_{inf}) and 2.1 (C_{max}) compared to healthy subjects.

5.3 Preclinical safety data

Hyperplasia in the gall bladder, hepatic biliary ducts, and pancreatic ducts were observed in subchronic and chronic toxicology studies. These observations were potentially associated with the expected intended pharmacology of teduglutide and were to a varying degree reversible within an 8-13 week recovery period following chronic administration.

Injection site reactions

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

Carcinogenicity / mutagenicity

Teduglutide was negative when tested in the standard battery of tests for genotoxicity.

In a rat carcinogenicity study, treatment related benign neoplasms included tumours of the bile duct epithelium in males exposed to teduglutide plasma levels approximately 32- and 155-fold higher than obtained in patients administered the recommended daily dose (incidence of 1 out of 44 and 4 out of 48, respectively). Adenomas of the jejunal mucosa were observed in 1 out of 50 males and 5 out of 50 males exposed to teduglutide plasma levels approximately 10- and 155-fold higher than obtained in patients administered the recommended daily dose. In addition, a jejunal adenocarcinoma was observed in a male rat administered the lowest dose tested (animal:human plasma exposure margin of approximately 10-fold).

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. Teduglutide was not associated with effects on reproductive performance, *in utero* or developmental parameters measured in studies to investigate fertility, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
L-histidine
Mannitol
Sodium phosphate monohydrate
Disodium phosphate heptahydrate
Sodium hydroxide (pH adjustment)

Hydrochloric acid (pH adjustment)

Solvent
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

After reconstitution, from a microbiological point of view, the solution should be used immediately. However, chemical and physical stability has been demonstrated for 3 hours at 25°C.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 mg teduglutide powder in vial (glass) with rubber stopper (bromobutyl).
0.5 ml of solvent in pre-filled syringe (glass) and plungers (plastic) for assembly with the pre-filled syringe.

Pack size of 28 vials of powder, 28 pre-filled syringes and 6 plungers.

6.6 Special precautions for disposal and other handling

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

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 pre-filled syringe must be assembled with the plunger and a reconstitution needle.
The powder in the vial must then 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. Once a clear colourless solution is formed in the vial, the solution should be sucked up into a 1 ml injection syringe with scale intervals of 0.02 ml or smaller (not included in the pack).
If two vials are needed, the procedure for the second vial must be repeated and the additional solution sucked 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.
The solution must be injected subcutaneously into a cleaned area on the abdomen, or if this is not possible, on the thigh (see section 4.2 Method of administration) using a thin needle for subcutaneous injection.

Detailed instructions on the preparation and injection of Revestive are provided in the package leaflet.

The solution must not be used if it is cloudy or contains particulate matter.

For single use only.
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.

7. MARKETING AUTHORISATION HOLDER

Nycomed Danmark ApS
Langebjerg 1
DK-4000 Roskilde
Denmark
Tel.: +45 4677 1111
info@nycomed.com

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim RCV GmbH & Co KG
Dr. Boehringer-Gasse 5-11
A-1121 Vienna
Austria

Name and address of the manufacturer responsible for batch release

Nycomed Danmark ApS
Langebjerg 1
DK-4000 Roskilde
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs
The PSUR cycle for the medicinal product should follow the standard requirements until otherwise agreed by the CHMP.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome. The study is designed to monitor the safety, tolerability and efficacy for PN/i.v. dependent SBS subjects taking Teduglutide. Final Study Report	 Q4 2013
International Short Bowel Syndrome Registry Non-interventional study (NIS) to gather further safety data, in order to further elucidate the potential and identified risk as outlined in the RMP, based on a CHMP approved protocol. Interim data for the NIS should be provided every second year. Final study report	 Four interim reports will be provided within six months after the data lock points (i.e., Q3 2015, Q3 2017, Q3, 2019, and Q3 2021). Q3 2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revestive 5 mg powder and solvent for solution for injection
Teduglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 5 mg of teduglutide. After reconstitution, each vial contains 5 mg teduglutide in 0.5 ml of solution, corresponding to a concentration of 10 mg/ml.

