

**Clinical
Commissioning
Policy Proposition:
Telotristat for treating
carcinoid syndrome
diarrhoea (Adults)**

Reference: NHS England 1745



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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About diarrhoea caused by carcinoid syndrome

Carcinoid syndrome (CS) describes the symptoms that can sometimes occur from a rare cancer called neuroendocrine tumours (NET) which affects the body's way of producing hormones (the neuroendocrine system). Hormones are natural substances that have an important role in making sure the body functions healthily. NETs can increase the amount of hormones produced, meaning that too many are released into the bloodstream, which can cause a number of symptoms including diarrhoea, flushing of the skin, wheezing, stomach pain and a disease of the heart known as carcinoid heart disease. Around 80% of people with CS will have diarrhoea, and if this is not controlled it can lead to weight loss, problems getting enough of the nutrients from food and water that the body needs to be healthy, and, in severe cases, it can cause death.

See also, section 4 for additional definitions of terms used in this document.

About current treatments

Diarrhoea caused by carcinoid syndrome occurs in patients with advanced disease (when the tumour has spread to other organs). There are a number of treatment options including treatment for helping to stop or reduce diarrhoea, and also to treat the NETs that are causing the diarrhoea. The choice of treatment will vary depending on factors such as the size and location in the body of the NETs, how many NETs there are, and the general health of the person with CS.

A multidisciplinary team (MDT) of healthcare specialists with different roles in the care of people with NETs will be involved in helping the patient to decide which treatment is best. These treatments may include:

- Treatment with drugs known as somatostatin analogues (SSAs, octreotide or lanreotide). SSAs help to reduce the amount of hormones the body is making and may also slow or stop tumour growth.
- If treatment with normal doses of SSAs do not work, the dose can be increased to the maximum amount that the patient is able to cope with, either by increasing the dose or increasing how often the dose is taken.
- Surgery to remove or reduce the tumour (only if possible – some people's disease will not be treatable with surgery, due to the site or stage of disease)
- Other treatments which try to reduce the size of the tumour.

About the new treatment

Telotristat is a drug known as a tryptophan hydroxylase (TPH) inhibitor. It is thought that this drug helps the body to stop producing too much of the hormone serotonin, which is overproduced in people with CS. Serotonin is an important hormone which helps the body with a number of important processes such as producing fluids in the body, movement and sensations in the stomach. Overproduction can cause a number of problems, including diarrhoea (the commonest symptom).

Telotristat is given in combination with an SSA.

What we have decided

NHS England has carefully reviewed the evidence to treat CS diarrhoea with telotristat. We have concluded that there is not enough evidence to make the treatment available at this time.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission telotristat in combination with SSA therapy in adults with CS diarrhoea that has been insufficiently controlled with SSA therapy. For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether telotristat will be not routinely commissioned will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

NETs are a rare type of cancer arising from the neuroendocrine system. The tumours can be subdivided into well differentiated (low, grade 1 or intermediate, grade 2) or poorly-differentiated (high grade, grade 3), based on their shape and form. About 70% of NETs start in the digestive system, and about 25% in the lung (Cancer Research UK).

Well-differentiated NETs can cause an excessive release of hormones, such as serotonin, into the bloodstream. This causes a number of symptoms collectively known as CS. These symptoms include diarrhoea (the focus of this policy proposition), which occurs in approximately 80% of people with NETs. If uncontrolled, this can lead to weight loss, malnutrition, electrolyte imbalance, and, in severe cases, malabsorption or death. Other symptoms of CS include flushing, bronchial constriction (wheezing), and development of fibrosis which can damage the heart valves (carcinoid heart disease) or the mesentery (bowel lining).

NETs are usually slow-growing and people can live for many years with the condition, even with advanced disease. The number of people living for at least 5 years after diagnosis ranges from approximately 60% to 95% for NETs originating in the small intestine and lung respectively (Cancer Research, UK).

Current treatment of CS diarrhoea involves treatment both of the underlying disease itself, as well as the symptoms of the disease. The choice of treatment will depend on the size, site and grade of the tumour, location of any other tumours, evidence that the disease is worsening (called disease progression) and general health of the patient. This means that the treatment pathway is complex and individualised for patient circumstances. Despite the complexities of defining a single treatment pathway, the following treatments are usually considered:

Licensed doses of the SSAs lanreotide and octreotide are usually given as the first line treatment, to help with symptom control by reducing the release of hormones (Ramage et al 2012) they can also positively affect tumour control. In addition the following treatments may also be considered:

- Surgery to remove or reduce the tumour, if clinically appropriate (that is, if site or stage of disease allows for this)
- Most commonly increasing the dosage of SSAs to above licensed doses, either by shortening the time between injections (to 3 weeks or sometimes 2 weeks) or increasing the dose (Pavel et al.2016). Short acting booster subcutaneous injections two or three times a day may be administered
- Alternative treatment to control tumour growth.

