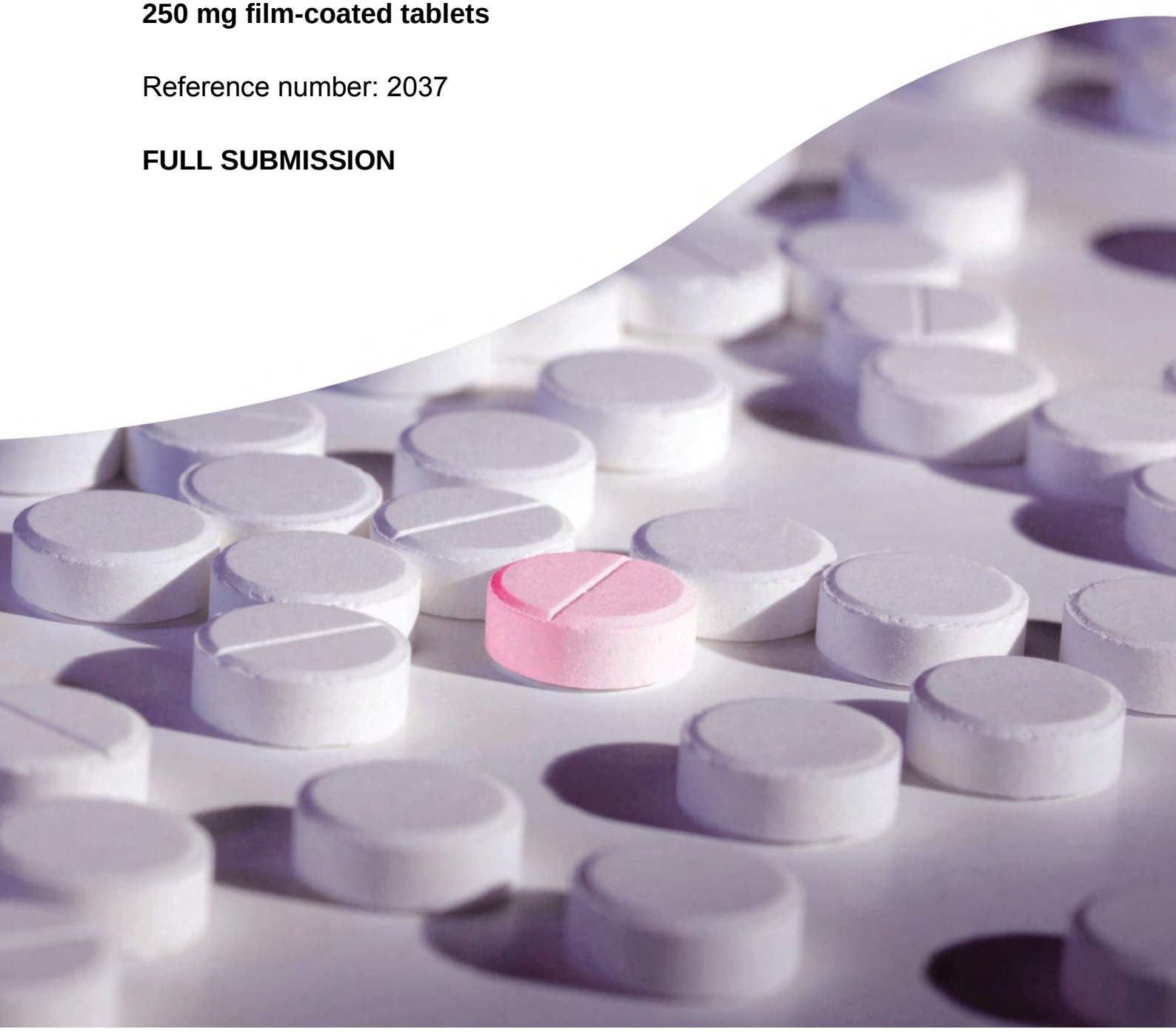
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Telotristat ethyl (Xermelo®)
250 mg film-coated tablets

Reference number: 2037

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

Please direct any queries to AWTTC:

All Wales Therapeutics & Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Telotristat ethyl (Xermelo®) 250 mg film-coated tablets. Reference number: 2037. June 2018.

AWMSG Secretariat Assessment Report
Telotristat ethyl (Xermelo®▼) 250 mg film-coated tablets

1.0 KEY FACTS

Assessment details	Telotristat ethyl (Xermelo®▼) for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy. The applicant company has submitted evidence for a subpopulation of the licensed indication and request that AWMSG consider telotristat ethyl for the treatment of carcinoid syndrome diarrhoea in patients who are inadequately controlled by SSA therapy and who experience an average of four or more bowel movements a day. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Current clinical practice	Long-acting SSAs, such as lanreotide Autogel® and octreotide LAR®, are the standard of care first-line treatment for controlling symptoms of carcinoid syndrome. Company-sought clinical expert opinion states that it is routine clinical practice to increase the dose of SSAs above that recommended, for people who need further symptom control despite using the maximum licensed dose. Telotristat ethyl is currently the only licensed medicine for the indication under consideration.
Clinical effectiveness	Data from one pivotal phase III study shows a treatment benefit for telotristat ethyl in combination with SSA therapy compared to placebo in terms of a significant reduction in bowel movement frequency, which was sustained with long-term treatment. The number of patients enrolled in the study is small, reflecting the low incidence and prevalence of the disease.
Cost-effectiveness	The company submission includes a cost-utility analysis of telotristat ethyl compared to SSA monotherapy for the treatment of carcinoid syndrome diarrhoea in patients who are inadequately controlled by SSA therapy and who experience an average of four or more bowel movements a day. Results of the base case analysis show that, when compared with SSA monotherapy, telotristat ethyl in combination with SSAs dominates SSA monotherapy with an increase of 0.0149 quality-adjusted life years (QALYs) and cost savings of [commercial in confidence figure removed] over a 30-year time horizon. Telotristat ethyl remains dominant in most scenario analyses. Probabilistic sensitivity analyses showed that telotristat ethyl plus SSA has a 76.2% and 78.2% chance of being the most cost-effective treatment at willingness-to-pay

	thresholds of £20,000 and £30,000 per QALY gained, respectively with 71% of simulations resulting in telotristat ethyl being the dominant treatment (more effective and less costly).
Budget impact	Incidence and prevalence of carcinoid syndrome associated with small intestinal neuroendocrine tumours who require further symptom control despite SSA use in Wales were estimated to be 2 new patients per year and 14 patients, respectively. All of these patients are eligible for treatment with telotristat ethyl and estimated uptake rate is assumed to be 10% in Year 1, increasing linearly to 50% in Year 5 at an annual cost per patient [commercial in confidence figure removed]. The introduction of telotristat ethyl is estimated to cost [commercial in confidence figure removed] in medicine acquisition costs in Year 1, increasing to [commercial in confidence figure removed] in Year 5.
Additional factors to consider	The company suggests that telotristat ethyl meets AWMSG's criteria for consideration as an ultra-orphan medicine.

