Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for teduglutide

Proprietary Product Name: Revestive

Sponsor: Shire Australia Pty Ltd

April 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	adverse event
AUC	Area Under the Curve
BSA	Body Surface Area
Cmax	Maximum observed concentration
CMI	Consumer Medicines Information
ECP	*Escherichia coli* protein
EMA	European Medicines Agency
GI	gastrointestinal
GLP-2	glucagon-like peptide-2
IV	intravenous (hydration)
PI	Product Information
PN	parenteral nutrition
RMP	Risk Management Plan
SAE	serious adverse event
SBS	Short Bowel Syndrome
$t_{1/2}$	elimination half life

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	17 May 2017
Date of entry onto ARTG	19 May 2017
Active ingredient:	Teduglutide
Product name:	Revestive
Sponsor's name and address:	Shire Australia Pty Ltd PO Box 6240 North Ryde NSW 2113
Dose form:	Powder for solution for injection vial with diluent pre-filled syringe
Strength:	5 mg
Approved therapeutic use:	Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. Patients should be stable at least to 4 weeks on their parenteral support regimen before initiating teduglutide therapy.
Route of administration:	Subcutaneous
ARTG number:	274911

Product background

This AusPAR describes the application by Shire Australia Pty Ltd to register Revestive (teduglutide) as a new biological entity. Teduglutide is a recombinant analogue of naturally occurring, human glucagon-like peptide-2 (GLP-2). The proposed indications are:

> *Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.*

The submission proposes registration of the following dosage form and strength:

> *Teduglutide 5 mg Powder and Solvent for Solution for Injection*

SBS results from surgical resection or congenital defect and is characterised by the inability to maintain protein energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet. Patients with SBS are highly prone to malnutrition, diarrhoea, dehydration, and an inability to maintain weight due to the reduced intestinal capacity to absorb macronutrients, water, and electrolytes. Current management of SBS is

supportive. Despite intestinal adaptation following resection, many SBS patients require the chronic use of parenteral support (parenteral nutrition/intravenous hydration [PN/IV]) to supplement and stabilise their hydration and nutritional needs.

Teduglutide has been approved in the US (2012), EU (2012), and Canada (2015), and evaluation reports from the corresponding regulatory agencies were provided to TGA to expedite the evaluation. Therefore, the evaluation can be termed as "hybrid".

Regulatory status

The international regulatory status at the time of submission to TGA is listed in Table 1.

Table 1: International regulatory status at the time of this submission to TGA.

Country	Submission date	Approval date	Indication
EU (Centralised Procedure)	3 Mar 2011	30 Aug 2012	Revestive is indicated for the treatment of patients aged 1 year and above with Short Bowel Syndrome. Patients should be stable following a period of intestinal adaptation after surgery.
US	30 Nov 2011	21 Dec 2012	Gattex (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.
Canada	25 Nov 2014	4 Sep 2015	Revestive (teduglutide) is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.
Israel	1 Jul 2013	13 Aug 2014	Gattex (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral nutritional support.
Switzerland	17 Dec 2014	1 Sep 2016	Revestive is indicated for the treatment of adults with short bowel syndrome, which is dependent on parenteral nutrition. After a surgical procedure, first, a phase of intestinal adaptation should be awaited, and patients should be in a stable phase.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The regulatory timeline of this submission is detailed in Table 2.

Table 2: Regulatory timeline of this submission.

Description	Date
Submission dossier accepted and 1st round evaluation commenced	31 May 2016
1st round evaluation completed	31 Oct 2016
Sponsor provides responses on questions raised in 1st round evaluation	5 Jan 2017
2nd round evaluation completed	9 Feb 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	3 Mar 2017
Sponsor's pre-Advisory Committee meeting response	21 Mar 2017
Advisory Committee meeting	6-7 Apr 2017
Registration decision	17 May 2017
Entry onto ARTG	19 May 2017
Number of TGA working days from submission dossier acceptance to registration decision *	196

* Legislative timeframe for standard applications: 255 working days (see *Therapeutic Goods Regulations 1990*)

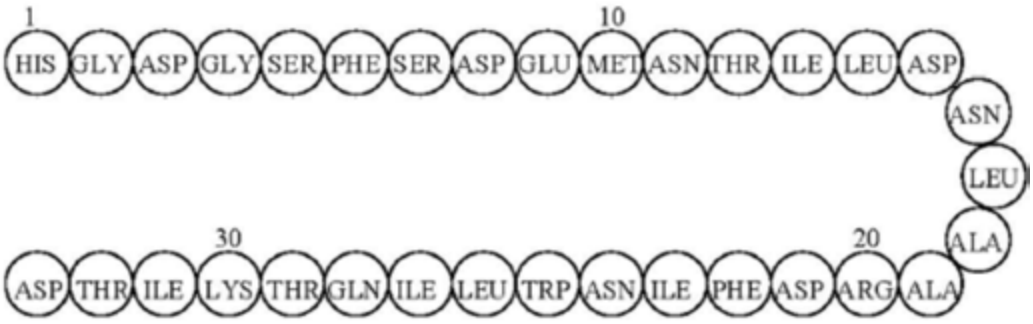
III. Quality findings

Introduction

Structure

Teduglutide is a single-chain polypeptide of 33 amino acid residues. Teduglutide does not have any disulfide bonds, glycosylation sites, or post-translational modifications. Teduglutide is a recombinant analogue of naturally occurring human GLP-2. GLP-2 is a peptide secreted by L cells of the distal intestine. Like GLP-2, teduglutide is 33 amino acids in length. Teduglutide differs from native GLP-2 by a single amino acid substitution in position two, where alanine in GLP-2 is substituted by glycine in teduglutide. This substitution confers the peptide with resistance to *in vivo* degradation by the enzyme dipeptidyl protease-IV (DPP-IV).

Figure 1: Primary sequence of teduglutide.



Physical and chemical properties

The physicochemical properties of teduglutide are listed in Table 3.

Table 3: Physicochemical properties of drug substance.

Attribute	Description
Appearance (color, physical form)	Clear, colorless to light straw-colored liquid
pH	6.9-7.9
Protein concentration (mg/mL)	10 – 21
Biological Activity	Relative potency 0.72 to 1.31
Molecular Mass	3752 g/mol

Teduglutide binds to the GLP-2 receptors located in intestinal subpopulations of enteroendocrine cells, sub-epithelial myofibroblasts and enteric neurons of the submucosal and myenteric plexus. Activation of these receptors results in the local release of multiple mediators including insulin like growth factor (IGF)-1, nitric oxide and keratinocyte growth factor (KGF).

Drug substance (active ingredient)

The manufacturing process is comprised of expression of teduglutide in *Escherichia coli* (*E. coli*) bacteria, harvest, purification, and filtration resulting in the teduglutide drug substance.

Drug product

The manufacturing of teduglutide drug product consists of: Buffer preparation; Drug substance thawing; Drug product compounding; Pre-filtration/Sterilising filtration; Filling/Stopper placement; Lyophilisation/Stoppering/Crimping; and Visual Inspection and Storage.

The production of the sterilised Water For Injection (WFI) pre-filled syringes at Vetter consists of: WFI generation; Compounding including bioburden reduction (first) filtration of WFI; Filling (with in-line filtration); Terminal sterilisation; Visual inspection; Labelling, Packaging and Storage.

Stability

Stability – Drug Substance: Teduglutide

The sponsor proposed a shelf life of 60 months in stainless steel containers stored at -20°C ± 5°C Stability data have been generated under real time and accelerated conditions.

Stability data were generated under real time conditions to characterise the stability profile of the substance and to establish a shelf life. The real time data submitted support a shelf life 60 months in stainless steel containers stored at -20°C ± 5°C.

Stability – Drug Product: Teduglutide for Injection

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data showed that the product is photostable.

The proposed shelf life 48 months when stored below 25°C is supported by the real time data.

In-use stability data have also been submitted. The proposed shelf life and storage condition for the reconstituted product is 3 hours when stored at 25°C.

Stability – Drug Product: Sterile Water for Injection

The sponsor proposed a shelf life of 48 months stored at 2°C to 30°C. Stability data have been generated under real time and accelerated conditions.

Stability data were generated under real time conditions to characterise the stability profile of the sWFI and to establish a shelf life. The real time data submitted support a shelf life 48 months stored at 2°C to 30°C.

Quality summary and conclusions

There is no objection on quality grounds to the approval of Revestive.

Good Manufacturing Practice (GMP) Clearance for all sites has been updated; hence, previously raised issues have been resolved.

