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TEDUGLUTIDE - A GLP-2 ANALOG IN THE TREATMENT OF SHORT BOWEL SYNDROME: A LITERATURE REVIEW

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ABSTRACT

Short bowel syndrome–associated intestinal failure (SBS-IF) is a rare but severe clinical condition characterized by insufficient intestinal absorptive capacity and frequent dependence on long-term parenteral support. Prolonged reliance on parenteral nutrition is associated with substantial morbidity, underscoring the need for targeted therapeutic strategies that enhance intestinal adaptation and reduce intravenous support requirements. Advances in the understanding of gut-derived trophic hormones have identified glucagon-like peptide-2 (GLP-2) as a key regulator of intestinal growth and function, leading to the development of GLP-2–based pharmacological therapies.

The aim of this narrative literature review is to critically synthesise current evidence regarding the physiological role of GLP-2, the pharmacological properties of teduglutide, and its clinical efficacy and safety in the management of SBS-IF. A comprehensive literature search was conducted using PubMed and Google Scholar, including randomised controlled trials, observational studies, systematic reviews, and meta-analyses relevant to GLP-2 biology and teduglutide therapy.

The available evidence demonstrates that teduglutide enhances intestinal absorptive capacity, promotes mucosal adaptation, and enables clinically meaningful and sustained reductions in parenteral support requirements in both adult and paediatric patients. In selected individuals, treatment may facilitate partial or complete achievement of enteral autonomy. However, given its intestinotrophic mechanism of action, appropriate patient selection, structured monitoring, and long-term safety surveillance remain essential. Overall, teduglutide represents a significant advance in the targeted treatment of SBS-associated intestinal failure.

KEYWORDS

Teduglutide, Short Bowel Syndrome, GLP-2, Intestinal Failure

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1. Introduction

Short bowel syndrome (SBS) is a rare yet severe clinical condition resulting from extensive anatomical or functional loss of the small intestine and represents the leading cause of chronic intestinal failure. Many affected patients remain dependent on long-term parenteral support to maintain adequate hydration and nutritional status. However, prolonged use of parenteral nutrition is associated with considerable morbidity, including infectious, metabolic, and hepatic complications, as well as a significant impact on quality of life. Consequently, the identification of therapeutic approaches that enhance intestinal absorptive function and reduce dependence on parenteral support remains a central objective in SBS management.

Following intestinal resection, the remnant bowel undergoes a process of physiological adaptation involving structural and functional changes aimed at increasing absorptive capacity. These adaptations include mucosal hyperplasia, alterations in motility, and changes in intestinal secretion. Nevertheless, adaptive responses are frequently insufficient, particularly in patients with extensive resections or unfavourable residual anatomy, resulting in persistent intestinal failure.

Glucagon-like peptide-2 (GLP-2) has emerged as a key intestinotrophic hormone involved in the regulation of intestinal growth and function. GLP-2 exerts pleiotropic effects on the gastrointestinal tract, including stimulation of mucosal growth, inhibition of enterocyte apoptosis, enhancement of mesenteric blood flow, and modulation of gastric secretion and intestinal motility. Despite these favourable physiological properties, the therapeutic utility of endogenous GLP-2 is limited by its short plasma half-life.

Teduglutide, a long-acting GLP-2 analogue engineered to resist enzymatic degradation, was developed to overcome this limitation and has emerged as a targeted therapeutic option for patients with SBS-associated intestinal failure. The present review aims to synthesise current evidence on the physiological role of GLP-2, the pharmacological characteristics of teduglutide, its clinical efficacy and safety, and its position within contemporary treatment strategies for short bowel syndrome.

2. Methods

This narrative literature review examines teduglutide as a therapeutic option for short bowel syndrome–associated intestinal failure. A comprehensive literature search was conducted across PubMed and Google Scholar. Eligible publications comprised randomized controlled trials, prospective and retrospective cohort studies, meta-analyses, and systematic reviews. The methodological quality of each study was rigorously appraised to ensure validity and minimize bias in the synthesis of evidence.

3. Physiology of Glucagon-Like Peptide-2 (GLP-2)

Synthesis and Secretion of GLP-2

Glucagon-like peptide-2 (GLP-2) is a 33-amino acid peptide hormone that is generated through post-translational processing of proglucagon, a precursor molecule expressed in enteroendocrine L-cells located in the distal ileum and colon (Burrin et al., 2001a). Within intestinal L-cells, as well as in the brain, proglucagon is cleaved by prohormone convertase 1/3 (PC1/3), giving rise to several biologically active peptides, including glucagon-like peptide-1 (GLP-1) and GLP-2 (Baccari et al., 2024).