This assessment report is based on evidence submitted by Ipsen Ltd and an evidence search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) on 26 March 2018.

2.0 BACKGROUND

2.1 Condition and clinical practice

People with advanced neuroendocrine tumours (NETs) may develop carcinoid syndrome, a condition where the tumour produces large amounts of serotonin and secretes it into the systemic circulation[1]. The excess serotonin can cause severe diarrhoea as well as flushing, wheezing, abdominal pain and valvular heart disease[1].

Treatment of carcinoid syndrome involves treating the tumour to delay the time to progression, as well as using medicines to control the symptoms of the disease[2,3]. Long-acting somatostatin analogues (SSAs), such as lanreotide Autogel® and octreotide LAR®, are the standard of care first-line treatment for controlling the symptoms and are also used to control the tumour[2,3]. Based on clinical expert opinion sought by the applicant company, it is routine clinical practice to increase the dose of SSAs above that recommended for people who need further symptom control[2].

2.2 Medicine

Telotristat ethyl is a tryptophan hydroxylase inhibitor that targets the rate-limiting step in the production of serotonin. The recommended dose is one 250 mg tablet three times a day[4].

The applicant company has submitted evidence for the use of telotristat ethyl for symptom control in a subpopulation of the licensed indication: in patients who are inadequately controlled by SSA therapy and whom experience an average of four or more bowel movements a day[2]. Telotristat ethyl (Xermelo®) is currently the only licensed (September 2017[5]) medicine for the treatment of carcinoid syndrome diarrhoea in combination with SSA therapy in adults inadequately controlled by SSA therapy[4].

2.3 Comparators

The company submission includes telotristat ethyl in combination with SSA therapy compared to SSA monotherapy[2]. The SSAs are lanreotide Autogel® and octreotide LAR®. The comparator is therefore best supportive care.

2.4 Guidance and related advice

- Pavel M, Valle JW, Eriksson B, et al. (2017). European Neuroendocrine Tumour Society (ENETS) consensus guidelines for the standards of care in neuroendocrine neoplasms: systemic therapy - biotherapy and novel targeted agents[6].
- Pavel M, O'Toole D, Costa F, et al. (2016). ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms and neuroendocrine neoplasms of unknown primary site[7].
- Ramage JK, Ahmed A, Ardill J, et al. (2012). UK and Ireland Neuroendocrine Tumour Society guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours[3].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, telotristat ethyl (Xermelo®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that telotristat ethyl (Xermelo®) may be supplied by a home healthcare provider[2].

3.0 CLINICAL EFFECTIVENESS

The company's submission includes evidence from one pivotal phase III study (LX301: TELESTAR) comparing telotristat ethyl with placebo, in combination with SSA therapy[2,8]. The study includes two treatment arms; patients received either telotristat ethyl 250 mg or 500 mg tablets. The 500 mg dose does not form part of the licensed indication for telotristat ethyl so these results are not reported. The company also provides results from a supportive phase III study (LX303: TELECAST)[9] and two phase II studies (LX202[10] and LX203[11]). These studies are not discussed further since patients in the study LX303 were excluded if they were experiencing ≥ 4 bowel movements per day while on concomitant SSA therapy, and studies LX202 and LX203 were dose-escalating studies. All patients completing the open-label extension periods of all four studies were eligible to enter a phase II open-label extension study (LX302)[2], which is mentioned briefly under section 3.2.

3.1 TELESTAR

The study design included comparing the efficacy of 250 mg telotristat ethyl with placebo over a 12-week double-blind treatment period, in patients not adequately controlled by current SSA therapy[2,8]. Patients were eligible if they had at least four bowel movements per day while on stable doses of SSA treatment[2,8], which they had been receiving for at least three months before entering the study[2,8]. During the study, patients were allowed to use rescue medication (short-acting SSA therapy) and anti-diarrhoeals for symptomatic relief[2,4]. Treatment with any tumour-directed therapy during the treatment period was not permitted[2,8].

Patients were randomly assigned 1:1 to receive oral doses three times a day. The primary endpoint was the change from baseline in the number of bowel movements per day, averaged over the 12-week period. Durable responders were pre-specified as patients who experienced a ≥ 30% reduction in bowel movement frequency (relative to

baseline) for ≥ 50% of the treatment period. Secondary endpoints included urinary 5-hydroxyindoleacetic acid (5-HIAA) levels at week 12, the number of cutaneous flushing episodes and the incidence of abdominal pain, as well as urgency to defecate, nausea and stool consistency. Subjective measures of symptom relief and disease specific patient-reported outcomes were also included. At the end of the 12-weeks, patients could participate in a 36-week extension period to assess long-term efficacy and safety. At this stage, all patients were offered treatment with telotristat ethyl 500 mg three times daily; downward dose adjustment was allowed in cases of intolerability[2,8].

Results for the bowel movement frequency and durable responder analysis are shown in Table 1. Treatment with telotristat ethyl significantly reduced the bowel movement frequency over 12 weeks compared with placebo ($p < 0.001$)[2,8]. In the durable responder analysis, 44% of patients who received telotristat ethyl had a durable response to treatment compared with 20% of patients who received placebo. The odds of patients having a durable response were significantly greater for telotristat ethyl ($p = 0.011$), relative to placebo[2,8].

Table 1. Bowel movement frequency and durable response

	Placebo (n = 45)		Telotristat ethyl (n = 45)		
Bowel movement frequency					
Daily change averaged over 12 weeks, mean (SD)	−0.62 (0.83)		−1.43 (1.36)		
Arithmetic mean treatment difference			−0.81		
H-L estimator of treatment difference (p-value)			−0.81 (< 0.001)		
Arithmetic mean bowel movement change for patients with baseline and week 12 data					
N	35		36		
Arithmetic mean treatment difference	−0.9		−1.7		
Durable responder analysis[a]					
	N (%)	**Mean (SD)**	**N (%)**	**Mean (SD)**	**p-value (OR) 95% CL**
Durable responders	9 (20)		20 (44)		0.011 (3.49) 1.33, 9.16
Change from Baseline in bowel movement frequency at Week 12					
Bowel movement responders[b]	9	−1.9 (0.8)	16	−2.6 (1.6)	
Bowel movement non-responders	26	−0.5 (1.1)	20	−1.0 (1.5)	

[a] Patients with a durable response were the responders with ≥ 30% reduction in bowel movement frequency for ≥ 50% of the time over the double-blind treatment period
[b] Only includes patients for whom both baseline and week 12 assessments were available
CL: confidence limit; H-L: Hodges-Lehmann; N: total number of patients; OR: odds ratio; SD: standard deviation

Findings from secondary endpoints conformed to those for the primary efficacy endpoints. Patients receiving telotristat ethyl had significantly reduced urinary 5-HIAA concentrations compared to those receiving placebo. In addition, those patients who experienced reductions in bowel movement frequency generally reported improvements in stool consistency and less urgency to defecate. No differences in the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 global health scores were observed[8]. There was however, an improvement in the diarrhoea symptom score[8].

