CPAG Summary Report for Clinical Panel – [Policy URN 1745: Telotristat for the treatment of carcinoid syndrome diarrhoea]

The Benefits of the Proposition –		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Although survival was not measured directly, TELESTAR reported one and three deaths (both out of 45 patients) in telotristat and placebo groups respectively. This suggests reports of mortality in people receiving telotristat were low. Results should be interpreted with caution because there are possible confounders (that is, factors other than treatment effectiveness influencing the results) which may disguise the true treatment effect of telotristat, including use of SSA rescue therapy, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes. In addition, this was not a primary outcome, and the study was not powered to detect an effect.
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	Depressive symptoms were reported. In TELESTAR, 6.7% in both telotristat and placebo reported a depressed mood during the study. Similar findings were reported in TELECAST. This suggests depressive outcomes were comparative between people receiving telotristat and placebo. Results should be interpreted with caution because there are possible confounders which may disguise the true treatment effect of telotristat, including use of SSA rescue therapy, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes.
8.	Replacement of more toxic treatment	
9.	Dependency on care giver /	

	supporting independence	
10.	Safety	Adverse events were noted by the investigators and graded as mild, moderate or severe. In TELESTAR 82% of telotristat reported experiencing a treatment emergent adverse event (TEAE) compared with 86.7% placebo. 6.7% telotristat discontinued treatment due to a TEAE compared with 13.3% placebo. In TELESTAR the most commonly reported GI symptom related adverse event was abdominal pain (11% telotristat, 17.8% placebo), which was supported by findings from TELECAST and Pavel et al, 2015. These results suggest telotristat was generally well-tolerated for people receiving a 250mg dose. Results should be interpreted with caution as stated in No. 7.
11.	Delivery of intervention	

Other health outcome measures determined by the evidence review		
1.	Bowel movement frequency	Bowel movement (BM) frequency was based on daily participant self-report. A meaningful treatment benefit was identified by having at least a 30% reduction from baseline in BM frequency for at least 50% of the 12 week study period or having fewer than 3 BMs per day. The main study (TELESTAR) reported the overall mean reduction from baseline in BMs per day was -1.43 for telotristat compared with -0.62 for placebo ($p<0.001$) at 12 weeks. It also reported that a meaningful treatment BM response rate was observed in 44% for telotristat compared with 20% for placebo. This finding was supported by the results of several other studies (TELECAST, Pavel et al. 2015 and Kulke et al. 2014). These findings suggest that telotristat increases the chances of a meaningful reduction in bowel movement frequency by 3.49 times when compared with placebo, with a 95% probability that the true value is within the range of 1.33 times to 9.16 times higher. Results should be interpreted with caution because there is no evidence beyond 12 weeks for the 250mg dose of telotristat. In addition the TELESTAR authors noted that a response rate for placebo (reported as 20%) was an unexpected finding, therefore other factors such as use of short-acting SSA rescue therapy (more common in the placebo arm); variability in the absorption of long-acting SSAs; differences in use of other antidiarrheal medications, and dietary changes, may have contributed to this finding, all of which may disguise the true treatment effect of telotristat.

2.	Change in urinary 5-hydroxyindoleacetic Acid (u5-HIAA) levels	The overproduction of serotonin (responsible for CS symptoms) was assessed by looking at the change from baseline in 24 hour 5-hydyroxyindoleacetic acid (5-HIAA) levels, which is used to show a reduction in serotonin values. A meaningful response was at least a 50% reduction in 24 hour u5-HIAA levels (or normalisation of levels in people who already had increased levels at baseline). Results were assessed at study endpoint (12 weeks). The best evidence is from TELECAST, which found u5-HIAA levels had reduced by a mean value of 33.16% in people receiving telotristat compared with a mean increase of 97.7% for placebo. This evidence was supported by TELESTAR and Pavel et al, 2015. These findings suggest serotonin levels (measured in 24 hour u5-HIAA levels) can be reduced by as much as 53.95% in people receiving telotristat compared with placebo, with the true reduction somewhere between -85.0% to -25.1% $p<0.001$). It is important to note that the clinical significance of 5-HIAA levels have not yet been fully established, although it is a commonly used marker of response in people with CS. In addition TELECAST included a population experiencing less severe symptoms than TELESTAR, and some people may have not had previously had SSA's, whereas in NHS practice SSAs would have been tried before moving on to telotristat.
3.	Patient reported change in CS symptoms	Patient reports of symptom change were largely obtained by interviewing participants at the end of the clinical trials. The best evidence came from Anthony et al (2017) which considered patient experience of symptom change at the end of TELESTAR. 29 out of the 35 people (83%) completing the interview reported BM frequency as more important to treat than stool form with patients reporting they felt the 3 most important symptoms to treat were diarrhoea, BM frequency, and urgency to defecate. The most frequently reported negative effects of CS symptoms were in social and physical activities with 28 (80%) of the 35 people interviewed reporting negative effects in these areas. This was followed by emotional symptoms (reported by 24 people (69%) and decreased energy (reported by 21 participants (60%). Of the 25 people completing the interview, 21 described experiencing a meaningful improvement, and in particular, improvement in BMs (with 7 participants receiving telotristat compared with 4 placebo stating their symptoms had improved). Twenty out of 21 participants (95%) stated their BM frequency had reduced, with 7 for telotristat described as a meaningful reduction, compared with 3 for placebo. These findings were supported by Kulke et al, 2014 and the exit interview of this trial (Gelhorn et al, 2016) where participants reported improvements in areas such as abdominal pain and diarrhoea. These findings suggest that after taking telotristat patients report improvements in their CS symptoms. However, results should be treated cautiously, Only a small number (35 out of 135) people originally participating in TELESTAR completed the exit interview and the interviews may have included