3. LIST OF EXCIPIENTS

Powder: L-histidine, mannitol, sodium phosphate monohydrate, disodium phosphate heptahydrate, sodium hydroxide (pH adjustment), hydrochloric acid (pH adjustment).
Solvent: Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection 5 mg powder in vial / 0.5 ml solvent in pre-filled syringe.
Pack size of 28 each (with 6 plungers).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
After reconstitution, from a microbiological point of view, the solution should be used immediately. However, chemical and physical stability has been demonstrated for 3 hours at 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nycomed Danmark ApS
Langebjerg 1
4000 Roskilde
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Revestive

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Revestive 5 mg powder for solution for injection
Teduglutide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg Teduglutide

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT PREFILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Revestive
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

For reconstitution

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Revestive 5 mg powder and solvent for solution for injection
Teduglutide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Revestive is and what it is used for

Revestive contains the active substance teduglutide. It improves the absorption of nutrients and fluid from your remaining gastrointestinal tract (gut).
Revestive is used to treat adults with Short Bowel Syndrome. Short Bowel Syndrome is a disorder arising from an inability to absorb food nutrients and fluid across the gut. It is often caused by surgical removal of all or part of the small intestine.

2. What you need to know before you use Revestive

Do not use Revestive
- if you are allergic to teduglutide or any of the other ingredients of this medicine (listed in section 6) or trace residues of tetracycline.
- if you have or are suspected to have cancer.
- if you have had cancer in the gastrointestinal tract, including liver, gallbladder or bile ducts, within the last five years.

Warnings and precautions

Talk to your doctor before using Revestive:
- if you have severely decreased liver function. Your doctor will consider this when prescribing this medicine.
- if you suffer from certain cardiovascular diseases (affecting the heart and/or blood vessels) such as high blood pressure (hypertension) or have a weak heart (cardiac insufficiency). The symptoms include sudden weight gain, swollen ankles and/or shortness of breath.
- if you have other severe diseases that are not well controlled. Your doctor will consider this when prescribing this medicine.
- if you have decreased kidney function. Your doctor may need to give you a lower dose of this medicine.

Medical check-ups before and during treatment with Revestive
Before you start treatment with this medicine, your doctor will need to perform a colonoscopy (a procedure to see inside your colon and rectum) to check for the presence of polyps (small abnormal growths) and remove them. It is recommended that your doctor performs these examinations at a minimum of five-year intervals. If polyps are found either before or during your treatment with Revestive, your doctor will decide whether you should continue using this medicine. Revestive should not be used if a cancer is detected during your colonoscopy.

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

Children and adolescents
This medicine is not recommended for children or adolescents below 18 years of age because it is unlikely to be safe.

Other medicines and Revestive
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other 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.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, the use of Revestive is not recommended.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

Driving and using machines
This medicine may cause you to feel dizzy. If this happens to you, do not drive or use machines until you feel better.

Important information about some of the ingredients in Revestive
This medicine contains less than 1 mmol sodium (23 mg) per dose. This means that it is essentially 'sodium-free'.
Caution is needed if you are hypersensitive to tetracycline.

3. How to use Revestive

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

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.

How to use Revestive
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. You will find detailed instructions for injections at the end of this leaflet.

If you use more Revestive than you should
If you inject more Revestive than you are told to by your doctor, you should contact your doctor, pharmacist or nurse.

If you forget to use Revestive
If you forget to inject this medicine (or cannot inject it at your usual time), use it as soon as possible on that day. Never use more than one injection in the same day. Do not inject a double dose to make up for a forgotten dose.

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

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek immediate medical attention if any of the following side effects occur:
Common:
- Congestive heart failure. Contact your doctor if you experience tiredness, shortness of breath or swelling of ankles or legs
- Inflammation of the pancreas (pancreatitis). Contact your doctor or the emergency unit if you experience severe stomach ache and fever
- Intestinal obstruction (blockage of the bowel). Contact your doctor or the emergency unit if you experience severe stomach ache, vomiting and constipation
- Reduced flow of bile from the gallbladder and/or inflammation of the gallbladder. Contact your doctor or the emergency unit if you experience yellowing of the skin and the whites in the eyes, itching, dark urine and light-coloured stools or pain in the upper right side or middle of the stomach area

Uncommon (may affect up to 1 in 100 people):
- Fainting. If heart rate and breathing is normal and you awaken fast, speak to your doctor. In other cases, seek help as soon as possible

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

Common (may affect up to 1 in 10 people):
- Flu (influenza)
- Decreased appetite
- Problems sleeping, anxiety
- Numbness and tingling of the skin
- Flushing
- Cough, shortness of breath
- Rash
- Joint pain
- Pain upon palpation in the kidney area, renal colic (pain in the back, side or groin, blood in the urine, fever, feeling sick)

- Chest pain, night sweats
- Increased level of C-reactive protein, which can be seen in results of blood tests

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Revestive

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the vial and the pre-filled syringe after EXP. The expiry date refers to the last day of that month.

Do not freeze.

After reconstitution, from a microbiological point of view, the solution should be used immediately. However, chemical and physical stability has been demonstrated for 3 hours at 25°C.

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.

