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Our reference
2023037718

Date 21 September 2023
Re: Advice on a potential candidate for conditional inclusion of teduglutide (Revestive®) for short bowel syndrome (SBS) (procedure: orphan drugs, *conditionals* and *exceptionals*)

Dear Mr Kuipers,

On 14 July 2023, the parties submitted an application for the conditional inclusion (CI) of orphan drugs, conditionals and exceptionals for teduglutide (Revestive®). Teduglutide is an analogue of the naturally occurring human *glucagon-like peptide-2* (GLP-2). It is registered for the treatment of patients aged 4 months corrected gestational age and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery. Based on the data in the CI dossier and the advice of the Scientific Advisory Board (WAR), the National Health Care Institute has concluded that treatment with teduglutide for a specific group of patients aged 6 months and above with short bowel syndrome meets the criteria for conditional inclusion. In this letter, we explain this advice.

Indication for which conditional inclusion is requested
The request for conditional inclusion relates to certain patients with short bowel syndrome. Firstly, these are patients 18 years and older who following surgery must be stable after a period of intestinal adaptation (according to the starting criteria as formulated in the position statement issued by the professional group). In addition, the following should apply:

- Inflammatory Bowel Disease (IBD) as a cause of intestinal resection and being dependent, at least 3 times a week, on total parenteral nutrition for at least 12 months, or,
- A parenteral support volume greater than 14 litres/week for at least 12 months.

Secondly, conditional inclusion is requested for children aged 6 months to 18 years with short bowel syndrome. For them, the selection criterion is that they receive a minimum of 30% of calories and/or fluids parenterally, with no or minimal increase in parenteral support in the past 3 months or more. The basis for the selection of these patients is the publication of a post-hoc analysis of the STEPS registration study (Chen *et al*., 2020[1]) and the *Position Statement: Gebruik*

[1] Chen K, Mu F, Xie J, et al. Impact of Teduglutide on Quality of Life Among Patients With Short Bowel Syndrome and Intestinal Failure. JPEN J Parenter Enteral Nutr 2020; 44: 119-28.

van peptidegroeifactoren bij patiënten met darmfalen door kortedarmsyndroom (2020) by the Dutch Society for Gastro-intestinal and Hepatic Specialists (NVMDL).

Disorder
Short bowel syndrome with intestinal failure is a rare condition. The main consequence of short bowel syndrome with intestinal failure is malabsorption of macronutrients and micronutrients, electrolytes and water. The deficit of fluids and electrolytes leads to increased ingestion of fluids that cannot be absorbed by the intestines. This results in a vicious circle, leading to increasingly severe chronic diarrhoea or extreme stomal output, sometimes several litres per day. The typical symptoms are stools containing excessive fat and diarrhoea, resulting in weight loss, dehydration, vitamin and mineral deficiencies and malnutrition. In case of impending malnutrition, patients may receive total parenteral nutrition (TPN), supplemented if necessary with intravenous fluids and electrolytes. Long-term use of TPN may be associated with rare but potentially life-threatening complications, such as liver disease. Furthermore, the use of chronic parenteral nutrition is a heavy burden on the patient, with a negative impact on the quality of life.

Background
Teduglutide was registered by the EMA in 2012. In 2018, after advice from the WAR-CG, the National Health Care Institute ruled that teduglutide does not meet the established medical science and medical practice for patients with short bowel syndrome and intestinal failure.[2] Although a reduction in parenteral support (over 20% volume reduction) is measured in the teduglutide user group (the reason for EMA to admit teduglutide on the market), it is unclear to what extent this effect is clinically relevant to the patient. After all, the patient remains partly dependent on parenteral nutrition. For the product to be considered as having therapeutic added value, the National Health Care Institute required a quality of life improvement. However, there was no evidence of a relevant beneficial effect on the quality of life at group level. In addition, it was not clear to what extent the measured effects are due to natural adaptation.

Several parties, including the professional group, indicated that they would like teduglutide to be available for a carefully selected group of patients with short bowel syndrome. The hypothesis is that teduglutide could ensure that patients have more parenteral support-free days and that there is a clinically relevant decrease in stomal output. This allows these patients more freedom to live a normal life and to be productive at work. This is expected to improve the quality of life.

Short bowel syndrome with intestinal failure is a rare condition. Experts estimate that during conditional inclusion 60 to 95 patients are expected to be eligible for teduglutide. This affects **40 to 63 adults** and **20 to 32 children**.

There is currently no alternative on the market for the treatment of malabsorption in short bowel syndrome. Studies are being carried out on glepaglutide (registration expected in 2024) and apraglutide (registration expected after 2024), two other GLP-2 analogues. However, because these two medicinal

[2] National Health Care Institute. Pharmacotherapy report on teduglutide (Revestive®) 2018.

products are not yet available for patients in the Netherlands, there is an unmet medical need.