Durable responders experienced greater improvements in daily bowel movement frequency, secondary endpoints and quality of life measures, than non-durable responders[2,8]. Interim analysis shows reduction in bowel movement frequency and urinary 5-HIAA were also sustained with long-term treatment up to 35 weeks[2,8].

3.2 Open-label extension study (LX302)

Patients who entered into the phase III studies (TELESTAR and TELECAST) and phase II studies (LX202[10] and LX203[11]) were eligible to enter an open-label 84-week extension phase III study (LX302)[2]. All patients received telotristat ethyl at the dose level identified in the original study. Since only ten patients have received 250 mg telotristat ethyl, the small sample size, lack of control group, and limited duration of treatment, for patients enrolled to date, precludes firm efficacy conclusions in this ongoing study in which safety is the primary objective[2].

3.3 Comparative safety

The safety of telotristat ethyl is based on a pooled safety analysis of 239 patients with carcinoid syndrome, 58 patients with ulcerative colitis, and 259 patients receiving the compound in early drug development[1]. In total, 170 patients with carcinoid syndrome have been exposed for at least 24 weeks, and 111 have been exposed for at least 48 weeks. Results showed a relatively benign adverse event profile which is mainly restricted to symptoms of the gastrointestinal tract, such as nausea, abdominal pain, constipation, abdominal distension and flatulence. These events were mostly mild to moderate in intensity. No serious adverse events were identified[1]. Safety concerns highlighted at licensing were the identified risks of constipation and raised liver enzyme; also the potential risk of depression and related conditions[1].

3.4 AWTTC critique

- Post hoc analysis of the data from TELESTAR revealed that above-licence SSA doses was reported for 42% of patients in the telotristat ethyl treatment group and 40% of patients in the placebo group[12].
- The number of patients enrolled in the TELESTAR study is small, reflecting the low incidence and prevalence of the disease. The inclusion of a 500 mg treatment arm that does not form part of the telotristat licence, reduces the available patient numbers. Also, the number of patients included in the safety analysis is considered by the European Medicines Agency to be too small to detect rate events or make any definitive conclusions[1].
- Subgroup analyses from the TELESTAR study suggest that the efficacy of telotristat ethyl in reduction of bowel movement frequency is not affected by the concomitant long-acting SSA dose or use of anti-diarrheal medications, narcotic analgesics, or short-acting rescue SSAs[12]. This is consistent with the different mechanism of action of telotristat ethyl, which relates directly to the pathophysiology of carcinoid syndrome. Reductions in urinary 5-HIAA with telotristat ethyl were seen regardless of concomitant long-acting SSA dose[12].
- In the TELESTAR study, the placebo group showed a reduction in bowel movement frequency. The company suggests that this reduction may be partially accounted for as more patients in the placebo group were using short-acting SSA rescue therapy[2,8]. Also, variability in the absorption of long-acting SSAs, differences in use of other anti-diarrheal medications and dietary changes were proposed to have contributed to the observed response[2,8].
- The safety database was considered limited by the Committee for Medicinal Products for Human Use (due to the low prevalence and incidence of the disease), and therefore too small for any definitive conclusions to be made[1]. However, it was accepted that data shows a relatively benign overall adverse event/adverse drug reaction profile. It is noted that the collection of long-term safety data is ongoing[1].
- Minimal changes in overall EORTC QLQ-C30 global health scores have been observed in previous studies in patients with NETs who received SSAs. It has been suggested that this domain may not be particularly sensitive in this patient population[8].

- The Summary of Product Characteristics states that available data suggest that a clinical response is usually seen within 12 weeks of treatment with telotristat ethyl[4]. If there is no response within this time period the benefit of continued therapy should be reassessed[4].

4.0 COST-EFFECTIVENESS

4.1 Context

The company submission includes a cost-utility analysis of telotristat ethyl 250 mg oral film-coated tablets in combination with SSA therapy (all SSA doses) compared to SSA monotherapy (all doses) for the treatment of carcinoid syndrome diarrhoea in patients who are inadequately controlled by SSA therapy and who experience an average of four or more bowel movements a day[2].

The cost-utility analysis takes the form of a 12-week decision tree followed by a Markov model, comprising of 1-week cycles over a lifetime horizon of 30 years. Costs and outcomes are discounted at an annual rate of 3.5% and the model adopts an NHS and Personal and Social Services perspective. The company's submission incorporates a simple Wales Patient Access Scheme (WPAS) discount for telotristat ethyl.

Patients enter the model at a mean age of 63.5 years, firstly in the decision tree where they either receive telotristat ethyl plus SSA or SSA monotherapy. After 12 weeks, patient durable response to treatment (defined as a ≥ 30% reduction in bowel movement frequency relative to baseline for ≥ 50% of the 12-week period based on the TELESTAR study[13]) is assessed. All patients who meet the response criteria at 12 weeks then enter the Markov model in the "remain on treatment" health state and continue treatment with either telotristat ethyl plus SSA or SSA monotherapy while they remain responders. Patients who do not show a durable response at week 12 start the Markov model in the "discontinue treatment" health state and will receive SSA monotherapy until death in addition to a weighted average subsequent treatment (including peptide receptor radionuclide therapy, debulking surgery and transarterial embolisation). Response is assessed after every week with a probability of discontinuing treatment due to loss of response or through withdrawal due to adverse events as well as death.

Patient baseline characteristics and probability of initial response were taken from the TELESTAR study[13] with the time to initial response set to six weeks. The long-term discontinuation probability for telotristat ethyl is based on data for telotristat ethyl 500 mg from the open-label extension of the TELESTAR trial while for SSA monotherapy is based on the initial 12-week study data. After treatment discontinuation due to loss of response or non-response, time to response to subsequent treatment was estimated by a company-sought Welsh clinical expert[14]. The model assumes that no treatment-related serious adverse events are associated with telotristat ethyl plus SSA or SSA monotherapy. Serious adverse events for subsequent therapies were included (with annual incidence of > 5% including infection, liver abscess, bone marrow suppression, vomiting, compensated cirrhosis) and were taken from published literature[15-17]. The probability of dying from carcinoid syndrome and NET (based on data from midgut NETs which accounted for 81.5% of all NETs in the TELESTAR study) was based on survival data from a study of lanreotide versus placebo in patients with NETs fitted using a Weibull distribution and assumed to be equal for telotristat ethyl and all SSAs[18]. Treatment-related mortality and all-cause mortality were considered in the model if NETs-associated mortality was lower than that of the general population. Assumptions and generalisability of the study results to the Welsh population were verified by a company-sought Welsh clinical expert[14].

