Two papers were put forward by a stakeholder that had not been included in the Evidence Review. Cella et al., Clin Ther 2018;40:2006-2020 and Weickert et al. Clin Ther 2018;40:952-962

Both papers were reviewed. Full text papers were read and assessed against search strategy terms and PICO criteria for the 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
A 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.

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 also a study based on post hoc analysis of the TELESTAR study which is included in the original Evidence Review as Kulke et al 2017. 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 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.

| Outcome | New evidence identified by stakeholders that falls within PICO and search methodology but does not materially affect the conclusions of the existing evidence review |