GLP-2 is secreted from enteroendocrine L-cells together with other proglucagon-derived peptides and is released at low basal levels under fasting conditions. This hormone enhances intestinal nutrient absorption by stimulating crypt cell proliferation, inhibiting enterocyte apoptosis, reducing gastric acid secretion, slowing small intestinal motility, and increasing mesenteric blood flow (Drucker, 2002). The primary physiological stimulus for GLP-2 secretion is enteral nutrient intake, with carbohydrates and lipids being particularly potent secretagogues (Drucker & Yusta, 2014). The mechanisms underlying GLP-2 secretion are multifactorial and involve both direct sensing of luminal nutrients by enteroendocrine L-cells and indirect regulation via enteroendocrine and neural pathways. Neural and paracrine signaling mechanisms are thought to facilitate rapid peptide release following nutrient ingestion, occurring even before digested nutrients reach the distal intestine (Burrin et al., 2001b). Postprandial GLP-2 secretion follows a dynamic temporal pattern, with evidence indicating that distinct macronutrients elicit differential secretory responses; carbohydrate-rich meals are frequently associated with an early secretory peak, whereas protein-rich meals may result in more sustained elevations in circulating GLP-2 levels (Prahm et al., 2023).

Following secretion, GLP-2 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), leading to a short plasma half-life of approximately 5–7 minutes, which is influenced by both enzymatic degradation and renal clearance mechanisms (Orhan et al., 2018).

Mechanism of GLP-2 action in the gastrointestinal tract

The physiological actions of glucagon-like peptide-2 (GLP-2) within the gastrointestinal tract are primarily mediated through activation of the GLP-2 receptor (GLP-2R), a G protein–coupled receptor (Drucker & Yusta, 2014). GLP-2R expression is predominantly restricted to non-epithelial cell populations within the gut, including enteric neurons, subepithelial myofibroblasts, and selected enteroendocrine cells, rather than intestinal epithelial cells themselves. This pattern of cellular distribution suggests that the biological effects of GLP-2 are largely indirect and are mediated through paracrine signaling mechanisms within the intestinal microenvironment (Dubé & Brubaker, 2007a).

Activation of GLP-2R initiates intracellular signaling cascades, including cyclic adenosine monophosphate-dependent pathways and mitogen-activated protein kinase signaling. These pathways lead to enhanced intestinal nutrient absorption through stimulation of crypt cell proliferation, inhibition of enterocyte apoptosis, reduction of gastric acid secretion, slowing of small intestinal motility, and increases in mesenteric blood flow (Drucker, 2002). Collectively, these trophic effects promote expansion of the mucosal surface area and support functional intestinal adaptation, processes that are of particular relevance in pathological conditions such as short bowel syndrome (Drucker & Yusta, 2014; Yusta et al., 2000).

Accumulating evidence indicates that several of the intestinotrophic effects of GLP-2 are mediated by secondary downstream factors, most notably insulin-like growth factor-1 (IGF-1) and nitric oxide (NO) (Dubé et al., 2006; Yusta et al., 2012). Activation of GLP-2R enhances local IGF-1–dependent signaling and NO-mediated increases in intestinal blood flow, which together contribute to epithelial proliferation and the maintenance of mucosal integrity (Guan et al., 2003).

Effects of GLP-2 on intestinal adaptation and nutrient absorption

Glucagon-like peptide-2 (GLP-2) promotes intestinal adaptation and enhances nutrient absorption, particularly after intestinal resection (Sigalet et al., 2006). Treatment with GLP-2 has been shown to increase villus height and crypt depth, resulting in expansion of the intestinal absorptive surface, and to improve intestinal absorption of energy, wet weight, and nitrogen in patients with short bowel syndrome (SBS) after extensive resection of the small intestine and colon. These structural and functional changes are associated with improvements in body composition and overall nutritional status (Jeppesen et al., 2001).

In preclinical models, GLP-2 administration has been demonstrated to stimulate nutrient transport and absorption through upregulation of nutrient transporter activity, such as sodium–glucose cotransporter 1 (SGLT1), and through enhancement of epithelial growth, thereby increasing the capacity for carbohydrate and macronutrient uptake (Moran et al., 2018). In addition, GLP-2 supports intestinal barrier function and may reduce intestinal permeability, facilitating more efficient nutrient absorption and limiting fluid loss, which further contributes to improved digestive function (Drucker, 2002).