IV. Nonclinical findings

Summary

- The sponsor has submitted a high quality, ICH compliant dossier to support registration of a new biological medicine, teduglutide (Revestive; recombinant [E. coli] [gly2]-human GLP-2, human clinical dose [HCD] = 0.05 mg/kg/d, qd, SC; near life-long treatment) for adjunctive treatment of SBS in adults who are PN dependent. The treatment objective is to ↑ intestinal nutrient bioavailability via replacing/increasing GLP-2 intestinotrophic stimulus.
- The 10 pharmacology of teduglutide resembles GLP-2 (but has a longer circulating t½). GLP-2 (teduglutide) intestinotrophy is complex, indirect, and in part, dependent on IGF-1, KGF and ErbB release from subepithelial myofibroblasts combined with VIP + NO release following enteric neuronal signalling. The sponsor provided substantial proof of concept data in rodents, ferrets, dogs, monkeys and minipigs (normal healthy animals & models of PN intestinal hypoplasia, SBS and inflammatory bowel disease) that teduglutide induces reversible intestinotrophic effects (enterothelial effects = ↑ crypt base/enriched stem cell zone early progenitor cells, ↑ intermediate stem cells, ↑ transit-amplifying cells, ↑ crypt epithelial cell mitotic index, ↓ crypt and villus apoptosis; intestinal effects = ↑ intestinal weight, ↑ crypt-villus height, ↑ the mucosal surface area, ↑ mucosal surface digestive activity, ↑ nutrient absorption, ↓ fecal output; ↑ intestinal barrier function). Intestinotrophy was predominantly small intestinal (especially duodenum and jejunum; less reliable large intestinal effects). There is limited evidence that teduglutide intestinotrophy increases nutrient bioavailability and weak evidence that it reverses PN induced immunosuppression (bacterial migration to mesenteric lymph nodes). Teduglutide intestinotrophy causes narrowing of the intestinal lumen (human clinical data correlate: ↑ risk of obstruction in humans; warning statement in the PI).
- There are no secondary/safety pharmacological effects of concern in normal animals. Teduglutide is highly GLP-2R specific (inactive at other G-protein coupled receptors [GLP-1R, 5HT1A, 1B, 1D, 2A, 2C, 6 or 7; D1, 2, 4 & 5; α1; M1 & 2]). Teduglitide (≤67X

Cmax free) was not mitogenic in normal and neoplastic enterothelial cells in vitro (human & animal), and lacked neuropharmacological effects (does not cross blood brain barrier). At high supraphysiological levels, GLP-2 inhibited GLP-1 release (no effects on insulin or somatotropin) in the ex vivo perfused rat pancreas (no evidence of this in vivo). Teduglutide at concentrations ≤0.15X Cmax free ↑ gut segmentation (i.e. ↓ intestinal propulsion, potentially ↑ digestion & absorption time). Teduglutide was not hERG channelopathic or Pukinje fibre arrhythmogenic. Teduglutide (≤≈121X HCD BSA) did not affect cardiovascular/ respiratory function in anaesthetised dogs. Teduglutide (≤1112X the HCD AUC) did not induce dyslipidaemia (despite ↑ lipid & cholesterol absorption).

- Teduglutide PK in normal healthy animals correlates with human PK (no species, strain, sex or age differences). The [Gly2] in teduglutide ↓ plasma enzymatic cleavage (cf GLP-2), and ↑ t½ to 0.36-3.1h. FAbs SC dosing = 75.2-99.3%. VSS SC dosing was low (62.9-264 mL/kg; implying distribution mostly to the circulation and extracellular fluid) with modest plasma protein binding (72.2-93.5% across species). Drug-associated tissue radioactivity Tmax ≈4 h (distributed to most tissues except CNS). Catabolism was to small peptides + amino acids. Bilateral nephrectomy significantly ($p < 0.05$) ↓ Cl but did not prevent rapid ↓ [plasma] i.e. non-renal catabolism plays a major role in clearance.
- Teduglutide (≤≈267X Cmax free) did not inhibit human CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 [10HMDZ and 6βT]) in vitro and interactions via P-glycoprotein are unlikely. Teduglutide may ↑ PO drug bioavailability (warning statement in PI). Teduglutide is a poor inducer of antidrug antibodies in normal healthy animals (did not affect efficacy or systemic exposure).
- Teduglutide (≤≈364X HCD, SC, BSA comparisons) was not acutely toxic in normal healthy mice.
- For experimental practicality, repeat dose studies were conducted in normal healthy mice, rats, monkeys and minipigs (formulations resembled the registered product). High relative exposures (AUC) were achieved. Primary pharmacological intestinotrophic effects occurred in all studies at all doses. The major adverse effect was adverse injection site effects (likely at the HCD and correlate with the clinical data; warning statement in PI). Teduglutide induced gallbladder epithelial hyperplasia ± cholecystitis occurred in mice. Gallbladder epithelial hyperplasia also occurred in the 1 year monkey study. Teduglutide associated intrahepatic biliary epithelial hyperplasia + cholangitis occurred in monkeys. Extrahepatic bile duct epithelial hyperplasia + wall thickening + mural ductile proliferation + fibrosis occurred in the 2 year rat study (≥10X HCD AUC). The biliary system effects in animals correlated with ↑ risk of cholecystitis, cholangitis, and cholelithiasis in the human clinical data (warning statement in the PI). Teduglutide treatment of monkeys induced reversible pancreatic ductal hyperplasia (+ chronic inflammation in the 13 week study). Duodenal papillary hyperplasia occurred following dosing at ≥≈7X HCD (AUC) for 28 d. These effects correlate with ↑ risk of pancreatic diseases in the human clinical data (acute pancreatitis, pancreatic duct stenosis, pancreas infection, ↑ serum amylase and lipase; warning statement in PI).
- Teduglutide (±S9) did not induce bacterial reverse mutations or chromosomal aberrations in vitro and did not induce polychromatic erythrocyte micronuclei in mice (≤≈1456X HCD, SC, BSA comparison) in valid assays. However, there is a legitimate risk of somatic growth factor mediated amplification of spontaneously mutated cells (warning statement in the PI). The genotoxicity testing battery used will not detect these effects.

- GLP-2 (and likely teduglutide) is pro-neoplastic in rodent chemical carcinogen and chronic colitis bowel cancer models (human relevance uncertain). GLP-2R is also expressed in ≈30% of human colon adenocarcinomas and rarely in non-GI neoplasia (lung, ♀ repro system, CNS, thyroid, prostate).[1] In male mice teduglutide treatment (LOAEL ≤ 13X HCD AUC) resulted in a low incidence of benign B-papillary adenomas (↑ ≤4.5X cf historical control, not dose related, human relevant, possibly indicative of human gallbladder adenomatous polyps of malignant potential). In male rats, teduglutide (NOAEL ≈32X HCD AUC) resulted in a low incidence of biliary cholangiomata (2% incidence; rare lesion in rats). Teduglutide dosing also resulted in a small ↑ incidence of intestinal neoplasia in rodents (mice: jejunal adenocarcinomas [rare location] were observed + overall ↑ incidence of adenocarcinomas in males [↑ ≤≈4.6X cf historical controls; not dose related; LOAEL ≤ 13X HCD AUC]; rats: a single jejunal adenomata and a single adenocarcinoma [polypoid, well-differentiated] occurred in males [NOAEL ≈32X HCD AUC]). A human-relevant, threshold, non-genotoxic, somatic growth factor type MOA is likely. The established/likely dose thresholds for teduglutide-associated neoplasia in rodents exceed the HCD i.e. human risk is likely low but not negligible. ↑ Intestinal neoplasia in animals may correlate with the ↑ risk of colon polyps in the clinical data. Relevant warning statements are included in the PI and the risk of exacerbation of neoplasia may be a consideration in relation to the benefit of treatment.
- Teduglutide (≤≈182X HCD BSA) did not affect rat reproduction or early embryonic development. Very high teduglutide doses (≈439X HCD AUC) negatively affected maternal body weight gain and food consumption resulting in skeletal developmental delay. These effects are unlikely at the proposed HCD. Apart from injection site effects, no effects on embryofetal development were noted in rabbits (≤≈420X HCD AUC). Teduglutide (≤≈182X HCD BSA) had no adverse effects on pre-postnatal development in rats. The sponsor's proposed pregnancy Category of B1 is appropriate.
- Apart from gall bladder/extrahepatic bile duct cystic mucous hyperplasia at doses ≤1 mg/kg, teduglutide had no adverse effects in juvenile minipigs. Teduglutide has adequate IV, IA and perivascular tolerance.
- The proposed impurity limits have been adequately qualified by submitted toxicity data, apart from residual *E. coli* protein (ECP). The sponsor's section 31 response included data to show that the proposed specified level for ECP in teduglutide will result in a detectable, but likely mild, endotoxin-like acute phase response. The sponsor claimed that this was not associated with adverse effects in the clinical program.

Conclusions and recommendation

- There are no nonclinical objections to the registration of teduglutide.
- The sponsor has provided substantial proof of the concept that teduglutide induces intestinotrophy in normal healthy animals and in animal models of SBS, PN induced intestinal hypoplasia and in animal models of inflammatory bowel diseases. There is more limited proof of the concept that that teduglutide intestinotrophy results in ↑ nutrient systemic bioavailability (critically, it does not ↓ nutrient bioavailability). Teduglutide likely does not prevent PN induced immunosuppression.

[1] Single case report of reputed GLP-2 therapy associated alveolar rhabdomyosarcoma in humans: Zyczynski LE, et al. Alveolar Rhabdomyosarcoma in a 69-Year-Old Woman Receiving Glucagon-Like Peptide-2 Therapy. *Case Rep Oncol Med.* 107479 (2015).