Research proposal conditional inclusion
Based on a post-hoc analysis and a position statement by the professional group, new selection and starting criteria for treatment with teduglutide have been established, and the indication for which reimbursement via conditional inclusion is sought has been limited. Within these subgroups, the effects of teduglutide are expected to be the most defined. It will be necessary to demonstrate whether this is indeed the case during the conditional inclusion procedure. Outcomes recorded during the conditional inclusion procedure include number of days of parenteral support, stomal output (volume) and quality of life. These outcomes are based on the professional group's position statement, and will be crucial for the final assessment. The clinical outcomes 'number of days of parenteral support' and 'stomal output' provide a better picture of the clinical relevance of the beneficial effects of teduglutide than the outcome parameter of 'percentage of reduction in parenteral nutritional volume', which the National Health Care Institute looked at in the 2018 assessment (primary outcome parameter in the STEPS registration study and was interpreted by the National Health Care Institute as surrogate for quality of life).

The applicants have submitted a research proposal for conditional inclusion based on a registry study (intra-patient comparisons). Dutch patient data is included in the Revestive Monitor. The patient population is small and highly heterogeneous. Attending physicians indicate that the uncertainties of an intra-individual comparison are less than the uncertainties of a comparison with a historical control group. The inter-individual variations in the patient population (resection of jejunum or ileum, remaining length of the intestine, ileo-caecal valve present or not, colon present or not, age, sex, aetiology) that have a major effect on the potential therapeutic outcomes of a treatment are excluded by applying an intra-patient comparison.

The National Health Care Institute acknowledges that randomisation and the application of a control group are difficult because of the small indication area combined with the strong heterogeneity of the disease, the absence of alternatives and the already unconditional inclusion on the European market (no *conditional*) which creates a patient and clinical equipoise. In addition, an indirect comparison with a historic control is challenging, as it is a small indication area and the disease is highly heterogeneous. The National Health Care Institute therefore considers an intra-patient comparison appropriate in this situation.

Assessment and conclusions
Based on the data in the CI dossier and the advice of the WAR, the National Health Care Institute has concluded that treatment with teduglutide for a selection of patients with SBS meets the criteria for conditional inclusion, namely:

- Teduglutide has been granted marketing authorisation by the EMA and has orphan drug status;
- There is an unmet medical need;
- The marketing authorisation holder is the dossier's lead applicant. The co-applicants are the attending physicians, an independent research institute and the patient association;
- This registry study (intra-patient comparison) is expected to provide an

answer to the package question on the basis of the collected data;
- The National Health Care Institute anticipates that the package question will be answered within 5 years.

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Advice
Based on these conclusions, we recommend that teduglutide (Revestive®) be designated as a potential candidate for conditional inclusion. Phase 2 of the procedure will commence when you adopt this advice. In this phase, we ask the parties to formulate their plans in greater detail and to draw up a covenant setting out the agreements needed to ensure that the conditional inclusion process is conducted carefully and successfully. At the same time, phase 2 is used by the Ministry of Health, Welfare and Sport to reach a financial arrangement together with the marketing authorisation holder. If the marketing authorisation holder is prepared to reach an acceptable price and the parties have drawn up an agreement, we will provide you with an additional advice on which to base your final decision on the inclusion of teduglutide in the conditional inclusion.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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Annex 1. Price and dosage teduglutide (Revestive®)

The pharmacy purchase price (AIP) of one package of Revestive® 1.25 or 5 mg per 0.5 ml injection solution is unknown. The calculations are therefore based on the prices provided to the National Health Care Institute by the marketing authorisation holder. Those are based on a WGP calculation based on prices in Belgium, France, England and Norway per 1 October 2023. One package of 1.25 mg per 0.5 ml injection solution costs €8,866.02. This is suitable for children up to 20 kg. One package of 5 mg per 0.5 ml injection solution costs €17,931.30. It is suitable for children from 20 kg and adults. One package of Revestive® consists of 28 vials and 28 pre-filled syringes with 0.5 ml resolutive.

Revestive® should be administered once a day by subcutaneous injection into the stomach or thigh. (Parents of) patients may administer this injection themselves.

One package of Revestive® is sufficient for a 28-day period of treatment. Based on this, patients will require no more than 13 packages per year. Thus, the annual treatment costs per patient are:

- 13 x €8,866.02 = €115,258.26 for children up to 20 kg, and;
- 13 x €17,931.30 = €233,106.90 for children from 20 kg and adults.

No further account is taken of the excess and/or personal contributions here, and patient compliance is assumed to be 100%. Table 1 contains an overview of the costs per patient per year.

Table 1: Cost per patient for use of Revestive® in short bowel syndrome with intestinal failure

	Revestive®
Daily dose	1 injection
Purchase price per package of 28 doses (Pharmacy Purchase Price) - Children up to 20 kg* - Children from 20 kg and adults	 € 8,866.02 € 17,931.30
Number of packages required per year	Up to 13
Total annual costs per patient (maximum) - **Children up to 20 kg*** - **Children from 20 kg and adults**	 € 115,258.26 € 233,106.90

* Experts estimate that approximately 5 patients who are eligible for teduglutide weigh less than 20 kg and will use the 1.25 mg/0.5 ml injection solution during the conditional inclusion procedure.