National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Teduglutide for treating short bowel syndrome [ID3937]
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	NHS England Paediatric Medicine Clinical Reference Group	Yes	Thank you. No action required.
	Takeda	The wording of the remit is appropriate	Thank you. No action required.
Timing Issues	NHS England Paediatric Medicine Clinical Reference Group	There are currently patients experiencing complications of Short bowel syndrome (SBS) that are life limiting and potentially life threatening due to complications of intestinal failure (such as catheter-related blood stream infections/sepsis and end stage liver disease). Treatment with teduglutide is potentially life changing and may mitigate need for intestinal transplantation and improve transplant-free survival by reducing dependency on parenteral nutrition (PN).	Thank you. the technology appraisal of teduglutide for treating short bowel syndrome is expected to start in June 2021.

Section	Consultee/ Commentator	Comments [sic]	Action
	Takeda	Short bowel syndrome (SBS) patients in England have been eager to have NHS access to teduglutide for many years since authorisation was granted by the European Medicines Agency (EMA) on 30 August 2012 and teduglutide has been commercially available in the UK for treating SBS since September 2014. Teduglutide has been approved by the Scottish Medicines Council (SMC) for use within its licensed indication and as such there is a lack of harmonisation, in terms of NHS access, for patients across the United Kingdom	Thank you. the technology appraisal of teduglutide for treating short bowel syndrome is expected to start in June 2021.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NHS England Paediatric Medicine Clinical Reference Group	SBS is a spectrum of malnutrition resulting from inadequate bowel length. The background omits to mention the causes in the paediatric population, which often occur at birth or shortly after. The most common causes are necrotizing enterocolitis, abdominal wall defects (e.g., gastroschisis), jejunal / ileal atresia, and mid-gut volvulus. Paediatric SBS is a complex condition and carries extensive morbidity and high mortality. These patients suffer repeated episodes of sepsis, dehydration, and metabolic derangements and often require multiple hospital readmissions. They also experience difficult psychosocial issues related their morbidity. Paediatric SBS is becoming more common, due to improved survival rates of infants born prematurely. We know that 389 children received HPN in the UK (2019); this gives a prevalence of 30/million and the majority of these had short bowel syndrome *.	Thank you, the background section has been amended to reflect some of your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		* Clinical Nutrition ESPEN Wiskin 42, 2021, 138-141	
	Takeda	The background information is accurate but we would highlight the additional information which is not currently captured: - Congenital abnormalities (e.g., intestinal atresia, Hirsprung's disease) are another cause of short bowel syndrome (SBS) - The symptoms and severity of SBS depend on the underlying cause, the length and location of the resection and the functional capacity of the remaining bowel - All patients with SBS will initially require parenteral support (PS) after resection. However, SBS has a wide variety of potential underlying causes, resulting in a highly heterogeneous patient population. Therefore, while some patients can be weaned off PS after intestinal adaptation, others will require long-term PS in order to maintain nutrition and hydration and sustain life - Parenteral support (PS) comprises parental nutrition (PN) and intravenous (IV) fluids, however within the disease area PS and PN are often used as interchangeable terms	Thank you, the background section has been amended to reflect some of your comments.
The technology/ intervention	NHS England Paediatric Medicine Clinical Reference Group	Yes	Thank you. No action required.