- The major nonclinical primary pharmacologically-mediated adverse effects (biliary system effects, pancreatic effects, injection site effects, narrowing of the intestinal lumen, potentially ↑ oral drug bioavailability; mostly occurred at doses > HCD in animals) correlate with the risks identified in the human clinical data. The exception is that effects on body water and electrolyte balances (↑ risk of acute fluid overload cardiac failure in humans with SBS being treated with TPN) occurred in humans but did not occur in the nonclinical studies. The weakness of the available animal repeat dose toxicology studies was that they were conducted, for reasons of experimental practicality, in normal healthy animals. However, the more limited data available from the primary pharmacology studies that utilised animal models of SBS and/or TPN did not identify any additional hazards.
- Teduglutide is not directly genotoxic. However, its somatic growth factor actions may allow for the accumulation of spontaneously mutated cells. A warning statement has been included in the PI.
- Teduglutide positively (and indirectly via somatic growth factor activity) influences chemical (mutagenic, promoting and/or irritant) gut neoplasia in rodents. Similar somatic growth factor effects in humans are possible (GLP-2R is expressed on ≈30% of human colon adenocarcinomas; more rarely in non-gastrointestinal cancers). There is limited evidence of non-genotoxic, threshold somatic growth factor-likes effects on intestinal neoplasia in rodents (NOEL likely substantially > HCD). The human carcinogenesis risk is regarded as being low, but not negligible. The neoplastic effects in rodents correlate with a ↑ risk of colorectal polyps in humans. Warning statements have been included in the PI. Testing of human neoplasms for GLP-2R expression before teduglutide could be considered.
- Teduglutide at the HCD is unlikely to be a reproductive and developmental (including juvenile development) hazard. Transplacental and non-colostral transmammary exposures are low in rodents. The sponsor's proposed pregnancy category of B1 is appropriate from the nonclinical perspective.
- The nonclinical aspects of the RMP are appropriate. The sponsor has agreed to the PI amendments proposed.
- The sponsor has proposed an ECP specification of 75 ppm, and the mean batch level of ECP (16 ppm) exceeds the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) Guidance 18 threshold of 10 ppm. Accordingly, clinical advice is sought regarding the suitability of these proposed levels of ECP in terms of clinical safety and registration.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

This clinical evaluation used relevant sections from comparative overseas evaluation reports. Where important points are made in this evaluation, the source is indicated.

Introduction

SBS is a rare, serious, disabling, socially incapacitating and potentially life threatening condition. SBS results from surgical resection or congenital defect and is characterised by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet. Patients with SBS are highly prone to malnutrition, diarrhoea, dehydration, and an inability to maintain weight due to the

reduced intestinal capacity to absorb macronutrients, water, and electrolytes. Additional potential consequences of SBS include dehydration, electrolyte disturbances, malabsorption of nutrients, gastric hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhoea, diarrhoea, small bowel bacterial overgrowth and weight loss.

The clinical care of SBS is mainly supportive and focuses on optimising remnant intestinal function through dietary interventions, oral rehydration solutions, anti-diarrheal and anti-secretory agents. Despite intestinal adaptation following resection, however, many SBS patients require the chronic use of parenteral support PN/IV to supplement and stabilize their hydration and nutritional needs.

Clinical rationale

Teduglutide is a 33-amino acid recombinant analog of human GLP-2, a peptide secreted primarily from the lower gastrointestinal tract that preserves mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth. Teduglutide accelerates intestinal adaptation after bowel resection and enhances selective barrier function in the small intestine.

Guidance

- CHMP/EWP/185990/06 Guideline on Reporting the results of Population Pharmacokinetic Analysis
- CPMP/ICH/375/95 ICH Topic E 1 Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety

Contents of the clinical dossier

- 5 Relevant in vitro studies
- 13 clinical pharmacology studies, including 8 that provided pharmacokinetic data and 5 that provided pharmacodynamic data
- 6 population pharmacokinetic analyses
- 2 double blind efficacy/safety studies
- 3 long term open label efficacy/safety studies
- Multiple PSURs, Integrated Summary of Efficacy, Integrated Summary of Safety, Integrated Summary of Immunogenicity

Paediatric data

The sponsor is not seeking adolescent or paediatric approval; data has been submitted to the EU for use down to 28 days (that is, excluding newborn and there is an agreed Paediatric Investigation Plan).

Good clinical practice

The studies were conducted in accordance with Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

See Table 4.

Table 4: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	Single dose, SC bioavailability random. 2-way crossover 0.12mg/kg	CL0600-006	*
	3-way crossover, 10mg, 3 different body sites	CL0600-015	*
	Ascending single SC doses single-blind, placebo-controlled	1621/13	*
	Multi-dose double blind 10-80mg OD for 8days	CL0600-022	*
PK in special populations	Moderate hepatic impairment subjects single dose 20mg compared to healthy subjects	CL0600-017	*
	Moderate severe and end stage renal impairment, single dose of 10mg Compared to Healthy Subjects	CL0600-018	*
In vitro relevant to PK interactions	Assessment of Human Liver Cytochrome P450 Inhibition Potential	P10-001	
	Assessment of Induction Potential in Primary Cultures of Human Hepatocytes	P10-002	
	P-gp Substrate and inhibitor Assessment	P10-005	
	Stability of teduglutide in Human Hepatocytes	P10-007	
	Determination of Potential to inhibit Cytochrome P450 Activity	PK-0600-E-011	
Population PK analyses	Healthy subjects & Target population Pop PKs from Phase I, II and III Study Data	NPS·RAS-004	*
	PopPK: Safety and Efficacy in SBS (Target population)	CL0600-004	*
	Pharmacokinetic Parameters for Study Cl0600-021 (Target population)	NPSP-RAS-017	*
	Other PopPK in SBS, Crohn's, hepatic or renal impairment.	PopPK Meta-analysis	*
	Other PopPK, Safety and Efficacy in Crohn's Disease	CL0600-008	*

* Indicates the primary PK aim
§ Subjects who would be eligible to receive the drug if approved for the proposed indication

Evaluator's conclusions on pharmacokinetics

The mean clearance is approximately equivalent to the GFR, which indicates that teduglutide is mainly cleared by the kidneys; however, this is an assumption and has not been demonstrated by for instance use of radioactive marked teduglutide.

No accumulation or change in the pharmacokinetics of teduglutide was observed after a 21-day once daily SC treatment.

Teduglutide is absorbed with a peak concentration at 3-5 hours after subcutaneous administration, and rapidly eliminated with $t_{1/2}$ of approximately 2 hours that has been confirmed for the to-be-marketed concentration (10mg/mL). However, as stated by the applicant, the ELISA assay detected teduglutide, endogenous GLP-2, and other GLP-2 related peptides. This cross-reactivity to native GLP-2 and GLP-2 related peptides may have had significant impact on the teduglutide concentrations measured by the ELISA method.

Pharmacodynamics

Studies providing pharmacodynamic data

See Table 5.

Table 5: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Single Dose. Random, Placebo and Active Control, Effect on cardiac Repolarisation and Conduction in healthy subjects	C09-001	*
	Effects on Gastric Emptying healthy subjects	C10-003:	*
	Effect on Gall Bladder in healthy subjects	TED-C10-004	*
Population PD and PK-PD analyses	Open-Label, Multicentre, Dose-Ranging, Pilot Safety, Tolerability and Effect of 21-day, Ascending, Multidose Subcutaneous Treatment with SBS (Target population)	ALX-0600-92001	
	A 24-week Double-blind safety, Efficacy and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Paediatric Subjects Through 17 Years of Age with Short Bowel Syndrome who are Dependent on Parenteral Support	TED-C14-006:	

* Indicates the primary PD aim
§ Subjects who would be eligible to receive the drug if approved for the proposed indication

Evaluator's conclusions on pharmacodynamics

From the pharmacodynamic data presented, it can be deduced that teduglutide acts on the GLP-2 receptor, and exerts a roughly dose-related effect on the architecture of the epithelia of the large and small intestine with an obvious early "saturation" of the PD effects. Teduglutide increases the absorption of fluids and nutrients by increasing the expression of transporter proteins at the cellular level, and exerts a trophic effect by inducing an increase in gastrointestinal tissue mass, as proven by the increased villus height and crypt depth in the small and large intestine.

Dosage selection for the pivotal studies

- Study 92001: An open-label dose-ranging, pilot study to examine the safety, tolerability and effect of a 21 day, ascending, multidose subcutaneous treatment with teduglutide in patients with short bowel syndrome. Any conclusion regarding dose-response relationship and the choice of the final dose for the phase III trials must necessarily be considered to be premature and bear a relatively high risk of error.
- Study CL0600-004 failed to meet its primary objective and was only considered hypothesis generating. Based on exploratory analyses of this study, the sponsor identified a dose of teduglutide (0.05mg/kg/day) which seemed efficacious.

Efficacy

Studies providing efficacy data

These studies included:

- CL0600-020: 24-Week, Double-Blind, Safety and Efficacy in SBS.

- CL0600-021: Long-Term, Open Label Study With Teduglutide for Subjects with Parenteral Nutrition Dependent SBS Who Completed Study CL0600-020.
- TED-C11-001: 1-Year, Open-Label Study with Teduglutide for Subjects with Parenteral Nutrition-dependent SBS who Completed Study CL0600·021.
- CL0600-004. Double-Blind, Safety and Efficacy in SBS.
- CL0600-005. Open-Label Extension of Study CL0600-004, Safety and Efficacy in SBS.