Collectively, these findings indicate that GLP-2 not only stimulates mucosal growth and structural adaptation, but also enhances intestinal absorptive function, thereby providing a strong rationale for the therapeutic use of GLP-2 analogues, such as teduglutide, in conditions characterized by reduced intestinal length and impaired nutrient absorption (Estall & Drucker, 2006).

4. Drug Characteristics

Teduglutide was first approved by the U.S. Food and Drug Administration (FDA) on December 21, 2012, for use in adult patients with short bowel syndrome requiring parenteral support. This approval was based on pivotal clinical trials demonstrating the drug's efficacy in reducing parenteral nutrition requirements in this population (*FDA Approves Gattex to Treat Short Bowel Syndrome*, n.d.). Subsequently, on May 17, 2019, the FDA expanded the indication for teduglutide injection to pediatric patients aged one year and older with SBS, making it the first GLP-2 analogue approved for pediatric use. These regulatory milestones reflect the accumulating clinical evidence supporting the safety and efficacy of teduglutide across different age groups (*FDA Approves Gattex (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

Chemical structure and differences from endogenous GLP-2

Teduglutide is a recombinant analogue of endogenous human glucagon-like peptide-2 (GLP-2), a peptide hormone secreted by enteroendocrine L-cells of the distal intestine in response to luminal nutrient exposure. Native biologically active GLP-2 (amino acids 1–33) is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) via cleavage at the alanine residue at position 2 from the N-terminus, generating the less biologically active metabolite GLP-2(3–33). Teduglutide differs from native GLP-2 by a single amino acid substitution, whereby alanine at position 2 is replaced by glycine. This structural modification confers resistance to DPP-4–mediated degradation, thereby prolonging its biological half-life relative to endogenous GLP-2 (Marier et al., 2008a, 2010).

Mechanism of action

Teduglutide exerts its biological effects through selective activation of the glucagon-like peptide-2 receptor (GLP-2R), a class B glucagon–secretin family receptor that is predominantly expressed within the gastrointestinal tract. GLP-2 receptors are predominantly localized on intestinal enteroendocrine cells, subepithelial myofibroblasts, and neurons of the enteric nervous system, with the highest expression observed in the jejunum, followed by the ileum, colon, and stomach. Receptor activation induces the local release of growth and signaling mediators, including insulin-like growth factor-1 (IGF-1), nitric oxide, and keratinocyte growth factor (KGF), which collectively contribute to the maintenance of intestinal mucosal integrity and enhancement of absorptive function (Dubé & Brubaker, 2007b).

Repeated administration of GLP-2 results in intestinal mucosal expansion, primarily through increased crypt cell proliferation and reduced enterocyte apoptosis (Jeppesen, 2012). In addition, GLP-2 enhances nutrient and fluid absorption (Jeppesen et al. 2009), inhibits gastric acid secretion (Jeppesen et al., 2009; Wøjdemann et al., 1999), delays gastric emptying (M. WØJDEMANN, 1998), reduces endotoxaemia, improves markers of intestinal permeability, and attenuates systemic and hepatic inflammation, oxidative stress, and macrophage infiltration (Cani et al., 2009) while also stimulating intestinal blood flow (Bremholm et al., 2009, 2011).

Pharmacokinetics and pharmacodynamics

The effects of teduglutide (GATTEX) on intestinal absorptive capacity were evaluated in a 21-day, open-label, multicenter, dose-ranging study involving 17 adult patients with short bowel syndrome (SBS), with two to three participants per dose group. Teduglutide was administered subcutaneously once daily at doses of 0.03, 0.1, and 0.15 mg/kg, corresponding to approximately 0.6- to 3-fold the recommended therapeutic dose. All dose levels except 0.03 mg/kg were associated with a marked enhancement of gastrointestinal fluid absorption, with increases in wet weight absorption of approximately 750–1000 mL/day. Treatment was also associated with structural adaptations of the intestinal mucosa, including increases in villus height and crypt depth. Importantly, even at doses up to five times the recommended level, teduglutide did not result in clinically meaningful prolongation of the QT interval (*U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