6. Contents of the pack and other information

What Revestive contains
- The active substance is teduglutide. One vial of powder contains 5 mg of teduglutide. After reconstitution, each vial contains 5 mg teduglutide in 0.5 ml of solution, corresponding to a concentration of 10 mg/ml.
- The other ingredients are L-histidine, mannitol, sodium phosphate monohydrate, disodium phosphate heptahydrate, sodium hydroxide (pH adjustment), hydrochloric acid (pH adjustment).
- The solvent contains water for injections.

What Revestive looks like and contents of the pack
Revestive is a powder and solvent for solution for injection (5 mg powder in vial, 0.5 ml solvent in pre-filled syringe). Pack size of 28 each and with 6 plungers.

The powder is white and the solvent is clear and colourless.

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This leaflet was last revised in {month YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Instructions for preparing and injecting Revestive

The following instructions explain how to prepare and self-inject a Revestive subcutaneous injection. There are four main steps to the procedure:

I. **Assembly** of the pre-filled syringe
II. **Dissolving** the powder
III. **Preparing** the injection syringe
IV. **Injecting** the solution

NOTE:
- Revestive is for injection under the skin (subcutaneous injection).
- Do not inject Revestive into a vein (intravenously) or muscle (intramuscularly).

Materials in the Revestive pack:
- 28 vials with 5 mg teduglutide as a powder
- 28 pre-filled syringes with solvent
- 6 plungers

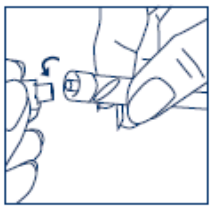
Materials needed but not included in the pack:
- Reconstitution needle (size 22G, length 1½" (0.7 x 40 mm))
- 1 ml injection syringe (with scale intervals of 0.02 ml or smaller) and a thin injection needle for subcutaneous injection (e.g. size 26G, length 5/8" (0.45 x 16 mm))
- Alcohol wipes
- A puncture-proof 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.

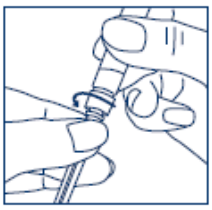
I. Assembly of the pre-filled syringe

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

1. Take the pre-filled syringe with solvent and attach (by screwing on) the plunger to the bottom part of it.



2. Flip off the top part of the white plastic cap on the pre-filled syringe so that it is ready for the reconstitution needle to be attached.



3. 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.

II. Dissolving the powder

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

1. Remove the green flip-off button from the powder vial and wipe the top with an alcohol wipe. Do not touch the top of the vial.

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

3. Taking the powder vial, insert the reconstitution needle of 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 solvent into the vial.

4. Remove the empty syringe and reconstitution needle from the vial and recap the needle.

5. Remove the plunger from the empty syringe and store for later use at your next dose.

6. After injecting the solvent into the vial, let the vial rest for approximately 30 seconds.

7. Gently roll the vial between your palms for about 15 seconds. Then gently turn the vial upside-down once.

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

8. Let the vial rest for about 2 minutes.

9. Observe the vial for any undissolved powder.

10. If any powder remains, repeat steps 7 and 8. 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: Once prepared, the solution should be used immediately. It should be kept below 25°C and maximum storage time is three hours.

III. Preparing the injection syringe

ection syringe (1 ml with 26G, 5/8"(0.45 x 16 mm) needle), remove the plastic without touching the tip of the needle. Insert the needle into the rubber stopper of the ing the solution for injection.

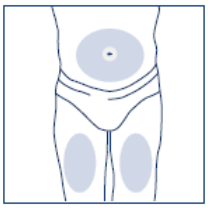
2. Turn the vial upside down and allow all the medicine to fill the syringe by pulling the plunger back gently.

NOTE: If your doctor has told you that you need two vials, prepare a second pre-filled syringe with solvent and a second powder vial as shown in the main steps I and II. Suck up the solution from the second vial into the same injection syringe by repeating the main step III.

3. 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.

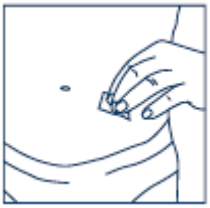
4. Your dose in ml has been calculated by your doctor. Expel any excessive volume from the syringe until your dose is reached. Recap the needle without touching the tip of the needle.

IV. Injecting the solution



1. Find an area on your belly, or if you have pain or hardening of the tissue on your belly, 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) to avoid discomfort. Avoid areas that are inflamed, swollen, scarred or covered by a mole, birthmark or other lesion.



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

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

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

6. Pull the needle straight out of the skin and recap the needle. 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.

7. 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.