Evaluator's conclusions on efficacy

From the Health Canada evaluation:

> *The efficacy of Revestive was demonstrated in Study CL0600-020 and extension Study CL0600-021. Taken together, results from both the pivotal and non-pivotal studies support the long efficacy of Revestive in the target patient population.*

From the EMA evaluation:

> *Based on the results of Study CL0600-020, teduglutide at a dose of 0.05mg/kg/day for up to 24 weeks of treatment was superior to placebo in reducing the volume of PN/I.V. in adult SBS subjects. The magnitude of the PN reduction (i.e. 4.4L/week vs. 2.3L/week) and the number of subjects achieving at least a 1-day reduction in weekly PN (21 vs. 9 patients) support the benefit of teduglutide. Furthermore, the results from the Study CL0600-004 although formally a failed study point in the same direction as the results from study CL0600-020.*
>
> *In the ongoing long-term follow-up safety Study CL0600-021 teduglutide continues to provide benefits to the subjects with SBS. Reductions in PN/IV volume achieved during 24 weeks of therapy in Study CL0600-020 are maintained during long-term therapy, and the frequency of parenteral nutrition was reduced by up to 3 days per week in a subset of subjects, with complete weaning from parenteral nutrition for 3 patients at interim cut-off date.*

This evaluator's comment:

> *While the effect of teduglutide on responder rate in study CL00-020 was double that of placebo, nevertheless there was 30.2% of placebo treated patients who had a 20 to 100% reduction from baseline in weekly PN/I.V. volume at both Weeks 20 and 24.*

Safety

Studies providing safety data

From the Health Canada evaluation:

> *Due to the small sample sizes in the pivotal studies, an integrated safety analysis is acceptable. Across all clinical studies, 595 subjects were exposed to at least one dose of Revestive (249 patient-years of exposure; mean duration of exposure was 22 weeks). Of the 595 subjects, 173 subjects were treated in Phase 3 SBS studies (77% at 0.05mg/kg/day and 23% at 0.10mg/kg/day).*
>
> *The most commonly reported (≥ 10%) adverse reactions in patients treated with Revestive across all clinical studies (n = 595) were: abdominal pain (31.3%), injection site reactions (21.8%), nausea (18.8%), headaches (16.3%), abdominal distension (14.8%), and upper respiratory tract infection (11.9%).*

In pivotal and extension studies, three subjects who received Revestive 0.05 mg/kg/day were diagnosed with malignancy; one (metastatic adenocarcinoma in the gastro-intestinal

tract) was determined by the investigator to be related to Revestive. Colorectal polyps were identified in 1.7% of subjects on placebo vs. 0.9% of subjects on Revestive 0.05 mg/kg/day. Twelve subjects experienced one or more episodes of intestinal obstruction/stenosis. Fluid overload was reported in 6.8% of subjects on placebo vs. 11.7% subjects on Revestive 0.05 mg/kg/day. Twelve percent of the patients in each of the placebo and Revestive 0.05 mg/kg/day treatment groups experienced an injection site reaction; the majority of reactions were moderate in severity and no occurrences led to drug discontinuation. The most common markedly abnormal clinical laboratory finding was C-Reactive Protein (CRP) ≥ 21 mg/L: 8.6% of subjects on placebo vs. 25% of subjects on Revestive 0.05 mg/kg/day.

Teduglutide has cross-reactivity to native GPL-2. Anti-teduglutide antibodies appear to have no impact on short term efficacy and safety; the long-term impact is unknown.

In the post-marketing phase the following adverse reactions were reported in patients receiving Revestive: cardiac arrest, cardiac failure, and cerebral haemorrhage.

Table 6: Exposure to teduglutide and comparators in clinical studies.

Study type/ Indication	Controlled studies		Uncontrolled studies	Total teduglutide
	Teduglutide	Placebo	Teduglutide	
Clinical pharmacology	281	145	47	328
Efficacy and Safety Studies (SBS)	109	59	153[a]	180
Other Studies (Crohn's disease)	75	25	65[a]	100
TOTAL	465	229	130	595

n = number of subjects in category specified
SBS = short bowel syndrome
a. Some subjects in the cell total have already been counted in the same column and primary study group by virtue of having participated in the placebo-controlled study. Subjects who received both teduglutide and placebo in a crossover study are counted once in the Placebo column, once in the teduglutide column, and once in the Total column.

Safety issues with the potential for major regulatory impact

Gastrointestinal disorders

From the EMA evaluation:

> *Primarily abdominal pain/distension, nausea/vomiting but difference regarding number of patients reporting intestinal obstruction.*
>
> *Although a large fraction being mild to moderate in severity GI adverse events were the main AE leading to premature discontinuation. The mechanism behind these events appears reasonable well explained on the basis of the pharmacological effects of the drug and the predisposition of the treated patients. It is considered a real, but manageable risk. Adequate warnings should be included in the SmPC.*

Gastrointestinal obstruction occurs more frequently in teduglutide treated patients than in placebo treated patients. Considering the pharmacological mechanism of the drug (increase in thickness of the intestinal mucosa) and the target population (subjects with multiple resections of the small and/or large intestine with anastomoses/stomas prone to narrowing, in particular in patients with Crohn's disease) the increased rate of cases of obstruction may not come as a surprise. The mechanism described by the applicant (increased thickness of mucosa due to the pharmacologic effect of teduglutide in a predisposed subject with a pre-existing sub-clinical stenosis) seems plausible although a component of impaired motility (due to increased absorption of the anti-propulsives that

most of these patients routinely are treated with) cannot be completely ruled out. In any case this is a real risk that treating physicians and patients should be made clearly aware of (in particular in patients with pre-existing stenosis of the intestine). On the other hand, as most of the cases reported resolved by conservative measures (such as NPO, nasogastric tube, pausing/discontinuing teduglutide) and as physician treating these patients are experienced in diagnosing and treating cases of intestinal obstruction, the risk is considered manageable.

Stomal complications

This evaluator has concerns about the high adverse event (AE) rate among stoma patients teduglutide 13/31 (42%) vs. placebo 3/22 (14%) although the numbers were small. There were 2 discontinuations among 31 (6%) stoma patients due to treatment related stomal AEs.

The sponsor's elaboration on "Stomal Complications" was:

> *In placebo controlled SBS studies "gastrointestinal stoma complications" occurred in 3 patients (13.6% of patients with stoma) of the placebo groups reporting 3 events and in 17 patients (37.8% of patients with stoma) of the teduglutide groups reporting 19 events. There was no apparent dose dependence, because the 0.05mg/kg/day teduglutide dose group had 41.9% of the patients with stoma reporting stoma complications and the 0.10mg/kg/ day teduglutide dose group had 28.6%.*
>
> *In all Phase III SBS studies (CL0600-004, CL0600-005, CL0600-020 and CL0600-021) "gastrointestinal stoma complications" occurred altogether in 28 patients with stoma (41.2%) reporting 47 events (Study ALX0600-92001 was not included in this analysis as no systematic data on the presence of a stoma were available). No tendency towards dose dependency could be seen. The 0.05mg/kg/day teduglutide dose group had 42.3% of the patients reporting stoma complications and the 0.10mg/kg/ day teduglutide had 37.5%.*
>
> *The verbatims behind the AE-term gastrointestinal stoma complications included typically stoma hypertrophy, stoma swelling, increased stoma nipple or other similar terms describing an enlargement of the stoma nipple. However, two cases describing actual complications on the verbatim level were also regarded serious.*
>
> *Thus, the majority of patients (28/68 SBS patients with stoma in the phase 3 SBS studies), experienced a stoma nipple enlargement which was described typically as stoma hypertrophy, stoma swelling or increased stoma nipple. In one patient this led to a bowel obstruction based on a hypertrophied ileal stoma, which resolved after 9 days. In addition, one patient reported the SAE "clotted stoma" which was found to be caused by food particles.*
>
> *Two patients in the teduglutide development program (both in Study CL0600-021) discontinued prematurely due to gastrointestinal stoma complications.*
>
> *From a pharmacological perspective it is known that GLP-2 and also teduglutide cause an increased mesenteric blood flow, which is probably the reason for the increased stoma nipple size under teduglutide treatment.*[2]

From the EMA evaluation:

> *Considering the pharmacological effect of teduglutide (swelling of intestinal mucosa due to hypertrophy of intestinal mucosa as well as increased intestinal blood flow)*

[2] Bremholm L, et al. Glucagon-like peptide-2 increases mesenteric blood flow in humans. *Scand J Gastroenterol* 44: 314-319 (2009).

swelling of the stoma and in some cases obstruction must be anticipated. The SmPC should include appropriate warning

Depression

Depression was reported by 11 patients treated with teduglutide (5.8 %) and by no patients treated with placebo. This is a major concern in view of the low number of patients included in the studies. In the Safety Summary only "depression" has been mentioned as a psychiatric adverse event. However, a look into the Integrated Safety Summary exposes more adverse events within this area; for example, anxiety, insomnia, nightmare, and sleep disorder - all only reported in the teduglutide groups. Furthermore, headache was reported in 38 (19.9%) teduglutide treated patients (placebo: two [4.9%] patients) in the phase 2/3 studies. Although the non-clinical data report no CNS related toxicity and demonstrate a low passage of teduglutide across the blood brain barrier in rats, these findings have not been explained.[3]

In the pooled analysis of the placebo controlled long term studies in SBS, 'depression' was not reported more often in the teduglutide group compared to the placebo group. Therefore 'depression' is not considered a specific risk for teduglutide. In contrast 'sleep disorders' and 'anxiety' was clearly more common among teduglutide treated patients than among placebo treated patients.

Liver function and liver toxicity

No hepatobiliary or pancreatic events were reported for placebo patients, while 36 events were reported for 18 teduglutide patients (9.4%). Two (1.0%) and 6 (3.1%) patients experienced serious pancreatic and hepatobiliary events, respectively. Adverse events of special significance were pancreatitis, abnormal faeces, cholecystitis (incl. acute), and gallbladder perforation. Of the serious events the events of pancreatitis, pancreatic duct stenosis, cholecystitis (incl. acute) deserve special attention.

One patient discontinued due to pancreatitis (in the 0.1mg/kg/d group). Furthermore, two patients discontinued because of either ALT or AST increase.

In conclusion, there is a signal of a biliary/pancreatic problems associated with teduglutide treatment of SBS patients.[4]

The assessment of this issue is complicated by the fact that SBS patients have an increased risk of bile stones.[5]

In SBS double-blind, placebo-controlled studies CL0600-004 and CL0600-020, biliary-related treatment-emergent AEs were reported in 4 of 109 subjects (3.7%) treated with teduglutide and 2 of 59 subjects (3.4%) in placebo groups

Biliary tract-related AEs were reported in 12 subjects in SBS extension studies CL0600-005 and CL0600-021, and in 4 subjects in Crohn's disease extension Study CL0600-009 (also referred to as 009). These subjects did not have biliary tract-related AEs reported in the respective core studies. Serious adverse events were reported in 8 of the 16 subjects.