Pharmacokinetic evaluations demonstrated that subcutaneously administered teduglutide exhibits high systemic availability, with an absolute bioavailability of approximately 88% in healthy subjects and peak plasma concentrations achieved within 3–5 hours after dosing. Following administration of a 0.05 mg/kg dose in patients with SBS, the median maximum plasma concentration (Cmax) was 36 ng/mL. No accumulation of teduglutide was observed with repeated administration. Both Cmax and area under the concentration–time curve (AUC) increased proportionally across the evaluated dose range of 0.05–0.4 mg/kg, corresponding to doses of up to eight times the recommended level. The volume of distribution in healthy individuals was approximately 103 mL/kg, consistent with distribution largely confined to the intravascular compartment (Marier et al., 2008b; *U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

Although the metabolic pathways of teduglutide have not been directly characterized in humans, the peptide is presumed to undergo proteolytic degradation into smaller peptides and amino acids via mechanisms analogous to the metabolism of endogenous GLP-2. Elimination studies conducted in healthy subjects demonstrated a plasma clearance of approximately 123 mL/h/kg, a value comparable to the glomerular filtration rate, thereby suggesting that renal clearance represents the primary route of elimination. The mean terminal half-life of teduglutide was approximately 2 hours in healthy individuals and 1.3 hours in patients with short bowel syndrome (SBS) (*U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

Pharmacokinetic assessment further revealed a progressive increase in systemic exposure to teduglutide with worsening renal impairment. Subjects with end-stage renal disease exhibited a 2.59-fold increase in AUC and a 2.08-fold increase in Cmax relative to healthy subjects, whereas moderate and severe renal impairment were associated with more modest increases in exposure. Consistent with these findings, mean plasma clearance declined in subjects with renal dysfunction, indicating a reduced elimination capacity (Nave et al., 2013a).

Dosage and route of administration

Administration of teduglutide is restricted to the subcutaneous route, with a recommended daily dose of 0.05 mg/kg for adults and children aged one year and older. In the event of a missed dose, it should be administered as soon as possible on the same day, ensuring that two doses are not given within a single day, as doses of 10 mg/kg did not demonstrate a statistically significant benefit over placebo, whereas 0.05 mg/kg/day showed clinically meaningful efficacy (Jeppesen et al., 2011; *U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.). To enhance local tissue tolerance, rotation of injection sites is recommended, including the abdomen, upper arms, and thighs (*U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.). In patients with renal insufficiency (eGFR <60 mL/min/1.73 m²), the teduglutide dose should be reduced by 50% to 0.025 mg/kg/day (Nave et al., 2013b; Pironi et al., 2024a; *U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

5. Clinical Applications

Indications for Use

Teduglutide is indicated for the treatment of adult and pediatric patients aged one year and older with short bowel syndrome (SBS) who are dependent on parenteral support.

Short bowel syndrome is an uncommon clinical condition characterized by substantial anatomical or functional loss of intestinal segments and represents the leading cause of intestinal failure (IF) (Pironi et al., 2016). SBS-associated intestinal failure (SBS-IF) develops when the remaining intestine is unable to absorb sufficient macronutrients, fluids, and electrolytes to maintain normal health or support growth (Pironi et al., 2016; Tappenden et al., 2013). The clinical presentation of SBS is highly heterogeneous, reflecting considerable variability in residual bowel anatomy and functional capacity among affected individuals (Jeppesen et al., 2012a).

In pediatric patients, SBS most commonly arises from congenital intestinal anomalies or from extensive bowel resection secondary to conditions such as necrotizing enterocolitis, intestinal malrotation with volvulus, or severe, treatment-resistant inflammatory bowel disease. This profound loss of absorptive surface frequently progresses to intestinal failure, often necessitating prolonged or lifelong parenteral nutrition (PN) (Wang & O'Daniel, 2025).

In adult patients, SBS-IF results from a broad range of etiologies, including recurrent Crohn's disease, thromboembolic events involving the mesenteric circulation, traumatic injury, intestinal malignancies, or complications of prior abdominal surgery (Jeppesen, 2014b). In these individuals, impaired intestinal absorptive capacity precludes maintenance of adequate hydration and nutritional status through enteral intake alone, thereby requiring long-term parenteral nutrition (Gigola et al., 2022).