Costs considered in the model comprised of treatment cost associated with telotristat ethyl plus SSA, SSA monotherapy and subsequent therapies (including administration), cost of monitoring all treatments and cost of subsequent treatment-related adverse events. Treatment dosing information was taken from the TELESTAR trial and costed using the Monthly Index of Medical Specialities[19]. Subsequent treatments were costed using published unit costs[20], literature[21] and company-sought clinical expert opinion[14]. Treatment administration was costed as 20 minutes of nurse time for all intragluteal injections and 70% of subcutaneous injections while telotristat ethyl and 30% of subcutaneous injections were considered self-administered with no additional costs. Consultant-led monitoring was assumed every six months for responders (until non-response) and every four weeks for non-responders (until response) with different follow-up and imaging schedules applied for debulking surgery, peptide receptor radionuclide therapy and transarterial embolisation based on company-sought clinical expert opinion[14] and published unit costs[20]. Costs of adverse events associated with subsequent therapies were taken from published literature[22-24] and unit costs[20]. Utility values were set to 0.771 for responders and 0.600 for non-responders based on values reported in the literature[25]. Disutilities associated with adverse events were obtained from published data[23-27].

Extensive one-way deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results. A range of scenario analyses investigated the impact of different survival estimates (including different parametric functions and alternative hazard ratio data), changes in dosages, monitoring schedules, response time, discontinuation rates and utility estimates on the model results. The company also supplied a scenario analysis comparing patients receiving the licensed dose of SSA in combination with telotristat ethyl versus licensed dose of SSA alone.

4.2 Results

The results of the base case analysis are detailed in Table 2. When compared with SSA monotherapy, telotristat ethyl in combination with SSAs is associated with an increase of 0.0149 quality-adjusted life year (QALY) and cost savings of [commercial in confidence figure removed]. In the base case, telotristat ethyl is therefore considered to dominate SSA monotherapy.

Table 2. Results of the base case analysis

	Telotristat ethyl plus SSA	SSA monotherapy	Difference
Total cost per patient	¶¶	£199,703	¶¶
Treatment acquisition costs	¶¶	£191,795	¶¶
Administration costs	£1,366	£1,366	£0
Monitoring costs	£5,587	£6,169	−£582
Adverse events costs	£321	£372	−£51
Total life-years	8.7702	8.7702	0.0000
Total QALYs per patient	5.6284	5.6135	0.0149
ICER (£/QALY gained)	¶¶		

¶¶ Commercial in confidence figure or text removed
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SSA: somatostatin analogue

One-way sensitivity analysis showed that results were sensitive to the parametric function fitted to survival data, subsequent therapy costs, discount rate, response rates and discontinuation rates. However, telotristat ethyl remained cost-effective within the upper and lower bounds of the top 10 most sensitive variables. Probabilistic sensitivity analyses showed that telotristat ethyl plus SSA has a 76.2% and 78.2% chance of being the most cost-effective treatment at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, respectively with 71% of simulations resulting in telotristat ethyl being the dominant treatment (more effective and less costly). Table 3 summarises the results of the scenario analyses.

Table 3. Results of scenario analyses

Scenarios	ICER	Plausibility
Scenario 1: Response based on the subgroup of patients receiving licensed dose of SSA (± telotristat ethyl)	¶¶ Incremental QALYs: 0.0158 ¶¶	This scenario offers an alternative to the base case, but does not reflect clinical practice where SSAs are used in higher off-label doses
Scenario 2: Use discontinuation data for telotristat ethyl plus SSA from the double-blind period of TELESTAR	¶¶	This scenario provides a plausible alternative to the base case. However, the long-term extrapolation of 12-week study data will introduce bias.
Scenario 3: OS using Gompertz curve	¶¶	This scenario provides a plausible alternative to the base case, given that this distribution offers a similar fit for the long term data.
Scenario 4: OS using log-logistic curve	¶¶	This scenario provides a plausible alternative to the base case, given that this distribution offers a similar fit for the long term data.
Scenario 5: OS using log-normal curve	¶¶	This scenario provides a plausible alternative to the base case, given that this distribution offers a similar fit for the long term data.
Scenario 6: OS using generalised gamma curve	¶¶	This scenario provides a plausible alternative to the base case. However, curve fit was worse compared to other parametric functions.
Scenario 7: Using actual dose of SSA observed in TELESTAR	¶¶	This scenario is plausible as it is a feasible alternative to the base case which uses a weighted average dose.
Scenario 8: Assuming 50:50 for octreotide and lanreotide	¶¶	The plausibility of this scenario is uncertain as it is an assumption while the base case was based on data from the TELESTAR trial. However, the 50:50 split was suggested by the Welsh clinical expert.
Scenario 9: Assuming consultant-led visit every 6 months after PRRT	¶¶	Plausibility of this scenario is uncertain as it is based on an assumption.
Scenario 10: OS using HR from Rinke et al (2017)[28]	¶¶	This scenario lacks plausibility as the trial was small with a confounding cross-over effect which might have biased results.
Scenario 11: OS using HR from Shen et al (2014) – distant[29]	¶¶	This scenario is less plausible than the base case as data were obtained retrospectively from a US data registry which might introduce bias.
Scenario 12: OS using HR from Shen et al (2014) – local[29]	¶¶	This scenario is less plausible than the base case as data was obtained retrospectively from a US data registry which might introduce bias.
Scenario 13: OS using HR from Halperin et al (2017)[30]	¶¶	This scenario is less plausible than the base case as this study, while large, did not look at the effect of SSA on OS.
Scenario 14: OS using exponential curve	¶¶	This scenario is less plausible as curve fit was worst amongst the parametric functions tested.
Scenario 15: Assuming time to response on telotristat ethyl plus SSA and SSA monotherapy to be 0 days	¶¶	This scenario is less plausible as an immediate effect is unlikely.
Scenario 16: Assuming time to response on telotristat ethyl plus SSA and SSA monotherapy to be 12 weeks	¶¶	This scenario is less plausible as a delayed effect is unlikely.
Scenario 17: Assuming market share of PRRT to be 100%	¶¶	This scenario is less plausible as complete dominance of one subsequent therapy is unlikely.
Scenario 18: Assuming the identical utility for responders and non-responders	¶¶	This scenario is less plausible as responders can be expected to experience an effect on quality of life through better symptom management.