Renal function and renal toxicity

It is acknowledged that there is no indication that teduglutide has a negative impact on serum creatinine. In patients with impaired renal function, reduction of teduglutide dose is recommended.[6]

[3] EMA evaluation, Day 80.
[4] EMA evaluation, Day 80.
[5] EMA evaluation, Day 150.
[6] EMA evaluation, Day 80.

Other clinical chemistry

It is acknowledged that the CRP increases noted were primarily of temporary nature and primarily noted in the short term pharmacology studies

However, the issue of the observed general increase in CRP and its possible clinical implications has not been fully resolved.

Changes in CRP and potential impact on cardiovascular risk remain an area of uncertainty.[7]

In the pooled analysis of the placebo controlled Phase III studies there was no difference between placebo and teduglutide as regards frequency of markedly abnormal post baseline calcium levels.[8]

Haematology and haematological toxicity

Mean increases were seen in platelet and WBC counts in subjects treated with teduglutide while mean decreases were seen in patients treated with placebo; however, these changes were not clinically relevant. No clinically meaningful changes were seen in any of the remaining analytes. Shift tables did not show any meaningful changes. The most common post-baseline markedly abnormal analyte was low haematocrit (≤ 37 % [M]; ≤ 32 % [F]) (42%, 25/59 for placebo, 32%, 24/74 for teduglutide 0.05 mg/kg/d, and 26%, 8/31 for teduglutide 0.10 mg/kg/d).[9]

Electrocardiograph findings and cardiovascular safety

Overall, it appears that teduglutide treatment entails the occurrence of fluid overload which might be due to the PD effect of teduglutide. Whether there is a relationship to CV AEs due to the PD effect of teduglutide or whether this is associated to fluid overload cannot be determined.[10]

Vital signs and clinical examination findings

The following vital signs were summarised by treatment group for the Safety Population: systolic blood pressure, diastolic blood pressure, heart rate, and body temperature. No clinically meaningful trends in changes in vital signs from baseline were noted.[11]

However, the evaluator also expressed concern about the incidence of pyrexia.

In the randomised, placebo controlled Phase III studies there was no difference between placebo and teduglutide in terms of frequency with which pyrexia was reported. Most cases of pyrexia were not associated with infection and pyrexia was neither associated with anti-ECP antibodies or teduglutide antibodies. The high rate of pyrexia remains unexplained. It does not appear to be related to teduglutide treatment but could be related to the underlying disease necessitating central venous line with increased risk of temporary, subclinical infections.

As regards catheter sepsis, it is acknowledged that in the placebo controlled Phase III studies the total number of AEs indicative of catheter sepsis was similar in placebo and teduglutide treated patients.[12]

Immunogenicity and immunological events

As regards immunogenicity, the data collected so far does not indicate that immunogenicity poses a significant risk to the safety and efficacy of the drug. However, as

[7] EMA evaluation, Day 150.
[8] EMA evaluation, Day 150.
[9] EMA evaluation, Day 150.
[10] EMA evaluation.
[11] EMA evaluation, Day 150.
[12] EMA evaluation, Day 150.

only relative short term studies are available, immunogenicity and potential impact on safety and efficacy should remain under observation.[13]

Serious skin reactions

Events of injection site pain were experienced by 33 teduglutide treated patients (16.8%) and by none in the placebo group. In this respect it is important to highlight that in monkey repeat dose toxicity studies a foreign body reaction (chronic active granulomatous inflammation with secondary necrosis and fibrosis) was recorded in the subcutaneous tissue at the injection site. The severity of the inflammation was increased compared to vehicle treatment and exhibited a clear teduglutide dose relation. It is currently not known if these reactions are related.[14]

Detailed review of this problem did not indicate that injection site reactions were more common for teduglutide (in the proposed dose, 0.05mg/kg/day) than for placebo. Thus injection site reactions do not constitute a major problem for teduglutide in the proposed dose.[15]

Post marketing data

From 1 September 2012 to 28 February 2014 the total exposure from marketing experience was vials, which were dispensed to 374 patients The total calculated subject years of exposure is 101.4 (36,996/365 days/year). Teduglutide was used to treat 357 subjects with SBS, 16 with an unknown indication and one subject with autoimmune enteropathy as part of a compassionate use program.

Of the 8 deaths on teduglutide in the US, the contribution of teduglutide could not be excluded in 2 cases. The Rapporteur and co-rapporteur day 150 joint response assessment report and other EMA reports contain information in relation to deaths. In 2 cases, a causal relationship could not be ruled out:

- Fluid retention was associated with a death when using teduglutide in the setting of progressive coronary artery disease, a prior history of respiratory failure and multiple comorbid conditions. Fluid overload could not be definitively attributed to either the effect of teduglutide or to the underlying disease.
- Patient died in her sleep and increased absorption of concomitant oral medication (narcotics) could not be excluded as a contributing factor to the death.

Important Identified Risks Cumulative post-marketing ACR reports as of 28 February 2014

Growth of pre-existing polyps, was a change in the known safety profile of teduglutide after marketing approval.

Additional case reports received from the completion of CL0600-021 revealed an additional 9 subjects diagnosed with intestinal polyps. As a result, the EU SPC was updated in May 2014 to include a recommendation for follow-up colonoscopies yearly for the first 2 years after start of treatment with teduglutide, and then every 5 years thereafter or more frequently as determined by the treating physician.

Biliary AEs

During the interval 1 September 2013 to 28 February 2014, no cases reported the preferred terms cholecystitis or cholelithiasis. Cumulative post-marketing ADR reports as of 28 February 2014 show that 5 patients reported 6 AEs: 3 patients reporting

[13] EMA evaluation, Day 150.
[14] EMA evaluation, Day 80.
[15] EMA evaluation, Day 150.

cholecystitis, one of whom also reported cholelithiasis; 1 patient reported cholelithiasis; and 1 patient reported cholecystectomy (1.3% of all post-marketing patients, n = 374).

Pancreatic AEs

2 patients reporting pancreatitis: one of whom reported acute and chronic pancreatitis, and the other reported acute pancreatitis (1.1% of post-marketing patients, n = 374).

Cardiovascular AEs associated with fluid overload

32 patients reported 38 events of symptoms indicative of fluid overload (8.8% of post-marketing patients, n = 374).

Gastrointestinal stenosis and obstruction

14 patients with intestinal obstructions: 10 reports of intestinal obstruction, 1 of obstruction gastric, 2 of small intestine obstruction and 1 of small intestine stenosis (3.7% of post-marketing patients, n = 374).

Gastrointestinal Stoma Complications

Cumulative post-marketing reports include 22 subjects reporting 24 events of gastrointestinal stoma complications (5.9% of post-marketing subjects, n = 374).

Pre-existing moderate or severe renal impairment, or end-stage renal disease (ESRD)

During the reporting period of 1 March 2013 to 30 August 2013, there was 1 case in a patient with medical history of chronic renal insufficiency. During the reporting period of 1 September 2013 to 28 February 2014, 5 cases (3 serious and 2 non-serious) reported a medical history which included pre-existing renal impairment or ESRD. For 4/5 there was no indication in the report that the patient's event was related to administration of teduglutide in the setting of moderate or severe renal impairment; and for 1/5, no additional information was provided to assess whether or not the patient's events were related to administration of teduglutide in the setting of moderate or severe renal impairment. Therefore, the cumulative post-marketing reports include 6 cases (1.6% of post-marketing patients, n = 374).

Growth of pre-existing polyps of the colon

Cumulative post-marketing AE reports include no reports of colonic polyps.

Benign neoplasia of the GI tract including the hepatobiliary system

Cumulative post-marketing ADR reports as of 28 February 2014 included 1 report of duodenal polyp and no other reports (0.26% of post-marketing patients, n = 374).

Tumour promoting ability

Cumulative post-marketing ADR reports as of 28 February 2014 include 3 reports: 1 of melanocytic naevus, 1 of acrochordon, and 1 of squamous cell carcinoma (0.8% of post-marketing patients, n = 374).

Occurrence of anti-teduglutide antibodies, cross reactivity with GLP-2, and occurrence of anti-ECP antibodies (and associated clinical immunogenicity reactions)

Cumulative post-marketing ADR reports as of 28 February 2014 included 34 patients reporting 48 AEs with at least one of these specific event terms (9.1% of Postmarketing patients, n = 374).

Important Potential Risks

The available case information is not sufficient to allow confirmation of a causal relationship with teduglutide of these risks.

Increased absorption of oral concomitant medications

4 reports of potentially increased absorption of oral concomitant medications (1.1% of post-marketing patients, n = 374).

Local skin reactions

24 patients reporting a total of 36 injection site events (6.4% of post-marketing patients, n = 374).

Evaluator's conclusions on safety

Post-marketing observation has added the increased risk of 'Growth of pre-existing polyps,' with the added precaution of more frequent colonoscopies, not themselves without added risks.

There is an increased risk of gastrointestinal complications particularly of the stoma. It is assumed by the EMA evaluator that this treatment will be supervised by a gastroenterologist.[16]

First round benefit-risk assessment

This evaluator's assessment

This evaluator considers efficacy was demonstrated. There is no similar treatment registered for this group of patients. However, the incidence of similar improvement without treatment was also high. While the effect of teduglutide on responder rate in Study CL00-020 was double that of placebo, nevertheless there was 30.2% of placebo treated patients who had a 20 to 100% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.

