SPECIALISED COMMISSIONING – RESPONSE TO AMENDMENTS REQUESTED TO EVIDENCE REVIEW DURING ENGAGEMENT OR CONSULTATION

URN	1745
POLICY TITLE	Telotristat for treating Carcinoid Syndrome diarrhoea (adults)
CRG:	Specialised Endocrinology
NPOC:	Internal Medicine
Date	21/09/2019

Description of comments during consultation (If studies have been suggested please provide a list of references)	Five papers were put forward by stakeholders that had not been included in the Evidence Review. Cella et al., Clin Ther 2018;40:2006-2020, Weickert et al. Clin Ther 2018;40:952-962, Molina-Cerrillo et al. The Oncologist 2019;24:e597-e599, Anthony et al. The Oncologist 2019;24:e662-e670 and Strosberg et al. The Oncologist 2019;24:1-7.
Action taken by Public Health lead	All papers were reviewed. Full text papers were read and assessed against search strategy terms and PICO criteria for the Evidence Review.
Outcome for studies suggested during consultation	
1. Evidence already identified during the evidence review	Please list studies for which this category applies or state none or not applicable

2.New evidence identified by stakeholders that does not fall within PICO and search methodology	Changes in Weight Associated with telotristat ethyl in the Treatment of Carcinoid Syndrome. Weickert et al., Clin Ther 2018;40:952-962. Weickert et al is a study based on post hoc analysis of the TELESTAR trial which is included in the original Evidence Review as Kulke et al 2017. Whilst this paper does provide additional supportive evidence for telotristat, this study would not have been included in the Evidence Review on the basis of title and abstract as it does not meet the inclusion/exclusion criteria set out in the PICO Framework since weight gain was not considered as an outcome. Furthermore, Weickert et al acknowledge that although weight gain was prespecified and added as an additional exploratory analysis to the statistical analysis plan of TELESTAR, it was not a registered secondary outcome of the study. Weickert et al report that up to 32.5% of patients treated with telotristat experienced dose response weight gain, associated with reduced diarrhoeal severity and improved biochemical and metabolic parameters which could have a positive impact on nutritional status. However, excluding patients receiving an unlicensed dose (i.e. the 500mg telotristat treatment arm in the Phase III double blind RCT) the true effect is smaller (n=7/41 patients [17.1%]) and based on a small sample size. Inhibition of Serotonin Synthesis May have Antitumour Activity? Long-term Efficacy in a Patient with Gastrointestinal Neuroendocrine Tumor. Molina-Cerrillo et al. The Oncologist 2019;24:e597-e599. Molina-Cerrillo et al is a case report of a 67 year old female patient with carcinoid syndrome diarrhoea enrolled in the TELESTAR trial which is included in the original Evidence Review as Kulke et al 2017. Whilst this paper does provide limited supportive lower level evidence for telotristat, it would not have been included in the Evidence Review on the basis of title and abstract as it does not meet the inclusion/exclusion criteria set out in the PICO Framework since it is not a trial comparing the addition of telotristat to an somatostatin analogue (SSA) treatment regimen with either standard treatment (SSA on its own) or standard treatment plus a comparator/placebo. Furthermore, whilst the primary outcomes reported do fit within the PICO Framework (bowel movement reduction, flushing episode reduction and reduction in 5-HIAA), the finding being reported is the hypothetical antitumour activity of telotristat as a peripheral inhibitor of serotonin synthesis. TELEPRO: Patient-Reported Carcinoid Syndrome Symptom Improvement Following Initiation of telotristat ethyl in the Real World. Strosberg et al. The Oncologist 2019;24:1-7. This study would not have been included on

	the basis of title and abstract as it does not meet the inclusion/exclusion criteria set out in the PICO Framework as it is a cohort study of patient reported outcomes from a nurse support programme. It provides lower level supporting evidence that participants reported reductions in bowel movements, flushing episodes, severity of nausea, urgency to defaecate and stool form, which are primary outcomes within the PICO Framework of the Evidence Review, but no statistical analysis has been performed. Whilst the authors describe the study as “real-world”, the intervention that is being studied is the pharmacy-based nurse support programme, not the addition of telotristat to SSAs for treating carcinoid syndrome diarrhoea without additional support. The is important in the English context, as pharmacy-based nurse support programmes are not routinely available in England therefore the findings are not generalisable to the English population.