¶¶ Commercial in confidence figure or text removed
HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PRRT: peptide receptor radionuclide therapy; QALYs: quality-adjusted life years; SSA: somatostatin analogue

Telotristat ethyl remains dominant in most scenario analyses. The only scenario where telotristat ethyl was not cost-effective with an incremental cost-effectiveness ratio (ICER) of [commercial in confidence figure removed] is based on the exponential function fitted to survival data which showed worst fit overall and resulted in an increase in survival that led to higher overall telotristat ethyl costs for ongoing treatment.

4.3 AWTTC critique

The results of the base case cost-utility analysis indicate that the use of telotristat ethyl in combination with SSA produces a small but positive QALY benefit compared to SSA monotherapy in adult patients with carcinoid syndrome diarrhoea associated with metastatic NETs who experience an average of four or more bowel movements a day despite SSA monotherapy. Despite the higher treatment cost associated with telotristat ethyl, the long-term model estimates the intervention to be cost saving, primarily driven by savings in monitoring costs associated with subsequent therapies. The broad range of sensitivity analyses findings corroborate the base case.

The submission is characterised by both strengths and limitations. Reasonable justifications are provided for the assumptions applied to the model.

Strengths of the economic analysis:

- The submission gives a detailed, transparent account of the methods and data sources with a well-structured and robust model underpinning the analysis.
- In the absence of other licensed treatments in Wales for the patient population, best supportive care appears to be the appropriate comparator for the cost-utility analysis for this patient group.
- A range of sensitivity analyses are reported that enable assessment of uncertainty surrounding the parameter and structural uncertainty.

Limitations of the economic analysis:

- A limitation of the analysis is the lack of available utility data as the TELESTAR trial did not collect QALY data and mapping of the EORTC QLQ-C30 responses would have introduced too much bias. For this reason, utility values for NETs from published literature were used[25]. However, these reflect patient utilities of stable disease without adverse events and stable disease with adverse events (including diarrhoea) in a different patient population rather than utilities of responders versus non-responders which might not accurately reflect the number of QALYs generated in either treatment arm. Furthermore, the utility differences between responders and non-responders used in the model (0.171) are higher than those calculated from mapping of EORTC QLQ-C30 questionnaire (0.08). As the number of QALYs generated in the model is driven by this difference and overall QALY gains over the 30-year time horizon are small (between 0.005 and 0.029), any bias or uncertainty in the utility estimates could have a large effect of the cost-effectiveness estimates. This is also demonstrated in the probabilistic sensitivity analysis which confirms that the ICER is highly unstable (76.2% probability of cost-effectiveness at £20,000 threshold despite dominating in the base case). While telotristat ethyl plus SSA still dominates SSA monotherapy when identical utilities are assumed for both responders and non-responders in scenario analysis, care should still be taken in drawing inferences from the ICER results.
- Similarly, disutilities for adverse events were obtained from various publications including breast cancer treatment and tuberculosis infection[26,27] and might not accurately reflect QALYs in people with carcinoid syndrome diarrhoea. However, the company states that the impact of disutilities due to adverse events on results was minor in the one-way sensitivity analysis.

- Long-term overall survival data for midgut NETs in the model was taken from an open-label extension study comparing lanreotide 120 mg to placebo[31]. This study included 88 participants of which 39% had NETs of the midgut whereas 38% were pancreatic NETs and 23% of unknown site. The small sample size and open-label nature of the alternate data source that was directly applied to telotristat ethyl will introduce bias and uncertainty and the appropriateness of the survival data used in the model is questionable.
- The analysis is limited by the lack of available data which required the model to rely on many simplifications and assumptions (such as for subsequent treatments and monitoring costs). These assumptions, as well as verification of data inputs and estimates used in the model were made by one company-sought Welsh clinical expert only. While the validation questionnaire and advisory board meeting notes appear thorough, the lack of a more varied clinical input might affect generalisability and introduce bias.
- The decision whether to remain on treatment or discontinue in the model is based solely on bowel movements (i.e. diarrhoea). The company states that the measure is likely to act as a proxy for other key elements of carcinoid syndrome because patients with durable response were also found to have a statistically significant improvement in their flushing, urinary 5-HIAA levels and abdominal pain[32]. However, this assumption is based on data on file which was not available for review and might underestimate the effects of treatment on patient quality of life.
- The long-term probability of discontinuation and adverse events modelled for telotristat ethyl plus SSA is based on the discontinuation rates observed in the open-label phase of the TELESTAR study during which all patients received telotristat ethyl at a dose of 500 mg. The company states that, during the double-blind period of the TELESTAR study, the proportion of subjects with response at Week 12 was similar for the telotristat 250 mg (44.4%) and telotristat 500 mg arms (42.2%). However, this could result in bias if efficacy and adverse event profile of telotristat ethyl differs for different dosages in the long-term.
- Data on the discontinuation probability of telotristat ethyl is based on the 36-weeks open-label extension of the TELESTAR study while long-term discontinuation rates for SSA monotherapy are taken from the 12-week double-blind phase of the trial. No data beyond these periods are available to support the assumption of long-term sustained effect. Any decrease in efficacy will change the results of the model.
- The model assumes that all patients who discontinue initial telotristat ethyl or SSA monotherapy treatment become responders in the “discontinue treatment” health state once they receive subsequent therapies following an initial period of non-response. The company states that in clinical practice patients will continue to receive alternative therapies until an adequate response to their condition is achieved. However, little evidence on the effectiveness of alternative treatment strategies is available and a greater number of patients receiving SSA monotherapy are non-responders compared to those receiving telotristat ethyl plus SSA. As non-responding patients will move more quickly to a therapy that is assumed to result in complete response, the model will overestimate the efficacy of these subsequent therapies and the QALY gain for the comparator arm (since it is assumed that the patient will respond to the first of the subsequent therapies and respond until death) and underestimate costs (as only the cost of the first subsequent treatment is taken into account).
- The model assumes that no serious adverse events are associated with telotristat ethyl and SSA treatments. However, in the TELESTAR study, one patient in the SSA monotherapy arm experienced a treatment-related serious adverse event (vomiting and nausea) and exclusion of treatment-related

adverse events might slightly overestimate QALYs and underestimate costs. However, the impact on model results is likely to be small and would favour the comparator arm.

- Some serious adverse events associated with subsequent treatment options which were identified by the company-sought clinical expert as important (e.g. postembolisation syndrome, renal toxicity) are not included in the model due to lack of data which might cause bias.