Although the remaining intestine undergoes physiological adaptation aimed at enhancing nutrient and fluid absorption—particularly in younger patients—this process is frequently insufficient to achieve enteral autonomy. Moreover, functional alterations, including intestinal dilatation and dysmotility, may further compromise absorptive efficiency and contribute to ongoing dependence on parenteral support (Muto et al., 2022). Within this clinical context, teduglutide is employed to enhance intestinal absorptive function and facilitate reduction in parenteral nutrition requirements in clinically stable patients with SBS-IF (Gigola et al., 2022).

Patient selection criteria and contraindications

Assessing a patient's eligibility for teduglutide therapy requires a comprehensive review of the medical history and careful evaluation of key factors, including the overall clinical condition, nutritional status, and the presence of existing nutrient deficiencies(Joly et al., 2020; Pironi et al., 2021). In addition, all contraindications, warnings, and precautions outlined in the summary of product characteristics for teduglutide should be thoroughly reviewed prior to treatment initiation (*U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

Teduglutide is contraindicated in patients with active malignancy and in individuals with a history of malignancies involving the gastrointestinal tract or hepatobiliary system, including the pancreas, or with any other malignancy diagnosed within the preceding five years. Additional contraindications include premalignant gastrointestinal conditions, ongoing radiation enteritis, chronic pancreatitis, clinically significant biliary disease, and conditions associated with structural or functional compromise of intestinal tissue (Pironi et al., 2021).

Prior to initiation of therapy, patients should undergo baseline gastrointestinal evaluation to exclude neoplastic disease and to assess intestinal anatomy. In adult patients, this typically includes colonoscopy and upper endoscopy with removal of detected polyps, whereas in pediatric patients, fecal occult blood testing is recommended initially, followed by endoscopic evaluation if indicated. In addition, baseline laboratory assessment of hepatic and pancreatic function, including measurements of bilirubin, alkaline phosphatase, lipase, and amylase, should be performed before commencing treatment (*U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

Efficacy assessment – reduction in parenteral nutrition requirements

The efficacy of teduglutide in reducing parenteral support (PS) requirements among patients with short bowel syndrome–associated intestinal failure (SBS-IF) has been robustly established in two pivotal Phase III randomized controlled trials, together with their open-label extension phases (Jeppesen, 2012).

In the first Phase III trial, STEPS (ClinicalTrials.gov identifier: NCT00798967), 83 patients were randomly assigned to receive teduglutide at doses of 0.05 or 0.10 mg/kg/day, or placebo. Among patients treated with the approved 0.05 mg/kg/day dose, 46% achieved a clinically meaningful reduction of ≥20% in

weekly PS volume by Week 20, with this response sustained through Week 24, compared with only 6% in the placebo group. Mean PS volume in the teduglutide group decreased from 9.6 L/week at baseline to 7.1 L/week, representing a reduction of 2.5 L/week, whereas the placebo group exhibited a more modest decrease from 10.7 L/week to 9.8 L/week (0.9 L/week reduction). Beyond reductions in PS volume, teduglutide treatment was associated with maintenance of oral fluid intake, increased urine output, weight gain, and improvements in surrogate markers of intestinal adaptation, including increased villus height, crypt depth, and plasma citrulline concentrations.

The 52-week open-label extension of the STEPS trial enrolled 25 patients and demonstrated a progressive and sustained treatment effect, with 68% of participants achieving a ≥20% reduction in PS requirements. The mean reduction in PS volume was 4.9 L/week, corresponding to a 52% decrease from baseline values. Notably, three patients achieved complete independence from parenteral support during the extension phase (Jeppesen, 2014a).

In a subsequent pivotal Phase III trial of similar design involving 86 patients, a comparable yet more pronounced reduction in parenteral support (PS) requirements was observed. By Week 24, 63% of patients receiving teduglutide at the approved dose of 0.05 mg/kg/day achieved a ≥20% reduction in PS, compared with 30% in the placebo group. Mean PS volume declined from 12.9 L/week to 8.5 L/week, corresponding to a reduction of 4.4 L/week in the teduglutide group, whereas the placebo group demonstrated a smaller mean reduction of 2.3 L/week (Vipperla & O'Keefe, 2013).