There is a demonstrated increased risk of GI complications particularly of the stoma. The theoretical concern of induction and/or promotion of benign and/or malignant tumour growth was not demonstrated in the limited studies, however post-marketing added the increased risk of 'Growth of pre-existing polyps.' The proposal of more frequent colonoscopies is not itself without added risk.

First round assessment of benefits across overseas evaluations

See Table 7.

Table 7: Assessment of benefits across overseas evaluations.

Benefits	Strengths and Uncertainties
The efficacy of the drug was demonstrated by achieving the primary endpoint and two pre-specified secondary endpoints in pivotal study CL0600-020. Long-term extension Study CL0600-021 confirmed the efficacy conclusions from the controlled study.[a]	
Due to the capacity of the intestine to undergo adaptation after surgical resection, PN requirements may not be permanent. Based on the mechanism of action, teduglutide could have the potential to improve/accelerate this adaptive process thereby providing a potential valuable additional treatment option to these patients with limited possibilities.[b]	• Study CL0600-004 failed to meet its primary objective and was only considered hypothesis generating. Based on exploratory analyses of this study, the applicant identified a dose of teduglutide (0.05mg/kg/day) which seemed efficacious • None of the subjects in the short term study could be weaned off PN/IV fluid completely which

[16] EMA evaluation, Day 150.

Benefits	Strengths and Uncertainties
Study CL0600-020 demonstrated that compared to placebo, teduglutide statistically significantly reduces the volume of PN/IV in SBS. The results showed that compared to placebo, teduglutide had statistically significant effect on the primary efficacy parameter, 20% or greater reduction in volume of PN/IV at weeks 20 and 24. The long-term extension trial indicated that the beneficial effects mentioned after 6 months treatment could be maintained, or even improved after 12 months of treatment, and that the beneficial effects shown in the placebo-controlled phase with active treatment could also be achieved when the substance was given to previously placebo-treated patients.	could constitute to a clear clinically relevant effect. As complete weaning off might only be realistic in a less severe population it may be more appropriate to show clinical relevance in the present setting with patients with a very short segment of remaining intestine and a substantial requirement for PN/IV in the reduction in number of days on PN/IV. • In the present study with the instrument applied (SBS-QoL) it was not possible to demonstrate any significant difference in QoL between placebo and teduglutide treated patients. • It seems therefore appropriate to evaluate the treatment effect after 6 months, because only very few patients with potential PN volume response might stop treatment inappropriately after this point in time. • Due to the unknown long-term risks associated with teduglutide treatment, a lifelong treatment without clear signs of efficacy is not justified.

[a] Source: Health Canada evaluation
[b] Source: EMA evaluation

First round assessment of risks

See Table 8.

Table 8: Assessment of risks across overseas evaluations.

Risks	Strengths and Uncertainties
Clinical data collected from almost 600 patients who received Revestive in clinical trials (249 patient-years of exposure) indicates an acceptable safety profile for this patient population. One malignancy was reported in an extension study that was determined to be related to Revestive.[a]	
Most of the adverse events observed following administration of teduglutide were mild and moderate in severity; one third of the adverse events were considered to be severe. The most commonly reported GI AEs for teduglutide vs. placebo were abdominal pain; nausea; vomiting; abdominal distension and constipation. While these events are important, the risk is well known. Hepatobiliary and pancreatic events were only reported in teduglutide patients. In this respect, it is a concern that a considerable part of the reports were serious. The non-clinical studies revealed hyperplastic and/or hypertrophic effects of teduglutide on intrahepatic and extrahepatic bile ducts, the gallbladder and pancreatic ducts.[b]	The causality assessment is more uncertain for the two other cases of cancer during teduglutide treatment (including open label treatment). From the theoretical point of view, due to its character of being a growth factor inducer and inducing epithelial hyperplasia, there is some concern of induction and/or promotion of benign and/or malignant tumours. The concerns are corroborated by the data derived in animals, where benign biliary tumours have been induced by high doses. The applicant has evaluated the occurrence of tumours and its precursors during the clinical studies and has found some colonic adenomatous changes, one being dysplastic in nature. The combined analyses of data from the placebo controlled SBS studies CL0600-004 and CL0600-020 showed a small overall increase in average CRP during teduglutide treatment (1.43mg/L above baseline at end of study) compared placebo treatment. Increased CRP values are a known predictor for an increased cardiovascular risk. In the SBS population an increased rate of cardiovascular

Risks	Strengths and Uncertainties
	AEs has not been observed in clinical trials with teduglutide.[b]
This evaluator in reviewing the post marketing data submitted noted an increase in pre-existing polyp growth	The result was a recommended increase in colonoscopy frequency which has in itself a risk e.g. perforation and in the associated sedation/anaesthesia. Only 280 patients were exposed in clinical SBS trials, with 68 for >12months.

[a] Source: Health Canada evaluation
[b] Source: EMA evaluation

First round assessment of benefit-risk balance across overseas evaluations

In Study CL0600-020 for subjects both with stoma as well as in those without stoma, the responder rate was higher in the teduglutide group (15/21 subjects, 71.4% and 12/22 subjects, 54.5%, respectively) than in the placebo group (3/17 subjects, 17.6% and 10/26 subjects, 38.5%, respectively).

This evaluator has concerns about the high AE rate among stoma patients teduglutide 13/31 (42%) vs. placebo 3/22 (14%). There were 2 discontinuations among 31 (6%) stoma patients due to treatment related stomal AEs.

Health Canada

The benefit vs. risk assessment favors the authorisation of Revestive for SBS patients who are dependent on parenteral support based on:

- Demonstrated efficacy: primary endpoint met in pivotal Study CL0600-020; pre-specified secondary endpoints in Study CL0600-020 such as absolute change in PN/IV; achievement of at least one day reduction in parenteral support in some patients.
- Rarity and seriousness of the disease treated. Also, there is currently no authorised therapy in Canada for this indication.
- Acceptability of the potential risks (malignancy; intestinal polyps; fluid overload; intestinal stenosis; other gastrointestinal complications) for the target population and disease treated.

EMA

The results from the pivotal study showed that compared to placebo, teduglutide had statistically significant effect on the primary efficacy parameter, 20% or greater reduction in volume of PN/IV at weeks 20 and 24. The results were robust and confirmed in a number of sensitivity analyses. Data from the long-term extension trial indicated that the beneficial effects mentioned after 6 months treatment could be maintained, or even improved after 12 months of treatment. The clinical relevance of the observed effects was confirmed by a number of experts in this field.

Most of the adverse events observed following administration of teduglutide were mild and moderate in severity; one third of the AEs were considered to be severe. Adequate measures have been identified to generate additional data in this rare condition to further elucidate particularly the safety profile. The SmPC is adequately describing the currently available information and provides appropriate guidance on the use of teduglutide.

Considering the serious and disabling nature of the condition with a considerable impact on QoL and only limited symptomatic treatment options, the demonstrated effect of clinical relevance clearly outweighs the safety concerns. Therefore, the benefit-risk

balance for teduglutide for the treatment of adult patients with SBS, who should be stable following a period of intestinal adaptation after surgery, is deemed positive.

First round recommendation regarding authorisation

This evaluator recommends authorisation; however, it is clearly considered essential that treatment be managed by a gastroenterologist.

What can also be said is that based on the risk benefit summaries made by other evaluators teduglutide has been approved in the US, Canada and EU, albeit with some restrictions.

Clinical questions

Clinical questions related to PI documentation.

Second round evaluation

The sponsor provided data in response to questions related to the PI.

Second round benefit-risk assessment

The assessment is unchanged.

Second round recommendation regarding authorisation

Approval of teduglutide is recommended for the treatment of adult patients with SBS who are dependent on parenteral support.

*Patients should be stable **for at least 4 to 8 weeks** on their parenteral support regimen before initiating teduglutide therapy.*

This achieves the same aim of not initiating parenteral support and teduglutide at the same time, while the recommended additional insertion matches the requirements of the main efficacy studies.

Commencing teduglutide is not without risk and the majority of patients receiving TPN would be for short term, for example, post-surgery where the use of teduglutide is unnecessary.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the RMP evaluator. Submitted RMPs were:

- European RMP:
  - Round 1 and 2 – version 7.4; date 24 May 2016 2016; DLP 5 February 2015
- Australian RMP:
  - Round 1 – version 1.0; date 11 April 2016; DLP 5 February 2015
  - Round 2 – version 1.0; date 12 December 2016

– Post Round 2 – version 1.1; date 17 February 2017

During Round 2 evaluation, the sponsor submitted an Australian Specific Annex (ASA, version 1.0, date 12 December 2016).

With the Post Round 2 response, an updated ASA version 1.1 (date 17 February 2017) was provided.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below.

Table 9: Summary of Safety Concerns.