4.4 Review of published evidence on cost-effectiveness

A literature search by AWTTC identified one study relevant to the cost-effectiveness of telotristat ethyl and SSA compared to SSA monotherapy, for symptom control in adult patients with carcinoid syndrome diarrhoea associated with metastatic NETs who experience an average of four or more bowel movements a day, despite receiving SSA therapy. This US cost-utility analysis[33] used efficacy data from the TELESTAR study and utility data for ulcerative colitis which resulted in 0.66 incremental QALYs at an incremental cost of $94,962 and an ICER of $142,545 per QALY gained. This result differs significantly from the one presented in this submission due to differences in the model inputs, use of US medical insurance claim data to cost healthcare resource use and a [commercial in confidence text removed].

5.0 BUDGET IMPACT

5.1 Context and methods

No specific incidence or prevalence data for carcinoid syndrome in Wales are available. Incidence estimates were based on the incidence of patients with lower gastro-intestinal NETs[34] of 2.78 in 100,000 population in England assuming similar epidemiological data for England and Wales[14]. Three quarters (75%) of these were well-differentiated NETs, resulting in 64.87 lower gastro-intestinal well-differentiated NETs diagnosed per year in Wales. Of these, 58% were assumed to be small intestinal NETs[35] of which 40% would be expected to have carcinoid syndrome with 80% experiencing diarrhoea as part of their carcinoid syndrome symptoms[9]. Approximately 17.5% of patients suffer from highly functional carcinoid syndrome (more than four daily bowel movements) and diarrhoea requiring further control despite SSA therapy[9], equating to a total of 2.11 new patients per year with carcinoid syndrome associated with small intestinal NETs and in whom further symptom control despite SSA use diagnosed in Wales. Prevalence was based on a large, retrospective US study[36] which suggests a 6.67-fold higher prevalence of NETs compared to incidence. This results in a prevalence estimate of 0.45 per 100,000 population and 0.02 per 100,000 population for patients with carcinoid syndrome associated with small intestinal NETs and lung NETs, respectively. Based on the latest population estimate for Wales[37], this equates to a total prevalent population for patients with carcinoid syndrome associated with small intestinal NETs and lung NETs who require further symptom control despite SSA of 14.69. Mortality and discontinuation due to lack of response and efficacy or adverse events is taken into account based on data from the TELESTAR[13] and CLARINET studies.

All of these patients are eligible for treatment with telotristat ethyl and estimated uptake rate is assumed to be 10% in Year 1, increasing linearly to 50% in Year 5[14]. The annual costs of telotristat ethyl 250 mg taken orally three times a day [commercial in confidence figure removed]. The analysis also considers the cost of subsequent therapies but does not include cost of SSA as this was assumed equal for both arms.

5.2 Results

The estimated net budget impact is shown in Table 4. The introduction of telotristat ethyl is estimated to cost [commercial in confidence figure removed] in medicine acquisition costs in Year 1, increasing to [commercial in confidence figure removed] in Year 5 with an overall 5-year budget impact of [commercial in confidence figure removed].

Table 4. Company-reported costs associated with the use of telotristat ethyl

	2018	2019	2020	2021	2022
Number of eligible patients (all licensed indications)	17	19	22	26	30
Sub-population of eligible patients (indication under consideration)	17	19	22	26	30
Uptake of new medicine (%)	10%	20%	30%	40%	50%
Number of patients receiving new medicine allowing for discontinuations*	2	4	7	10	15
Medicine acquisition costs in a market without new medicine	£0	£0	£0	£0	£0
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶

* The impact of mortality and discontinuation is accounted for in the cost calculations, and is therefore not considered in the estimated number of patients to avoid double counting
¶¶ Commercial in confidence figure removed
All costs based on 2017 prices.

If downstream healthcare resource use is considered, the company reports that the introduction of telotristat ethyl has potential to save [commercial in confidence figure removed] in Year 1 (including subsequent therapies for telotristat ethyl plus SSA and SSA monotherapy), cost [commercial in confidence figure removed] in Year 2 and produce cost savings from Year 3 onwards. The full 5-year budget impact including downstream healthcare resource use is estimated to be a cost saving of [commercial in confidence figure removed].

A scenario analysis calculates the cumulative 5-year budget impact of telotristat ethyl including subsequent therapies and downstream healthcare resource use to be [commercial in confidence figure removed] if it is based on the subgroup of the TELESTAR study that only received licensed doses of SSA in combination with telotristat ethyl.

5.3 AWTTC critique

- The budget impact calculations and attached workings were of a high standard and offered a transparent and realistic estimate of costs.
- The analysis is limited by the lack of available prevalence and incidence data. While the company's approach appears valid and uses the best available data, the generalisability issues cannot be excluded and the assumptions made will introduce bias. Furthermore, the company suggests that more recent incidence and prevalence figures (which were used for the orphan section but not the budget impact model submitted to AWTTC) suggest a slightly lower number of eligible patients which might overestimate the budget impact.
- Costs of SSA treatment are excluded from the analysis as the company argues that they are equal for telotristat ethyl plus SSA and SSA monotherapy. Furthermore, efficacy, response rates and discontinuation are based on data from patients who received any dose of SSA in combination with telotristat ethyl. While this might be true for the TELESTAR study[13], it is inconsistent with

the licence indication in question and the more appropriate comparators would have been telotristat ethyl plus within-licence SSA and SSA monotherapy (at all dosages, including above licence). While this omission will introduce bias, it is likely to result in a conservative estimate as SSA costs would increase, resulting in more cost savings achieved with the new treatment as shown in the scenario analysis provided by the company.

- Uptake rates are estimates and any changes to the uptake rate will affect the budget impact of telotristat ethyl.

5.4 Comparative unit costs

Acquisition costs for telotristat ethyl and SSAs for adult patients with carcinoid syndrome diarrhoea are given in Table 5.

Table 5. Examples of medicine acquisition costs

Regimens	Unit cost	Example doses	Approximate costs per patient per year
Telotristat ethyl (Xermelo®) 250 mg	£1,120.00 for 90 tablets (30 day supply) ¶¶	One tablet three times daily with food in addition to SSA. Reassess after 12 weeks.	£13,636 per year (in addition to SSA) ¶¶
Octreotide (Sandostatin® LAR®) 30 mg	£998.41 per 30 mg	One intragluteal injection of 30 mg every 4 weeks (maximum licensed use) One intragluteal injection of 30 mg every 3 weeks (above licence) One intragluteal injection of 40 mg every 3 weeks (above licence)	£12,979 per year £17,306 per year £26,834 per year
Lanreotide (Somatuline® Autogel®) 120 mg	£937.00 per 120 mg	One subcutaneous injection every 4 weeks (maximum licensed use) One subcutaneous injection every 3 weeks (above-licence used)	£12,181 per year £16,297 per year

¶¶ Commercial in confidence figure and text removed
See relevant Summaries of Product Characteristics for full licensed indications and dosing details[4,38-40].
Costs are based on the Monthly Index of Medical Specialities list prices as of 26 March 2018[19], assuming vial wastage.
Costs of administration are not included.
SSA: somatostatin analogue; WPAS: Wales Patient Access Scheme

6.0 ADDITIONAL FACTORS TO CONSIDER

6.1 AWMSG's policy for orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The applicant company suggests that telotristat ethyl in the given population meets the All Wales Medicines Strategy Group (AWMSG) criteria for an ultra-orphan medicine. AWMSG defines an ultra-orphan medicine as a medicine that has been granted European Medicines Agency designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[41].