The long-term open-label extension study, STEPS-2 (ClinicalTrials.gov identifier: NCT00930644), evaluated the durability and progression of PS reductions with prolonged teduglutide therapy. Patients who completed the initial 24-week placebo-controlled phase continued once-daily subcutaneous teduglutide (0.05 mg/kg) for up to 24 months. At study completion, patients who had received teduglutide during both the parent and extension studies (TED/TED) experienced a mean PS reduction of 7.6 L/week, representing a 66% decrease from baseline. Those who transitioned from placebo to teduglutide (PBO/TED) achieved a mean reduction of 3.1 L/week (28%), while previously untreated patients (NT/TED) demonstrated a mean reduction of 4.0 L/week (39%). Importantly, 13 patients achieved complete independence from parenteral support during the extension period. Collectively, these findings demonstrate that long-term teduglutide treatment not only sustains but may further augment reductions in PS requirements, thereby reinforcing its therapeutic role in facilitating intestinal adaptation and reducing long-term dependence on parenteral nutrition in patients with SBS-IF (Schwartz et al., 2016a).

The efficacy of teduglutide in reducing parenteral support (PS) requirements has also been demonstrated in pediatric patients with short bowel syndrome–associated intestinal failure (SBS-IF). In a 24-week, randomized, double-blind, Phase III trial, 59 pediatric patients aged 1–17 years were enrolled. Of these, 50 patients received teduglutide at doses of 0.025 mg/kg/day (n = 24) or 0.05 mg/kg/day (n = 26), while 9 patients received standard of care (SOC) alone. The primary endpoint, defined as a clinically meaningful reduction in PS requirements, was achieved by 13 patients (54.2%) in the 0.025 mg/kg/day group, 18 patients (69.2%) in the 0.05 mg/kg/day group, and 1 patient (11.1%) in the SOC group. By Week 24, the mean reduction in PS volume reached 42% relative to baseline. Notably, 12% of patients treated with teduglutide at 0.05 mg/kg/day achieved complete independence from parenteral support during the study period. Importantly, the safety profile observed in pediatric patients was broadly consistent with that reported in adult populations, with no new safety signals identified (Kocoshis et al., 2020).

6. Safety and Adverse Effects

Data derived from the STEPS clinical trial program indicate that adverse events (AEs) associated with teduglutide therapy are predominantly gastrointestinal in nature, reflecting both the underlying disease characteristics of SBS-IF and the intestinotrophic mechanism of action of the drug. Abdominal pain was the most frequently reported AE, while other commonly observed events included catheter-related bloodstream infections, nausea, headache, nasopharyngitis, vomiting, and weight loss. Additional reported complications encompassed upper respiratory tract infections, dehydration, and electrolyte disturbances. The most frequently reported serious adverse events were catheter-related complications, intestinal obstruction, and pyrexia (Gigola et al., 2022; Jeppesen et al., 2012b; *Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome−Associated Intestinal Failure: STEPS-3 Study - Seidner - 2018 - Nutrition in Clinical Practice - Wiley Online Library*, n.d.; Schwartz et al., 2016b). Consistent with its pharmacological role as a glucagon-like peptide-2 analogue, teduglutide has the potential to induce hyperplastic changes within the gastrointestinal and hepatobiliary tracts, as suggested by preclinical findings. In the STEPS-2 trial, gastrointestinal polyps were identified in 9 of 51 patients who underwent colonoscopic evaluation during 24 months of treatment; however, no cases of dysplasia or malignancy were detected (Schwartz et al., 2016b).

7. Monitoring

Patients should therefore be advised to systematically monitor and document fluid balance, including oral intake, urine output, and stoma output, and to promptly report any concerning symptoms such as vomiting, abdominal pain, or reduced appetite (Seidner et al., 2013). In light of reported hepatobiliary and pancreatic adverse effects, periodic assessment of liver function is recommended, with testing performed at six-month intervals or more frequently where clinically warranted (*U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

In addition, surveillance colonoscopy is recommended after one year of treatment and subsequently at intervals of no less than five years. Patients receiving concomitant medications with a narrow therapeutic index should be monitored closely, given the potential for enhanced drug absorption during therapy (*U.S. FDA Approves GATTEX® (Teduglutide) for Children 1 Year of Age and Older With Short Bowel Syndrome (SBS)*, n.d.).

Patients with jejunostomy require closer clinical surveillance due to their heightened susceptibility to rapid fluid and electrolyte disturbances. Key monitoring parameters include fluid balance, renal function, and body weight, as the development of peripheral edema or rapid weight gain may signal inadequate tapering of intravenous support (IVS), particularly among patients with high baseline parenteral requirements (Pironi et al., 2024b). Early phases of treatment are frequently associated with gastrointestinal adverse events, including nausea, thereby underscoring the importance of close monitoring of oral intake. The majority of treatment-related gastrointestinal adverse events occur within the first 12–24 weeks and typically resolve with continued therapy (*Teduglutide for the Treatment of Adults with Intestinal Failure Associated with Short Bowel Syndrome: Pooled Safety Data from Four Clinical Trials - Ulrich-Frank Pape, Kishore R. Iyer, Palle B. Jeppesen, Marek Kunecki, Loris Pironi, Stéphane M. Schneider, Douglas L. Seidner, Hak-Myung Lee, John Caminis, 2020*, n.d.).