3.New evidence identified by stakeholders that falls within PICO and search methodology but does not materially affect the conclusions of the existing evidence review	Relationship Between Symptoms and Health-Related Quality-of-life Benefits in Patients with Carcinoid Syndrome: Post Hoc Analyses from TELESTAR. Cella et al., Clin Ther 2018;40:2006-2020. This study would have been included on the basis of title and abstract had it been published in a peer reviewed journal at the time of the original Evidence Review as it meets the inclusion/exclusion criteria set out in the PICO Framework. Cella et al is a study based on post hoc analysis of the TELESTAR study, included in the original Evidence Review as Kulke et al 2017. The TELESTAR Phase III RCT randomised 135 patients with metastatic neuroendocrine tumours and CS to receive telotristat ethyl (TE) 250mg; TE 500mg or placebo three times daily during a 12-week double-blind treatment period (DBTP). After the DBTP,115 patients received TE 500 mg three times daily in an open label extension up to 48 weeks. The licensed dose of TE is 250mg three times daily therefore results based on other dosages should not be included in the Evidence Review, which means that the OLE study findings should not be considered as part of the Evidence Review. Cella et al (2018) report HRQoL and symptom control in patients enrolled in the TELESTAR study, comparing patients who achieved the predefined durable response (DRs; reduction in BM/day of more than 30% over at least 50% of the 12 week DBTP) with those who were non-durable responders (NDRs). Relationship between clinical improvement and quality of life during the DBTP:-Daily Bowel Movement (BM) frequency at week 12 was -2.7 for DR and -0.9 for NDRs (around 2 fewer BMs daily for DRs)Other CS symptoms – DRs also had significant and greater improvements over the DBTP in daily flushing episodes (DRs:-1.2, NDRs:-0.1); abdominal pain severity (0-10 scale): DRs:-1.1, NDRs:0.1; urgency to defaecate: DRs:-0.4, NDRs:-0.1. At Week 12, DRs showed a meaningful, medium-sized improvement in EORTC QLQ-C30 global health status: DRs:5, NDRs:-3.6. Meaningful improvements were also seen in diarrhoea: DRs -26.3, NDRs -11.8 and pain (DRs:-13.7, NDRs:2.3). Small but meaningful improvements were seen in nausea and vomiting and dyspnoea in DRs vs NDRs. The results show reduction in daily BM frequency associated with improvements in CS symptoms based on a small sample size over a 12 week treatment period. The analysis has been presented comparing DRs with non DRs and no sub-group analysis has been performed by intervention group (i.e. TE 250mg vs TE 500mg) in the DBTP so it is not possible to differentiate between DRs given a licensed or an unlicensed dosage. It is possible that the

	true size of the effect is smaller when restricting analysis to patients receiving the licensed dose. Long-term Safety Experience with Telotristat Ethyl Across Five Clinical Studies in Patients with Carcinoid Syndrome. Anthony et al. The Oncologist 2019;24:e662-e670. Anthony et al is a non-systematic review without meta-analysis of five clinical trials, two Phase II and three Phase III trials (which the authors state are all the clinical studies of telotristat in patients with carcinoid syndrome). This study could have been included on the basis of title and abstract had it been published in a peer reviewed journal at the time of the original Evidence Review as the clinical trials which it summarises meet the inclusion/exclusion criteria set out in the PICO Framework. However, whilst systematic reviews and meta-analyses of good quality RCTs provide the highest level of clinical evidence, Anthony et al do not present inclusion/exclusion criteria as would be standard within a systematic review and therefore this study is of lower level evidence. Anthony et al report the adverse events data for patients enrolled in 5 studies, including TELESTAR (included in the original Evidence Review as Kulke et al 2017) and TELECAST (included in the original Evidence Review as Pavel et al 2015), providing supporting evidence for the long-term safety of telotristat. The review includes data on 239 participants, followed up for a median treatment duration of 59.9 weeks. Although all of the trials included an arm with a treatment dose of 250mg, all of the clinical trials had at least one other dosing arm and the findings were presented for total study populations. It is therefore possible that the discontinuation rate in participants receiving the licensed dose was different from the results presented.
4.New evidence identified by stakeholders that falls within PICO and search methodology, that does materially affect the conclusions of the existing evidence review. Updated evidence review to be undertaken (agreed with CET)	None identified.