	Takeda	The description of the technology is accurate but does not outline: - The full range of intestinotrophic effects of glucagon like peptide 2 (GLP-2) - That teduglutide is a novel product with an important substitution of an amino acid to extend the half life of teduglutide compared to GLP-2 - The fact that teduglutide is administered once daily into alternating sites in the abdomen - The contraindication of teduglutide in people with hypersensitivity to the active substance or any excipients or to trace residues of tetracycline and in people with suspected malignancy To address this, we suggest the	Thank you, the section has been amended to reflect some of your comments. The committee will consider the intervention within its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
		following edits to the description of the technology (additions represented by blue text, deletions represented by strike through): "Teduglutide (Revestive, Takeda) is an analogue of glucagon like peptide 2 (GLP-2), a naturally-occurring hormone which has a number of intestinotrophic effects, including slowing of gastric emptying, reduction of gastric secretions, increase of intestinal and portal blood flow, and stimulation of growth of the gastrointestinal epithelium ~~promotes the growth of nutrient absorbing cells on the surface of the intestine~~ . Teduglutide is administered once daily by a subcutaneous injection into alternating sites between 1 of the 4 quadrants in the abdomen. Compared to GLP-2, teduglutide has a substitution of alanine for glycine in position 2 of its 33 amino acids structure. This substitution results in resistance to degradation by the dipeptidyl peptidase-IV (DPP-IV) enzyme. As a result, the terminal half-life of teduglutide is approximately 2 hours in healthy subjects and 1.3 hours in patients with SBS compared with the 7- minute half-life of GLP-2. This results in longer exposure to teduglutide compared with native GLP-2, allowing more time for its intestinotrophic effects to be exerted. Teduglutide has a marketing authorisation in the UK for treating short bowel syndrome in people aged 1 year and over. The summary of product characteristics stipulates that patients should be stable following a period of intestinal adaptation after surgery ~~and that intravenous fluid and nutrition support should be optimised and stabilised before starting treatment~~ . Teduglutide cannot be used in people with *hypersensitivity to the active substance or any excipients or to trace residues of tetracycline, an active or suspected* malignancy, or a history of malignancies in the gastrointestinal tract within the last 5 years."	
Population	NHS England Paediatric Medicine Clinical	No, it is not defined appropriately. The population should specifically state that it applies also to infants, children and young people	Thank you The committee will consider the intervention within its marketing. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Reference Group		
	Takeda	In line with the marketing authorisation for teduglutide, we recommend that is specified that people should be *aged 1 year and over*. To address this, we suggest the following edits to the definition of the population (additions represented by blue text): “People aged 1 year and over with short bowel syndrome who are stable following a period of intestinal adaptation after surgery”	Thank you The committee will consider the intervention within its marketing. No action required.
Comparators	NHS England Paediatric Medicine Clinical Reference Group	The standard of care comparators mentioned are not appropriate as they do not treat the condition. There are no evidence-based medications as comparators or alternatives to compare.	We recognise that there is not a NICE recommended comparator for SBS/ That is why established clinical management without teduglutide is considered the most appropriate comparator.
	Takeda	The comparators listed are appropriate and represent ‘best alternative care’	Thank you. No action required.
Outcomes	NHS England Paediatric Medicine Clinical Reference Group	Patients’ outcomes should include symptoms (e.g., chronic diarrhoea, abdominal pain, perianal soreness/dermatitis, night-time disturbance due to infusion pumps), school attendance (children), psychological morbidity and overall survival. Additionally, complications of SBS such as hospitalisations, central venous line infections, development of intestinal failure related liver disease should be included.	Thank you for your comment. Appreciate that patient related symptom outcomes would have value. However, these outcomes have not been included in the

Section	Consultee/ Commentator	Comments [sic]	Action
		Outcomes should also include assessment of ability of parents or carers of children with SBS to maintain employment outside the home, and their social & mental well-being.	primary clinical trial. In addition many of the state outcomes are captured within the quality of life measurement. The scope has been amended to include overall survival and impact on carers.
	Takeda	Improvement in parental support (PS) requirements can be measured in terms of reductions in either the volume of PS received or the frequency of PS received. For simplicity, our economic model will focus on reductions in PS requirements in terms of frequency alone (number of days per week of PS), however the effect of teduglutide on patients' PS volume requirements will also be described in our dossier.	Thank you. No action required.
Economic analysis	NHS England Paediatric Medicine Clinical Reference Group	Patients face financial constraints, including decreased employment for index patients and parents of children with SBS. Patients and families may face large out-of-pocket expenses for medications, and supplies. Furthermore, HPN technology and HPN-related complications and sequelae contribute to the rapid overall increase in the costs of healthcare systems.	Thank you. NICE methods evaluate technologies according to the perspective of the NHS and personal social services No action required.
	Takeda	No comments	Thank you. No action required.