8. Teduglutide in the Context of Other GLP-2 Therapies and Alternative Approaches

Other GLP-2 analogs in clinical development

The success of teduglutide has catalysed the development of next-generation GLP-2 analogues aimed at optimising pharmacokinetic properties, most notably through prolongation of half-life to permit reduced injection frequency (Lafferty et al., 2021).

Among these agents, apraglutide, a long-acting GLP-2 analogue formulated for once-weekly subcutaneous administration, has demonstrated enhanced intestinal fluid and nutrient absorption in open-label Phase I and II clinical trials, with a safety profile comparable to that of established GLP-2–based therapies. A pivotal Phase III trial has recently been completed (NCT04627025), and the full efficacy and safety outcomes are currently awaited (Eliasson et al., 2022).

Additional long-acting GLP-2 analogues, such as glepaglutide, have been evaluated in randomised, placebo-controlled clinical trials involving patients with short bowel syndrome and intestinal failure. Administration of glepaglutide twice weekly was associated with statistically significant reductions in parenteral support requirements and a favourable tolerability profile, whereas once-weekly dosing failed to demonstrate comparable therapeutic efficacy (Jeppesen et al., 2025).

Position of teduglutide in the treatment algorithm for SBS

Management of short bowel syndrome (SBS) follows a stepwise, hierarchical treatment algorithm, beginning with supportive and dietary interventions and progressing, when necessary, to targeted pharmacologic therapies, including teduglutide. Initial management focuses on optimization of fluid and nutrient intake while minimizing factors known to exacerbate diarrhea and fluid losses. Patients are routinely advised to avoid hypotonic or high-sugar beverages lacking adequate electrolyte content, such as plain water, carbonated drinks, fruit juices, and caffeine-containing beverages, as these may aggravate intestinal fluid losses.

Pharmacologic management is introduced when dietary measures alone are insufficient and typically includes antidiarrheal agents, such as diphenoxylate–atropine, loperamide, tincture of opium, and codeine, as well as bile acid sequestrants (e.g., cholestyramine) in appropriately selected patients. Additional adjunctive therapies may include pancreatic enzyme supplementation with pancrelipase and acid suppression therapy using proton pump inhibitors (PPIs) or H_2-receptor antagonists. In patients with high-output stomas or refractory diarrhea, octreotide may be considered, administered either as short-acting daily injections or as long-acting formulations given every 3–4 weeks.

Within this therapeutic framework, teduglutide, a glucagon-like peptide-2 (GLP-2) analogue, occupies a later position in the treatment algorithm and is reserved for patients who remain dependent on parenteral support, including total parenteral nutrition (TPN) or intravenous fluids (IVF), despite optimization of conventional medical and dietary therapies. Teduglutide is the most extensively studied GLP-2 analogue to

date and currently represents the only GLP-2–based therapy approved for clinical use, reflecting its established efficacy and safety profile in this population (*ESPEN Guideline on Chronic Intestinal Failure in Adults e Update 2023*, 2023; ESPGHAN, n.d.; Jamie Dickey, DNP, MSN, AGACNP-BC et al., 2025).

9. Conclusions

Short bowel syndrome–associated intestinal failure continues to represent a complex clinical challenge, frequently necessitating long-term dependence on parenteral support. Teduglutide, a glucagon-like peptide-2 analogue, constitutes a significant therapeutic advancement by facilitating intestinal adaptation and enhancing the absorption of nutrients and fluids. Accumulating clinical evidence indicates that teduglutide therapy enables sustained reductions in parenteral support requirements and, in carefully selected patients, may permit partial or complete achievement of enteral autonomy. Given its intestinotrophic mechanism of action, appropriate patient selection, structured monitoring, and ongoing safety surveillance are essential to optimize clinical outcomes. The ongoing development of long-acting GLP-2 analogues underscores the dynamic evolution of this therapeutic area and holds promise for further improving the management of short bowel syndrome–associated intestinal failure.

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