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	Biliary adverse events such as cholecystitis	✓	✓	✓	–
	Pancreatic adverse events such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase	✓	✓	✓	–
	Cardiovascular adverse events associated with fluid overload	✓	✓	✓	–
	Gastrointestinal stenosis and obstruction	✓	✓	✓	–
	Gastrointestinal stoma complications	✓	–	✓	–
	Growth of pre-existing polyps of the colon	✓	✓	✓	–
	Benign neoplasia of the gastrointestinal tract including the hepatobiliary system	✓	✓	✓	–
	Tumour promoting ability	✓	✓	✓	–
	Occurrence of antiteduglutide antibodies, cross-reactivity with GLP-2, and occurrence of anti-ECP antibodies (and associated clinical immunogenicity reactions)	✓	–	✓	–
	Anxiety	✓	–	✓	–
Important potential risks	Adverse events associated with increased absorption of oral concomitant medications	✓	✓	✓	–
	Medication errors	✓	–	✓	–
	Increased C-reactive protein	✓	✓	✓	–
	Local skin reactions	✓	–	✓	–
	Potential for off-label use in patients with active Crohn's disease	✓	–	✓	–
	Compromised nutritional status	✓	–	✓	–
Missing information	Lack of experience in pregnant or lactating women	✓	✓	✓	–
	Lack of experience in the paediatric population	✓	✓	✓	–
	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)	✓	✓	✓	–
	Long term safety in the paediatric population	✓	✓	✓	–
	Limited longer-term safety data over 1 year of exposure	✓	✓	–	–
	Lack of data in subjects with pre-existing severe hepatic impairment	✓	✓	✓	–

Highlighted safety concerns were added to the safety summary during Section 31 response.

- With the Section 31 response, the sponsor provided a revised summary of safety concerns which aligned with that of EU-RMP.
- A Patient Registry is proposed as an additional pharmacovigilance activity, and will address all safety concerns except medication errors and gastrointestinal stoma complications.
- Routine risk minimisation activities are planned for all safety concerns.

New and outstanding recommendations: Post-Round 2

It is noted that the sponsor has committed to provide the reports of the planned pharmacovigilance studies when available.

The Sponsor has maintained its decision not include 'Hypersensitivity to trace residues of tetracycline' as a contraindication, and has provided justification for this. Considering the absence of comments relevant to this issue from the Delegate or the Advisory Committee on Medicines (ACM), the sponsor's decision not to include 'Hypersensitivity to trace residues of tetracycline' as a contraindication is considered acceptable.

There are no outstanding issues.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *Implement EU-RMP (version 7.4, date 24 May 2016, DLP 5 February 2015), with ASA (version 1.1; date 17 February 2017), and any future updates as a condition of registration.*

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Primary evaluation as per the evaluator:

- There is no objection to the registration of Revestive on quality grounds. GMP Clearance for all sites has been updated.
- It is a condition of registration that all batches of Revestive imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- It is a condition of registration that each batch of Revestive imported into/manufactured in Australia is not released for sale until samples and the

manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

- The sponsor must supply:
  - Certificates of Analysis of all active ingredient (drug substance) and final product.
  - Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
  - Evidence of the maintenance of registered storage conditions during transport to Australia.
  - 5 vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.
  - Samples and data should be forwarded to the Laboratories Branch, Biochemistry Section, before release of each batch and with sufficient lead time to allow for testing.

  Note: This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until the sponsor is notified in writing of any variation.

Secondary evaluations as per the evaluator:

- Sufficient evidence has been provided to demonstrate that the risks related to the presence of adventitious agents in the manufacturing of Teduglutide (Revestive) have been controlled to an acceptable level.
- There are no further objections from a microbiological viewpoint to the approval of the application to register Teduglutide (Revestive) 5 mg Powder for Solution for Injection Vial with Diluent Pre-filled Syringe.

Nonclinical

- There are no nonclinical objections to the registration of teduglutide.
- The nonclinical evaluator noted the inclusion of the recommended PI amendments in the revised PI submitted with the Section 31 response.
- The Sponsor has proposed an ECP specification of 75 ppm, and the mean batch level of ECP (16 ppm) exceeds the ARGPM Guidance 18 threshold of 10 ppm. Accordingly, clinical advice is sought regarding the suitability of these proposed levels of ECP in terms of clinical safety and registration.

  Clinical advice: The Delegate accepts the microbiology evaluator's comment that there are no further objections from a microbiological viewpoint, to the approval of the application to register Teduglutide (Revestive) 5 mg Powder for Solution for Injection Vial with Diluent Pre-filled Syringe.

Clinical

Indications

- Proposed:

  Revestive is indicated for the treatment of adult patients with SBS who are dependent on parenteral support.

- Proposed modified indication:

  Revestive is indicated for the treatment of adult patients with SBS who are dependent on parenteral support.

  *Patients should be stable **for at least 4 to 8 weeks** on their parenteral support regimen before initiating teduglutide therapy.*

Pharmacology

As an analogue of human GLP-2, teduglutide increases intestinal and portal blood flow, and inhibit gastric acid secretion. Because it acts to increase absorption across the GI mucosa it can be anticipated to increase absorption of oral medicines. Dose adjustment of these medicines may be required as the patient responds to treatment with teduglutide, particularly for narrow therapeutic index medicines. Teduglutide is not associated with QT prolongation.

The pharmacology data supported once daily subcutaneous dosing at the proposed dose of 0.05 mg/kg/d. Pharmacokinetics are linear. Bioavailability is high (~87%), Tmax is achieved 3 to 5 h after subcutaneous injection. When given at the proposed dose of 0.05 mg/kg subcutaneous dose in subjects with SBS theCmax was 36 ng/mL and the median area under the curve (AUC0-inf) was 0.15 µg•hr/mL. No accumulation of teduglutide was observed following repeated subcutaneous administrations. Vd was 103 mL/kg, similar to blood volume.

As a peptide, teduglutide is expected to be degraded into small peptides and amino acids via catabolic pathways, similar to the catabolism of endogenous GLP-2. CL was ~123 mL/h/kg, similar to the GFR suggesting that teduglutide is primarily cleared by the kidney. terminal t½ was ~ 2 hours in healthy subjects and 1.3 hours in SBS subjects.

Moderate hepatic impairment was associated with a small reduction in Cmax and AUC (10 ~15%). Teduglutide PK was not assessed in subjects with severe hepatic impairment.

Moderate to severe renal impairment or end stage renal disease was associated with increases in Cmax and $AUC_{0\text{-}inf}$. Cmax was increased 2.1 fold and $AUC_{0\text{-}inf}$ by 2.6 fold in subjects with ESRD subjects compared to healthy subjects. No differences in PK were seen for age or gender.

Efficacy

The clinical evaluator identified five studies on efficacy.

Study -020 was considered pivotal

This was a randomised, double blind, placebo controlled, multinational, multicentre clinical trial to evaluate the efficacy, safety, and tolerability of teduglutide compared with placebo in adult subjects adults with SBS who were dependent on PN/IV support for at least 12 months and required PN at least 3 times per week.

A total of 86 subjects were randomised, 43 to teduglutide and 43 to placebo. Teduglutide (0.05 /kg/day) or placebo was administered by the SC route once daily into one of the four quadrants of the abdomen or either thigh, for 24 weeks. Study subjects had SBS as a consequence of major intestinal resection and had received continuous parenteral nutrition for at least 12 months.

The primary efficacy endpoint was based on a clinical response, defined as a subject achieving at least 20% reduction in weekly PN/IV volume from baseline (immediately before randomisation) to both Weeks 20 and 24.

Regarding efficacy outcome:

- the response rate was 63% (27/43) for teduglutide vs. 30% (13/43) for placebo (p = 0.002).
- at Week 24, the mean reduction in weekly PN/I.V. volume was 4.4 L for teduglutide - treated subjects (from pre-treatment baseline of 12.9 L; a 34.1% reduction) vs. 2.3 L for placebo-treated subjects (from pre-treatment baseline of 13.2 L/week; a 17.4% reduction) (p <0.001).
- twenty-one subjects (53.8%) on teduglutide vs. 9 (23.1%) on placebo achieved at least a one-day reduction in PN/I.V. support. No subjects discontinued PN/IV at the end of the study.

Study-021 was a 2-year, open-label extension of Study-020.

This study demonstrated continuing efficacy of teduglutide in reducing dependence on PN, with efficacy appearing to increase over time.

Safety

A total of 595 subjects were exposed to teduglutide in the clinical development program with mean duration of exposure of 22 weeks. These subjects received either the proposed dose (77%) or double the proposed dose (23%).

The most frequently reported (≥ 10%) adverse reactions in patients treated with Revestive across all clinical studies (n = 595) were: abdominal pain (31.3%), injection site reactions (21.8%), nausea (18.8%), headaches (16.3%), abdominal distension (14.8%), and upper respiratory tract infection (11.9%).

In the pivotal and extension studies, three subjects who received teduglutide 0.05mg/kg/day were diagnosed with malignancy; one (metastatic adenocarcinoma in the gastro-intestinal tract) was determined by the investigator to be related to teduglutide. Colorectal polyps were identified in 1.7% of subjects on placebo vs. 0.9% of subjects on Revestive 0.05mg/kg/day.

Twelve subjects experienced one or more episodes of intestinal obstruction/stenosis.

Post-marketing data has also supported the association between teduglutide and intestinal polyps. Cases of cholelithiasis, pancreatitis, fluid overload and intestinal obstruction have also been reported post-market.

Risk-benefit analysis

Delegate's considerations

Because it acts to increase absorption across the GI mucosa it can be anticipated to increase absorption of oral medicines. Dose adjustment of these medicines may be required as the patient responds to treatment with teduglutide, particularly for narrow therapeutic index medicines.

The magnitude of effect in reducing dependence on PN is clinically significant with a difference in response rates for teduglutide vs. placebo of 33% and an absolute difference in mean reduction from baseline in weekly PN volume of 2.1 L. These reductions were demonstrated to continue over up to 30 months.