	NHS England Paediatric	Age is a protected characteristic.	Equality issues will be recorded in the equality

Section	Consultee/ Commentator	Comments [sic]	Action
Equality and Diversity	Medicine Clinical Reference Group	Adequate description has not been given to the physical and psychological morbidity, and life-threatening nature of SBS in infants and children.	impact assessment forms. Particular attention will be given to any issue that has a potential discriminatory impact on a protected group.
	Takeda	No equality considerations have been identified	Thank you. No action required
Other considerations	NHS England Paediatric Medicine Clinical Reference Group	None	Thank you. No action required.
	Takeda	Short bowel syndrome and parental support requirements are not only a burden to the patient themselves but also to their family and caregivers, who suffer a lack of social activities, difficulties with relationships, lost income and employment difficulties and, in some cases, depression. Our dossier and economic analysis will also take caregiver burden into consideration	All direct health effects are relevant, whether for patients or, when relevant, carers
Innovation	NHS England Paediatric Medicine Clinical Reference Group	Yes. There is currently no treatment for SBS. In reducing dependence on parenteral nutrition, teduglutide is anticipated to benefit patients in terms of reducing life-threatening complications, spending less time on PS and, therefore, increasing independence.	Thank you for your comment. The committee will consider innovative nature of the technology, in particular its potential to make a

Section	Consultee/ Commentator	Comments [sic]	Action
		Patients experience chronic diarrhoea, abdominal pain, impaired sleep and daytime fatigue because of pump noises, equipment alarms, and nocturia – and chronic ill health can cause additional psychological issues. Children also have reduced HRQL. Fatigue due to sleep disruption, decreased mobility, and reduced activities including school attendance. It is anticipated that reducing PN dependence will lead to an improved HRQoL Parents are unpaid caregivers – this impacts on daily living, leisure activities, relationships, work and finances, as well as emotional, mental and social impacts are considerable. Psychosocial burdens on families of HPN-dependent patients include decreased social activities, disrupted family relationships and friendships, and depression. Financial constraints, including decreased employment and large out-of-pocket expenses and medications, and supplies. Home parental nutrition (HPN) technology and HPN-related complications and sequelae contribute to the rapid overall increase in the costs of healthcare systems. In some cases, if there is reduced reliance on families/carers, treatment will offer potential wider societal benefits, such as reducing patient/carer unemployment, and a potential reduced dependence on state benefits.	significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	Takeda	For patients with chronic short bowel syndrome and intestinal failure (SBS-IF) who are stable following a period of intestinal adaptation after surgery (i.e., the population of interest), parental support (PS) has been a life-long and	Thank you for your comment. The committee will consider

Section	Consultee/ Commentator	Comments [sic]	Action
		permanent restriction in most patients' lives, and offers no opportunity for restoration of the natural physiological function of the intestine. There are no pharmacological options for SBS-IF which address the underlying condition. Teduglutide is innovative as the first pharmacological treatment to have been approved that specifically improves the absorptive capacity of the remaining intestine in order to reduce dependence on PS. As discussed above in the 'Outcomes' section, improvement in PS requirements can be measured in terms of reductions in either the volume of PS received or the frequency of PS received, although for simplicity our economic model will focus on reductions in PS requirements in terms of frequency alone (number of days per week of PS). By focusing on the number of days per week of PS our QALY calculations will not account for the improvement in quality of life that some patients may achieve by reducing the volume of PS they receive each day (thereby reducing the amount of time per day spent connected to a machine), even if their number of days on PS does not change. There are indeed some patients who would prefer to spend fewer hours 'hooked up' to a machine each night than to receive a full day off PS entirely. The benefits of teduglutide to these patients will be underestimated by our model however we will present clinical trial data and real-world evidence within our dossier which will demonstrate the impact of teduglutide on PS volumes and we will estimate the impact of PS volume change on QALYs for the Committee to take account of these benefits. Another aspect to consider is that our model will generalise trial results from adults to children. In doing so our QALY calculations are likely to underestimate the health-related benefits of teduglutide experienced by paediatric patients. This is because, unlike adults, children may have continued intestinal growth with age and therefore have greater opportunity for continued adaptation and recovery. An important aspect in supporting and promoting adaptation in children is providing enteral nutrition (EN); when this is introduced soon after surgery, it has been shown to improve intestinal adaptation and reduce dependency on PS. Increasing the amount of EN that can be tolerated is consequently an important goal of	innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		therapy which teduglutide can support. We will present to the Committee short-term paediatric clinical trial data and evidence from clinical opinion to validate that our QALY calculations are likely to underestimate the benefit for children.	
