Swiss Summary of the Risk Management Plan (RMP) for Teduglutide (REVESTIVE)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risk as well as to prevent or minimise them.

The RMP summary of Revestive is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Revestive in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Revestive.

Summary of risk management plan for Revestive (Teduglutide)

This is a summary of the risk management plan (RMP) for Revestive. The RMP details important risks of Revestive, how these risks can be minimised, and how more information will be obtained about Revestive's risks and uncertainties (missing information).

Revestive's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Revestive should be used.

This summary of the RMP for Revestive should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Revestive's RMP.

I. The medicine and what it is used for

Revestive is authorised for the treatment of patients 1 year and above with Short Bowel Syndrome (SBS) (stable following a period of intestinal adaptation after surgery) (see SmPC for the full indication).

The indication extension is being proposed in patients 4 months corrected gestational age and above. It contains teduglutide as the active substance and it is given by subcutaneous route.

Further information about the evaluation of Revestive's benefits can be found in Revestive's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/revestive.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Revestive, together with measures to minimise such risks and the proposed studies for learning more about Revestive's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Revestive is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Revestive are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Revestive. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs

further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Biliary AEs • Pancreatic AEs • Cardiovascular AEs associated with fluid overload • GI stenosis and obstruction • GI stoma complications • Intestinal Polyps • Benign neoplasia of the GI tract including the hepatobiliary system • Tumour promoting ability • Anxiety
Important potential risks	• AEs associated with increased absorption of oral concomitant medications • Local skin reactions • Potential for off-label use in patients with active Crohn's disease • Medication errors • Compromised nutritional status
Missing information	• Lack of experience for administration of teduglutide in subjects 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 • Lack of experience in pregnant or lactating women • Long-term safety in the paediatric population • Limited long-term safety data over 1 year of exposure • Lack of data in subjects with pre-existing severe hepatic impairment

II.B Summary of important risks and missing information

Important Identified Risk: Biliary adverse events	
Evidence for linking the risk to the medicine	Non-clinical: Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts were observed in nonclinical studies and may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. Clinical studies: Biliary events like cholecystitis, cholangitis, and cholelithiasis have been observed in clinical trials. No obstruction of the bile ducts has been observed in clinical and nonclinical studies with

	teduglutide.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Risk factors for cholecystitis mirror those for cholelithiasis. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence. Additional risk factors include rapid weight loss and pregnancy (elevated progesterone levels during pregnancy may cause biliary stasis). Also, recent operation and consequences of previous intestinal surgery are associated with the occurrence of cholecystitis.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2, Section 4.4 and Section 4.8. PL section 4. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important Identified Risk: Pancreatic adverse events	
Evidence for linking the risk to the medicine	Non-clinical: Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts were observed in nonclinical studies and may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. Also, hyperplasia of the pancreatic duct has been shown in nonclinical studies. Clinical studies: 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.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Pancreatitis is generally caused by toxic-metabolic events (e.g., alcohol, smoking, hyperlipidaemia), by duct obstruction and may also have a genetic, idiopathic or autoimmune aetiology. Thus, risk factors for pancreatitis partially mirror those for cholelithiasis and sludge. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence. Also, the use of PN and the potential hyperlipidaemia might contribute to the occurrence of pancreatitis.

Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2, Section 4.4 and Section 4.8. PL Section 4. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important Identified Risk: Cardiovascular adverse events associated with fluid overload	
Evidence for linking the risk to the medicine	Clinical Trials: Fluid overload and congestive heart failure have been observed in adults in clinical trials
Risk factors and risk groups	The SBS population is too small for stratification.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2, Section 4.4 and Section 4.8. PL Section 2 and Section 4. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important Identified Risk: Gastrointestinal stenosis and obstruction	
Evidence for linking the risk to the medicine	Clinical Trials. Cases of intestinal obstruction have been reported in adult clinical studies.
Risk factors and risk groups	The SBS population is too small for stratified data analysis.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2, Section 4.4 and Section 4.8. PL section 4. Additional risk minimisation measures: No risk minimisation activities.

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important Identified Risk: Gastrointestinal stoma complications	
Evidence for linking the risk to the medicine	Clinical Studies: Stoma complications have been observed in clinical studies.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 and Section 4.8. PL section 4. Additional risk minimisation measures: No risk minimisation activities.

Important Identified Risk: Intestinal polyps	
Evidence for linking the risk to the medicine	Nonclinical: Teduglutide bears the potential risk to enhance the growth of colon polyps. In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. Clinical: Polyps were observed in adult patients in clinical studies.
Risk factors and risk groups	The SBS population is too small for stratified data analyses and the existence of risk groups is unknown. However, data from literature and from other populations indicate the following risk factors: Age Background prevalence between 23 and 41% in persons between ages of 50 and 82 years and between 7 and 40% for persons younger than 50 years of age. **Crohn's Disease / Ulcerative Colitis** The risk for colorectal cancer for subjects with active Crohn's disease/ulcerative colitis is approximately an 18-fold increase greater than for a person without chronic inflammatory bowel disease. Presence of colon Within the intestinal tract, colonic neoplasms are most frequent in men. Therefore, SBS subjects with colon may represent a subgroup with increased risk compared with subjects without colon.
Risk minimization measures	Routine risk minimisation measures:

	SmPC Section 4.2, Section 4.3, Section 4.4 and Section 4.8. PL Section 2 and Section 4. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important Identified Risk: Benign neoplasia of the gastrointestinal tract including the hepatobiliary system	
Evidence for linking the risk to the medicine	Nonclinical: In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. Clinical: These observations were not confirmed in clinical studies of more than one year duration.
Risk factors and risk groups	The SBS population is too small for stratified data analyses and the existence of risk factors or groups is unknown. However, data from literature and from other populations indicate the following risk factors and groups: Populations at risk of small bowel neoplasia include subjects with Crohn's disease, celiac disease, polyposis syndromes, or a history of small bowel-diverting surgeries and subjects elder than 50 years of age. Based on known risk factors for cholangiocarcinoma, it can be assumed that subjects with chronic inflammation of the biliary ducts or with liver cirrhosis of different origin are at increased risk for the occurrence of cholangiomas.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2, Section 4.3, Section 4.4, and Section 5.1. PL Section 2. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important Identified Risk: Tumour promoting ability

Evidence for linking the risk to the medicine	Nonclinical: 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). Clinical studies: The clinical studies conducted could neither exclude nor confirm such an increased risk.
Risk factors and risk groups	The SBS population is too small for stratified data analyses and the existence of risk factors or groups is unknown. In general, risk groups are subjects with an increased risk for developing any kind of tumours such as an elderly population. In addition, certain subject characteristics like smoking, immune suppression therapy or previous cancers, which are known to be associated to a higher incidence / prevalence of neoplasias, are considered additional risk factors.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2, Section 4.3, Section 4.4, and Section 5.1. PL Section 2. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important Identified Risk: Anxiety	
Evidence for linking the risk to the medicine	In the placebo-controlled studies CL0600-004 and CL0600-020, a higher reporting rate of subjects with anxiety has been observed in the teduglutide group compared with the placebo group. A potential mechanism for this observation is unknown. However, due to the facts that anxiety can have severe consequences and that no reports occurred in the placebo group, anxiety is considered an important identified risk.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the

	existence of risk groups is unknown.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.8. PL Section 4. Additional risk minimisation measures: No risk minimisation activities.

Important Potential Risk: Adverse events associated with increased absorption of oral concomitant medications	
Evidence for linking the risk to the medicine	Clinical Trials: Based upon the pharmacodynamic effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products. No confirmed event of increased absorption of concomitant medications has occurred in the teduglutide development program.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.4 and Section 4.5. PL Section 2. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important Potential Risk: Local skin reactions	
Evidence for linking the risk to the medicine	Non-Clinical: Treatment-related inflammatory lesions at the injection sites were observed in all preclinical animal species. Clinical Studies: Injection site reactions occurred in 26% of SBS patients treated with teduglutide, compared to 5% of patients in the placebo arm. The reactions included injection site haematoma, injection site erythema, injection site pain, injection site swelling and injection site haemorrhage. The majority of reactions were moderate in severity and no occurrences led to drug discontinuation.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Risk minimization measures	Routine risk minimisation measures:

	SmPC Section 4.8. PL section 4. Additional risk minimisation measures: No risk minimisation activities.

Important Potential Risk: Potential off-label **use in patients with active Crohn's disease**	
Evidence for linking the risk to the medicine	Post marketing reports
Risk factors and risk groups	The Risk group might be patients with active Crohn's disease with concomitant SBS not adequately treated for Crohn's disease.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.1 and Section 4.2. PL Section 1 and Section 3. Additional risk minimisation measures: No risk minimisation activities

Important Potential Risk: Medication errors	
Evidence for linking the risk to the medicine	Clinical Studies and Post Marketing: Reports of accidental overdose were seen in clinical studies. Reports of medication errors are seen during the post-marketing period.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2, Section 4.9 and Section 6.6. PL Section 3 and Section 5.

Important Potential Risk: Compromised nutritional status	
Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Overall, all patients getting partially, or fully independent form PN/IV could be at risk for an imbalance of nutritional status.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2. PL Section 2.

	Additional risk minimisation measures: No risk minimisation activities.

Missing Information: Lack of experience for administration of teduglutide in subjects 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	
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.4. PL Section 2. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Missing Information: Lack of experience in pregnant or lactating women	
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.6. PL Section 2. Additional risk minimisation measures: risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Missing Information: Long-term safety in the paediatric population	
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 and Section 4.8. PL Section 1 and Section 4. Additional risk minimisation measures: No risk minimisation activities.
Additional	Additional pharmacovigilance activities:

Missing Information: Long-term safety in the paediatric population	
pharmacovigilance activities	Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Missing Information: Limited long-term safety data over 1 year of exposure	
Risk minimization measures	No risk minimisation activities are proposed at this time. Additional safety data will be available following completion of the NIS.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Missing Information: Lack of data in subjects with pre-existing severe hepatic impairment	
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2. PL Section 2. Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry TED-R13-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study name: Registry TED-R13-002: A Prospective, Multi-centre Registry for Patients with Short Bowel Syndrome

Purpose of the study:

Primary objective: To evaluate the long-term safety profile for patients (adults and children) with SBS who are treated with teduglutide in a routine clinical setting.

Secondary objective: To evaluate long-term clinical outcome in subjects with SBS.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for Revestive.