ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 a patient is stable following a period of intestinal adaptation. Optimisation and stabilisation of intravenous fluid and nutrition support should be performed before initiation of treatment.

Treatment effect should be evaluated after 6 months. Clinical 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 all patients should be closely monitored on an ongoing basis according to clinical treatment guidelines. Continued treatment is recommended for patients who have weaned off parenteral nutrition.

Posology

Adults

The recommended dose of Revestive 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

The safety and efficacy of Revestive in children below 18 years old has not been established (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. Once yearly follow-up colonoscopies (or alternate imaging) are recommended during the first 2 years of Revestive treatment. 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 treatment 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 medication
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.

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