Telotristat ethyl is designated an orphan medicine by the European Medicines Agency for the treatment of carcinoid syndrome. The European Medicines Agency states that carcinoid syndrome affects 0.7 in 10,000 people in the European Union which is below the orphan designation ceiling of 5 in 10,000 population.

The company states that the incidence and prevalence of carcinoid syndrome in Wales has not been documented. However, extrapolating NET figures reported in England[34] to the Welsh population[37] results in an incidence of two new patients per year and a prevalence of nine patients (with an estimated maximum number of 14 small intestinal NETs and 2 lung NETs requiring additional symptom control). This extrapolation assumes that 14.1% of NETS are small intestinal NETs and 19.5% are lung NETs, and that 40% of patients with well-differentiated small intestinal NETs would be likely to experience carcinoid syndrome: 80% of which had carcinoid syndrome diarrhoea. Of these 80% of patients with carcinoid syndrome diarrhoea, 35% would have highly functioning carcinoid syndrome (≥ 4 daily bowel movements)[9] and need further control of carcinoid syndrome despite use of SSAs.

The criteria for assessing clinical effectiveness and cost-effectiveness of ultra-orphan medicines are the same as those applied to other medicines, but recognising that the evidence base may be weaker. The New Medicines Group (NMG)/AWMSG will consider evidence on the following to inform their decisions (see Table 6).

Table 6. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	Symptoms of carcinoid syndrome include diarrhoea, flushing and fatigue. Small intestinal neuroendocrine tumours grow slowly with a median survival of approximately five years even when diagnosed in advanced stages[36]. Thus patients live with decreased QoL and impaired physical, emotional and social functioning[42] for many years and effective symptom control is an important clinical management focus. Patients with unmanaged carcinoid syndrome may experience frequent diarrhoea, urgency, incontinence and night-time episodes[9]. The most important carcinoid syndrome symptoms to treat are diarrhoea, too frequent bowel movements and urgent bowel movements, with 83% of patients reporting bowel movement frequency was more important to treat than stool consistency[43]. According to a recent survey, approximately 25% of patients experience on average 4 to 6 bowel movements a day with approximately 10% of patients having seven or more bowel movements per day. A higher frequency of bowel movements is associated with worse health-related QoL, including fatigue, sleep disturbance, anxiety, depression, pain and physical and social functioning[42].
Whether the medicine addresses an unmet need (for example, no other licensed medicines).	No other medicines specifically indicated for the improvement of carcinoid syndrome diarrhoea in patients not experiencing adequate control of symptoms with SSA treatment are currently licensed.
Whether the medicine can reverse or cure, rather than stabilise the condition.	Telotristat ethyl will not reverse or cure the condition.
Whether the medicine may bridge a gap to a "definitive" therapy (for example, gene therapy) and that this "definitive" therapy is currently in development.	Telotristat ethyl does not bridge a gap to definitive therapy.
The innovative nature of the medicine.	There is a high unmet medical need for innovative treatments providing symptom control in patients with carcinoid syndrome not adequately controlled by SSAs. Telotristat ethyl is an orally administered small molecule tryptophan hydroxylase inhibitor. It is produced in hippurate salt form and is an ethyl ester pro-drug. It acts locally within the gastrointestinal tract and systemically to reduce peripheral serotonin synthesis. As such, telotristat ethyl targets the rate-limiting step in the production of serotonin, directly affecting the cause of carcinoid syndrome diarrhoea.
Added value to the patient which may not adequately be captured in the QALY (for example, impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	According to patient interviews (n = 35) in the pivotal TELESTAR study[43], the biggest impact of carcinoid syndrome symptoms was reported on social and/or physical activities/hobbies as well as on emotional areas and energy levels, with the most impactful symptoms being too frequent bowel movements and bowel movement urgency. Patients receiving telotristat ethyl reported meaningful improvements in bowel movement frequency (88% of patients), stool consistency (79%) and bowel movement urgency (58%) as well as significant decreases in generalised pain and fatigue, and increased energy allowing them to better enjoy life, leave the house, and participate in social and other activities.
Added value to the patient's family (for example, impact on a carer or family life).	Patients in the TELESTAR study reported negative impact of carcinoid syndrome symptoms on social and/or physical activities/hobbies (80% of patients), emotional areas (69%) and energy (60%), with the greatest impact due to the frequency and urgency of bowel movements (69% and 40% respectively)[43]. No published evidence reports the impact of the use of telotristat ethyl on families and carers. However, telotristat ethyl may benefit family and carers through reduction in psychological and physical burden. Family members/carers may see patients return to previous activities and patients may be able to continue working if their symptoms are better controlled. Partners may be able to get uninterrupted sleep if night time symptoms are controlled, and reduced hospital admissions would be of benefit to family and carers.
QALY: quality-adjusted life year; QoL: quality of life; SSA: somatostatin analogue	