As with any compound that promotes growth, malignancy is a safety concern, particularly as it is proposed that teduglutide be able to be administered long term. This potential has been demonstrated in the clinical trials. The sponsor has recommended colonoscopy (or alternate imaging) of the entire colon with removal of polyps should be done within 6 months prior to starting treatment with teduglutide. A follow-up colonoscopy (or

alternate imaging) has been recommended at the end of 1 year of teduglutide. If no polyp is found, subsequent colonoscopies should be done no less frequently than every 5 years. If a polyp is found, adherence to current polyp follow-up guidelines is recommended.

It has also been recommended that patients should undergo initial laboratory assessments (bilirubin, alkaline phosphatase, lipase and amylase) within 6 months prior to starting treatment with teduglutide. Subsequent laboratory assessments are recommended every 6 months.

The clinical evaluator has recommended that the indication be amended to:

> *Revestive is indicated for the treatment of adult patients with SBS who are dependent on parenteral support.*
>
> *Patients should be stable **for at least 4 to 8 weeks** on their parenteral support regimen before initiating teduglutide therapy (probably so as to be in line with the EU indication).*

Note: The sponsor has accepted the amendment

The evaluators have recommended approval of teduglutide with amendments to the draft Product Information. Amongst others, the clinical evaluator has suggested that the clinical trials section should include a statement on the difference from placebo in mean absolute reduction from baseline in weekly volume of parenteral nutrition as this was only 2.1 L. It puts the proportional reductions from placebo in perspective. It could also be included that 30.7% more patients given teduglutide were able to reduce the number of days in which they received PN.

The approval letter needs to include the conditions of approval for a biological.

Summary of issues

The pivotal trial showed that even despite careful selection, there was a considerable trend to improvement (30%) with regard to the need for parenteral support. However, given the incidence of AEs, it would not be appropriate to initiate teduglutide at the same time as commencing parenteral support and, there was also no evidence submitted for such a process. Hence, the recommended modification to the proposed indication (and probably to be in line with the EU approved indication).

Proposed action

The Delegate has no reason to say, at this time, that the application for teduglutide (Revestive) 5 mg powder and solvent for solution for injection) should not be approved for registration subject to resolving issues, arising from the ACM deliberations and finalisation of matters pertaining to the dPI and RMP to the satisfaction of the TGA.

Request for ACPM advice

- Acceptability or otherwise of the submitted and already evaluated efficacy/safety data package
- Acceptability or otherwise of the modified indication for approval.
- The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

Shire appreciates the opportunity to provide our response to address some issues raised in the Delegate's Overview.

Revestive (teduglutide), a GLP-2 analogue, is proposed for the treatment of adult patients with SBS. Shire considers that the application for registration has provided a body of clinical evidence which supports the safety and efficacy of teduglutide in patients with SBS.

Revestive has received marketing approval for SBS in a number of countries including the EU, Switzerland, USA and Canada.

Overview of the efficacy/safety data

SBS is a rare, serious, disabling, socially incapacitating, and potentially life-threatening condition. SBS can result from surgical resection or congenital or acquired defect, and is characterised by the inability to maintain protein energy, fluid, electrolyte or micronutrient balances when on a conventionally accepted, normal diet. Clinical consequences of SBS include dehydration, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhoea, diarrhoea, hypotension, muscle weakness, cardiac arrhythmia and kidney failure.

In Australia, there is currently no approved pharmacological treatment for patients with SBS. The current clinical care of SBS is mainly supportive and has focused on optimising remnant intestinal function through dietary measures, oral intake or parenteral nutrition. For patients who are not able to compensate for the malabsorption of fluids, electrolytes and nutrients by increasing their oral intake and adapting metabolically, they become dependent on parenteral nutrition including intravenous nutrients and/or fluid supplementation. However, this approach is complex and invasive, and can be associated with serious complications such as catheterrelated sepsis, blood clots or liver damage. The symptoms of SBS and the inconvenience and complications in relation to parenteral support can cause significant impairment of the quality of life in these patients.

Revestive is a targeted therapy that addresses the underlying problem of inadequate absorptive capacity in patients with SBS. Teduglutide is a recombinant analogue of naturally occurring GLP-2, a peptide by L-cells of the distal intestine. It 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.

The Revestive development program shows that it provides significant and sustained clinical benefits, including reduction of the need for parenteral support. The results from Studies CL0600-020 and CL0600-004 have demonstrated efficacy of teduglutide 0.05 mg/kg/day compared with placebo. In CL0600-020, the number and percent of subjects with a clinically relevant response at week 24 was significantly greater in the teduglutide group compared with the placebo group (63% versus 30%; $p = 0.002$), with greater mean reduction in weekly PN/IV support (4.4 L versus 2.3 L; $p<0.001$). The results in CL0600-004 were supportive of the results in CL0600-020. In addition, during Study CL0600-021 (a 2-year open-label extension of CL0600-020), the efficacy observed in CL0600-020 was maintained or further enhanced with reductions from baseline in weekly PN/IV volume reduction and days off weekly PN/IV support. A total of 13 subjects were weaned off their PN/IV support while on treatment with teduglutide up to 30 months. During Study CL0006-005 (an extension study of CL0600-004 in which patients received teduglutide for up to an additional 28 weeks), 75% of the responders in CL0600-004 who entered CL0600-005 demonstrated durability in the effect of Revestive after one year of treatment. The subjects who had been completely weaned off PN/IV support in CL0600-004

remained off PN/IV support through CL0600-005. One additional subject was weaned off PN/IV support during this study.

Based on our reading of the Delegate's Overview, it is our understanding that the Delegate is not objecting to the conclusion drawn by the clinical evaluator and is seeking an endorsement by the ACM on the approval recommendation. The sponsor has interpreted this to mean the Delegate is seeking advice from the ACM as to the Committee's acceptance or otherwise of:

- the benefit/risk assessment conclusion drawn by the clinical evaluator after undertaking thorough assessments of the submitted efficacy and safety data to recommend authorisation,
- the intended decision of the Delegate that they have no reason to say, at this time, that the application for teduglutide should not be approved for registration.

The issue raised by the Delegate has been addressed by the proposed modified indication with the addition of a statement such that patients should be stable on their parenteral support regimen before initiating teduglutide therapy. This was also considered acceptable by the clinical evaluator as the statement achieves the same aim of not initiating parenteral support and teduglutide at the same time, in particular in patients receiving parenteral support for short term, for example, post-surgery.

Proposed indication

Following two rounds of TGA evaluation and the sponsor's responses to the evaluation reports, the clinical evaluator and the Delegate have proposed the following modified indication:

> *Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.*
>
> *Patients should be stable* ***for at least 4 to 8 weeks*** *on their parenteral support regimen before initiating teduglutide therapy.*

The sponsor concurs with the indication in principle and supports the proposed modified indication which recommends stabilisation prior to commencing teduglutide.

With regards to the suggested text 'for at least 4 to 8 weeks', upon further review it has occurred to us that the text 'for at least 4 to 8 weeks' is not entirely grammatically correct and may cause confusion to practitioners. Shire proposes to simplify the wording to just 'for at least 4 weeks'. Grammatically, it is confusing to include both a lower range (at least 4 weeks) and then a range (4-8 weeks) in the same sentence. The edited text 'for at least 4 weeks' covers the 'for at least 4- 8 weeks', and also allows patients who may be stable for longer than 4-8 weeks to be eligible for teduglutide therapy.

Summary and conclusion

In view of the morbidity and disabling nature of the condition of SBS, the limited treatment options, the complications of the parenteral support, and the efficacy and safety data of teduglutide, the sponsor believes that Revestive will have an important position in clinical treatment of patients with SBS.

The sponsor concurs with the Delegate on the proposed modified indication, however, a slightly modified wording, that is, for at least 4 weeks, may improve readability as 'for at least 4 weeks' already covers the period of 'for at least 4 to 8 weeks'.

The use of teduglutide for treatment of patients with SBS has been approved by major overseas regulatory authorities including the EMA and FDA. Its benefit/risk profile has been thoroughly assessed by the TGA clinical evaluator and the Delegate. Based on our reading of the Delegate's Overview, the Delegate is not objecting to the conclusion drawn by the clinical evaluator and is seeking an endorsement by the ACM on the approval

recommendation. The sponsor is committed to resolving any outstanding matters arising from the deliberations of the application by the ACM to enable patients to gain access to the first pharmacological therapy developed for the treatment of SBS in Australia.

In conclusion, Shire supports the recommendation to approve registration of Revestive, and proposes the following indication:

> *Revestive is indicated for the treatment of adult patients with SBS who are dependent on parenteral support.*
>
> *Patients should be stable **for at least 4 weeks** on their parenteral support regimen before initiating teduglutide therapy.*

Advisory Committee considerations

The ACM advised the following in response to the Delegate's specific questions on the submission.

- *1. Acceptability or otherwise of the submitted and already evaluated efficacy/safety data package*

ACM advised that the submitted and already evaluated efficacy and safety data package was acceptable.

- *2. Acceptability or otherwise of the modified indication for approval*

ACM advised that the proposed indication could be more specific by stating "up to 4 weeks on their parenteral support" as opposed to "for at least 4 to 8 weeks on their parenteral support".

- *3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application*

ACM strongly encouraged the sponsor to provide paediatric data, which are available in the EU, as these would be relevant and beneficial to the current submission.

ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Revestive teduglutide 5 mg powder for solution for injection vial with diluent pre-filled syringe indicated for:

> *Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.*
>
> *Patients should be stable at least to 4 weeks on their parenteral support regimen before initiating teduglutide therapy.*

Specific conditions of registration applying to these goods

- The Revestive (teduglutide) EU-RMP, version 7.4, dated 24 May 2016, (DLP 5 February 2015), with ASA (version 1.1, dated 17 February 2017) and any subsequent revisions, as agreed with TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Revestive at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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