		people who received a different dose of telotristat to the licensed 250 mg dose.
4.	Stool form and consistency	Patients reported any change in stool form and consistency in a daily self-report assessment using the Bristol Stool Form Scale whereby a reduced score showed a decrease in diarrhoea symptoms. TELESTAR (Kulke et al, 2017) found although at endpoint, the mean change from baseline in stool consistency for people receiving telotristat had reduced by -0.26 points, this did not statistically significantly differ to the reduction of -0.22 points on the Stool form scale for people receiving placebo. Similar results were reported in TELECAST (Pavel et al, 2018) and the phase II RCT (Kulke et al, 2014). These findings suggest although patients in both treatment and placebo groups reported an average reduction in diarrhoea symptoms it is difficult to identify any clear differences in stool consistency, (graded using a stool form scale) for people receiving telotristat compared with placebo. Results should be interpreted with caution because data in the trial may have been affected by differences in the population, compared with people in NHS clinical practice.
5.	Urgency to defecate	Patients were asked to describe if they experienced a sense of urgency to defecate daily using self-report measures. The best evidence came from TELESTAR where the proportion of days participants reported a sense of urgency was averaged at end-point (12 weeks). TELESTAR found the mean proportion of days with a sense of urgency to defecate for people receiving telotristat (0.66) did not greatly differ compared with placebo (0.75). Findings from TELECAST, Kulke et al, 2014 and Pavel et al, 2015 were similar. Results suggest a change in urgency cannot be differentiated between people receiving telotristat compared with those receiving placebo. Results should be interpreted with caution as No.7 section 1.
7.	Abdominal pain and discomfort	Patients were asked to record any experience of abdominal pain and/or discomfort using a daily self-report assessment on a pain scale where higher values showed patients were experiencing higher levels of pain and discomfort. The daily values were averaged at study-endpoint (12 weeks) and results compared between treatment and placebo groups. The best evidence came from TELESTAR which found at end-point participants receiving telotristat reported an average reduction of pain -0.49 points on the pain scale compared with an average reduction of -0.23 points for placebo. Similar findings were reported in TELECAST, Kulke et al, 2014 and Pavel et al, 2015. These findings suggest although patients reports of abdominal pain decreased in both telotristat and placebo groups, results cannot

		show that treatment with telotristat is any better or worse compared with placebo treatment. Results should be interpreted with caution as No.7 section 1.
8.	Change in number of flushing episodes per day	Patients were asked to record the number of flushing episodes they experienced using a daily self-report assessment. The daily values were averaged at study-endpoint (12 weeks) and results compared between treatment and placebo groups. The best evidence came from TELESTAR which showed an overall mean reduction in flushing episodes at endpoint but this was not statistically significant different for people receiving telotristat (which reduced by -0.30 counts/ day) compared with placebo (reducing by -0.16 counts per day). TELECAST reported similar findings and Kulke et al, 2014 reported there were no clear differences between people treated with telotristat compared to placebo. Pavel et al, 2015 reported a statistically significant change from baseline, with the mean number of flushing episodes decreasing by -0.75 counts per day (95%CI -1.46, -0.03) (27% reduction; p= 0.04). However, since this is a single arm non-randomised study, and treatment with telotristat was not compared with another therapy or placebo treatment, this study cannot provide evidence that telotristat is any better or worse than other treatments. Although these results suggest although patients report a decrease in the number of flushing episodes per day, there may be some uncertainty regarding results, which results cannot show that treatment with telotristat is any better or worse compared with placebo. Results should be interpreted with caution as No.7 section 1.
9.	Change in frequency of short acting SSA therapy	The use of rescue short-acting SSA therapy was a measure used to identify participants who required further control of their symptoms. It was assessed by average change in the number of injections per day, assessed at end-point (12 weeks). The best evidence came from TELESTAR which found the change from baseline in frequency of rescue short acting SSA therapy had reduced by -0.11 injections per day for telotristat compared with an increased use of 0.18 injections per day for placebo, although this result was not statistically significant. TELECAST also reported a non-significant difference. These results suggest that although people receiving telotristat required fewer rescue remedies to treat their CS symptoms, it is difficult to identify any overall difference in the need to use additional rescue treatment for people receiving telotristat compared with people receiving placebo. Results should be interpreted with caution as No. 7 section 1.
10.	Quality of life outcomes	Quality of life outcomes were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the GI.NET-21, whereby higher scores on the global health status indicated improved

		health, higher scores on the symptom subscales indicated worse symptoms. Results were assessed at end-point (12 weeks). The best evidence came from TELESTAR which found global health status improved by 1.7 points on the subscale score of the EORTC-QLQ-C30 for people receiving telotristat compared with a worsened global health for people receiving placebo from the original average baseline rating (on a 0 to 100 point scale averaged over the 12 week treatment period), This was not statistically significant. When participants were asked to report their experiences of diarrhoea, people receiving telotristat reported a mean statistically significant improvement of 19.2 points in the diarrhoea subscale compared with a mean score of 8.5 points for people receiving placebo. The study authors noted that these similarities across treatment arms suggest there was no detriment to overall quality of life as a result of treatment. It is important to note that the assessment of quality of life outcomes in TELESTAR were based on a subset of the people who were originally randomised and therefore it is difficult to broaden this finding to the wider NHS clinical population. Furthermore, the study authors noted that minimal changes in global health scores had also been found in previous studies of patients with NETs who received SSAs, and suggested the EORTC QLQ-C30 tool may not be sensitive for this domain.