REFERENCES

1. European Medicines Agency. Assessment Report: Xermelo®. Procedure No.: EMEA/H/C/003937/0000. Jul 2017. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003937/human_med_002168.jsp&mid=WC0b01ac058001d124. Accessed Apr 2018.
2. Ipsen Ltd. Form B: Detailed appraisal submission. Telotristat ethyl (Xermelo®). Mar 2018.
3. Ramage JK, Ahmed A, Ardill J et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *GUT.* 2012;61:6-32.
4. Ipsen Ltd. Xermelo®. Summary of Product Characteristics. Jan 2018. Available at: https://www.medicines.org.uk/emc/product/8429. Accessed Apr 2018.
5. European Medicines Agency. Xermelo®. Procedural steps taken and scientific information after the authorisation. Mar 2018. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003937/human_med_002168.jsp&mid=WC0b01ac058001d124. Accessed Apr 2018.
6. Pavel M, Valle JW, Eriksson B et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms: systemic therapy - biotherapy and novel targeted agents. *Neuroendocrinology.* 2017;105:266-280.
7. Pavel M, O'Toole D, Costa F et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology.* 2016;103:172-185.
8. Kulke MH, Horsch D, Caplin M et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *Journal of Clinical Oncology.* 2017;35:14-23.
9. Lamarca A, Barriuso J, McNamara MG et al. Telotristat ethyl: a new option for the management of carcinoid syndrome. *Expert Opinion Pharmacotherapy.* 2016;17(18):2487-2498.
10. kulke MH, O'Dorisio T, Phan A et al. Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide. *Endocrine-Related Cancer.* 2014;21(5):705-714.
11. Pavel M, Horsch D, Caplin M et al. Telotristat etiprate for carcinoid syndrome: a single-arm, multicenter trial. *Journal of Clinical Endocrinology & Metabolism.* 2015;100(4):1511-1519.
12. Anthony LB, Kulke MH, Horsch D et al. Impact of concomitant medication on efficacy of telotristat ethyl - a post hoc subgroup analysis of the phase III TELESTAR study in carcinoid syndrome. Presented at European Neuroendocrine Tumor Society (ENETS) Conference. March 8-10, 2017.
13. Lexicon Pharmaceuticals. A phase 3, randomized, placebo-controlled, parallel-group, multicenter, double-blind study to evaluate the efficacy and safety of telotristat etiprate (LX1606) in patients with carcinoid syndrome not adequately controlled by somatostatin analog (SSA) therapy - LX1606.1-301-CS final clinical study report (2013-002596-18). Data on file. 2017.
14. Ipsen Ltd. Clinical validation meeting report - telotristat as an adjunct to somatostatin analogue therapy for the treatment of carcinoid syndrome diarrhoea to improve symptom control in Wales. Data on file. 2017.
15. Boudreaux JP, Putty B, Frey DJ et al. Surgical treatment of advanced-stage carcinoid tumors: lessons learned. *Annals of Surgery.* 2005;241(6):839-845.

16. Chen JX, Rose S, White SB et al. Embolotherapy for neuroendocrine tumor liver metastases: prognostic factors for hepatic progression-free survival and overall survival. *Cardiovascular Interventional Radiology.* 2017;40(1):69-80.
17. Strosberg J, El-Haddad G, Wolin E et al. Phase 3 trial of (177) Lu-Dotatate for midgut neuroendocrine tumors. *The New England Journal of Medicine.* 2017;376(2):125-135.
18. Caplin ME, Pavel M, Cwikla JB et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *The New England Journal of Medicine.* 2014;371(3):224-233.
19. Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Mar 2018. Available at: http://www.mims.co.uk/. Accessed Mar 2018.
20. Department of Health. NHS reference costs 2016/17. 2017. Available at: https://improvement.nhs.uk/resources/reference-costs/. Accessed Mar 2018.
21. National Institute for Health and Care Excellence. Lung cancer- costing report - the diagnosis and treatment of lung cancer (update). 2011. Available at: https://www.nice.org.uk/guidance/cg121. Accessed Mar 2018.
22. Crossan C, Tsochatzis EA, Longworth L et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. *Health Technology Assessment.* 2015;19(9):1-409, v-vi.
23. Elliot RA, Putman KD, Franklin M et al. Cost effectiveness of a pharmacist-led information technology intervention for reducing rates of clinically important errors in medicines management in general practices (PINCER). *Pharmacoeconomics.* 2014;32(6):573-590.
24. National Institute for Health and Care Excellence. TA449. Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease. Jun 2017. Available at: https://www.nice.org.uk/guidance/ta449. Accessed Mar 2018.
25. Swinburn P, Wang J, Chandiwana D et al. Elicitation of health state utilities in neuroendocrine tumours. *Journal of Medical Economics.* 2012;15(4):681-687.
26. Beauchemin C, Letarte N, Mathurin K et al. A global economic model to assess the cost-effectiveness of new treatments for advanced breast cancer in Canada. *Journal of Medical Economics.* 2016;19(6):619-629.
27. Sadatsafavi M, Marra C, Marra F et al. A quantitative benefit-risk analysis of isoniazid for treatment of latent tuberculosis infection using incremental benefit framework. *Value Health.* 2013;16(1):66-75.
28. Rinke A, Wittenberg M, Schade-Brittinger C et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): results of long-term survival. *Neuroendocrinology.* 2017;104(1):26-32.
29. Shen C, Shih YC, Xu Y et al. Octreotide long-acting repeatable use among elderly patients with carcinoid syndrome and survival outcomes: a population-based analysis. *Cancer.* 2014;120(13):2039-2049.
30. Halperin DM, Shen C, Dasari A et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *The Lancet Oncology.* 2017;18(4):525-534.
31. Caplin M, Pavel M, Cwikla JB et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. *Endocrine Related Cancer.* 2016;23:191-199.
32. Ipsen Ltd. Advisory board on cost-effectiveness modelling in carcinoid syndrome. Data on file. 2016.
33. Joish VN, Frech F, and Lapuerta P. Cost-effectiveness analysis of telotristat ethyl for treatment of carcinoid syndrome diarrhea inadequately controlled with somatostatin analogs. *Journal of Medical Economics.* 2018;21(2):182-188.

34. Public Health England. Incidence and survival in neuroendocrine tumours and neuroendocrine carcinomas (NETs/NECs) in England, 2013-2014. 2016.
35. Ellis L, Shale MJ, and Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *The American Journal of Gastroenterology.* 2010;105(12):2563-2569.
36. Yao JC, Hassan M, Phan A et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology.* 2008;26(18):3063-3072.
37. Welsh Government. Mid-year population estimates (2009 onwards), by Welsh health boards, for single year of age and gender. 2016. Available at: https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/Local-Health-Boards/populationestimates-by-welshhealthboard-year. Accessed Mar 2018.
38. Ipsen Ltd. Somatuline® Autogel®. Summary of Product Characteristics. Nov 2017. Available at: https://www.medicines.org.uk/emc/product/8257/smpc. Accessed Mar 2018.
39. Novartis Pharmaceuticals UK Ltd. Sandostatin® LAR®. Summary of Product Characteristics. Mar 2018. Available at: https://www.medicines.org.uk/emc/product/7828/smpc. Accessed Mar 2018.
40. Novartis Pharmaceuticals UK Ltd. Afinitor®. Summary of Product Characteristics. Jun 2017. Available at: https://www.medicines.org.uk/emc/product/6658/smpc. Accessed Mar 2018.
41. All Wales Medicines Strategy Group. AWMSG orphan, ultra-orphan and rare disease medicines. May 2015. Available at: http://awmsg.com/industry_alldocs.html. Accessed Mar 2018.
42. Beaumont JL, Cella D, Phan AT et al. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas.* 2012;41(3):461-466.
43. Anthony L, Horsch D, Ervin C et al. Assessing treatment benefit of telotristat etiprate in patients with carcinoid syndrome: patient exit interviews. Abstract #C1. Presented at North American Neuroendocrine Tumor Society: 2015 Neuroendocrine Tumor Symposium, NANETS.