Questions for consultation	NHS England Paediatric Medicine Clinical Reference Group	Real world data has emerged and shows that patients continue to benefit from treatment beyond 6 months from starting therapy with Teduglutide. Data shows that and there is an ability to target which patients who may benefit most from teduglutide. Weaning off PN in adults was more likely with the following factors - • Higher oral intake (p = 0.02). • Presence of colon (p = 0.04), • Lower PN volume (p = 0.03) Joly et al, *Clin Nutr. 2020 Sep;39(9):2856-2862* Real life data in children has been published to show that outcomes in children are more favourable than that seen in published clinical trials and no new safety concerns have been reported. *Boluda et al, Journal of Pediatric Gastroenterology and Nutrition: December 2020 - Volume 71 - Issue 6 - p 734-739*	Thank you, your comments have been noted
	Takeda	For patients with chronic short bowel syndrome and intestinal failure (SBS-IF) who are stable following a period of intestinal adaptation after surgery (i.e., the population of interest), parental support (PS) has been a life-long and permanent restriction in most patients' lives, and offers no opportunity for restoration of the natural physiological function of the intestine. There are no pharmacological options for SBS-IF which address the underlying condition. Teduglutide is innovative as the first pharmacological treatment to have been approved that specifically improves the absorptive capacity of the remaining intestine in order to reduce dependence on PS.As discussed above in the	Thank you, your comments have been noted

Section	Consultee/ Commentator	Comments [sic]	Action
		'Outcomes' section, improvement in PS requirements can be measured in terms of reductions in either the volume of PS received or the frequency of PS received, although for simplicity our economic model will focus on reductions in PS requirements in terms of frequency alone (number of days per week of PS). By focusing on the number of days per week of PS our QALY calculations will not account for the improvement in quality of life that some patients may achieve by reducing the volume of PS they receive each day (thereby reducing the amount of time per day spent connected to a machine), even if their number of days on PS does not change. There are indeed some patients who would prefer to spend fewer hours 'hooked up' to a machine each night than to receive a full day off PS entirely. The benefits of teduglutide to these patients will be underestimated by our model however we will present clinical trial data and real-world evidence within our dossier which will demonstrate the impact of teduglutide on PS volumes and we will estimate the impact of PS volume change on QALYs for the Committee to take account of these benefits. Another aspect to consider is that our model will generalise trial results from adults to children. In doing so our QALY calculations are likely to underestimate the health-related benefits of teduglutide experienced by paediatric patients. This is because, unlike adults, children may have continued intestinal growth with age and therefore have greater opportunity for continued adaptation and recovery. An important aspect in supporting and promoting adaptation in children is providing enteral nutrition (EN); when this is introduced soon after surgery, it has been shown to improve intestinal adaptation and reduce dependency on PS. Increasing the amount of EN that can be tolerated is consequently an important goal of therapy which teduglutide can support. We will present to the Committee short-term paediatric clinical trial data and evidence from clinical opinion to validate that our QALY calculations are likely to underestimate the benefit for children	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Takeda	Two related NICE documents have been reviewed and/or updated more recently than currently specified in the scope: - Clinical Guidelines No. 32, Feb 2006, 'Nutrition support in adults: Oral nutrition support, enteral tube feeding and parenteral nutrition' was reviewed in July 2017 and no new evidence was found that affected the recommendations in this guideline - The NICE Pathway for 'Nutritional support in adults' was most recently updated in August 2017.	Thank you, the scope has been revised to include the latest iterations of related NICE documents.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None