These treatments can be repeated as required if they can be tolerated, although any treatment decision for people who require further symptom control despite maximal licensed SSA dosing should be discussed at an MDT (Pavel et al 2016; Ramage et al 2012). MDT discussions also ensure that causes of diarrhoea other than CS have been properly investigated.

Telotristat is an oral TPH inhibitor which targets the overproduction of the hormone serotonin, and therefore may help to reduce the diarrhoea associated with CS. It is given in combination with an SSA. Section 8 of the policy proposition outlines that the maximum tolerated dose of SSA should have been tried before considering telotristat.

4 Definitions

- Somatostatin analogue (SSA): a drug used to reduce the amount of hormones secreted by NETs
- Neuroendocrine tumour (NET): rare tumours that develop in cells of the neuroendocrine system
- Neuroendocrine system: the body system responsible for making hormones
- Carcinoid syndrome: a collection of symptoms people may get when a NET releases hormones such as serotonin into the bloodstream
- Diarrhoea: frequent passing of faeces in loose or liquid form
- Bristol stool chart: a medical tool used to classify human faeces into 7 separate categories from Type 1 (severe constipation) to Type 7 (severe diarrhoea).

5 Aims and Objectives

This policy proposition considered: The evidence for telotristat in combination with an SSA for treating people with CS diarrhoea that has been insufficiently controlled with SSA therapy.

The objectives were to:

- Define the clinical commissioning position for telotristat.
- Define the commissioning arrangements required for telotristat.

6 Epidemiology and Needs Assessment

NHS England estimates that around **185** people have CS requiring further symptom control after SSAs (162 patients from lower GI NETs and 23 patients from lung NETs). This is based on:

- For lower gastrointestinal NETs (approximately 35% of NETs, **6,643** patients):

- 75% of gastrointestinal NETs are well differentiated lower GI NET's (G1/G2) (**4,982** patients)
- 58% of well differentiated lower GI NETs are small intestinal NET's (**2,890** patients)
- 40% of people with small intestinal NETs have CS (**1,156** patients)
- 80% of people with CS have CS diarrhoea (**925** patients)
- 17.5% of people with CS diarrhoea require further symptom control after maximum dose SSAs (**162** patients)
- For lung NETs (approximately 22% of NETs, **4,155** patients):
 - 36% are well-differentiated lung NET's (G1/G2) (**1,496** patients)
 - 5% of patients with well-differentiated lung NETs have CS (**75** patients)
 - 30.5% of people with CS require further symptom control after maximum dose SSAs (**23** patients)

7 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Summary of evidence

NHS England considered evidence from 6 studies on the clinical effectiveness and safety of telotristat for CS diarrhoea in adults with disease inadequately controlled by SSA therapy. These included one phase III multicentre, double-blind, placebo-controlled, randomised controlled trial (RCT; TELESTAR; Kulke et al, 2017, n=135) which included people with CS diarrhoea despite receiving stable dose SSA therapy. An additional phase III RCT (TELECAST, Pavel et al, 2018, n=76) provided effectiveness evidence in people with CS, some of whom either had or had not received treatment with SSA therapy, but were experiencing less severe

gastrointestinal symptoms than people who had participated in the TELESTAR trial. Additional supportive evidence came from 2 phase II trials involving dose escalation (an RCT, Kulke et al, 2014 (n=23) and a single arm study, Pavel et al, 2015, (n=15), and two qualitative studies based upon exit interviews, from TELESTAR (Anthony et al, 2017, n=35), and the phase II multiple dose escalation RCT (Gelhorn et al, 2016, n=10).

The studies included doses ranging from 150mg to 500mg. However the licensed dose for telotristat is 250mg three times a day, therefore only the results for the 250mg are reported unless otherwise stated or referring to exit interview studies (which included all doses). All studies provided evidence relating to the effectiveness of telotristat 250mg three times daily for people with CS.

The best available evidence for telotristat comes from TELESTAR. This is a high quality, robust, double-blind, RCT, and it is supported by another high quality RCT (TELECAST) plus several other studies, all of which report highly relevant outcomes for patients with CS diarrhoea. However, when interpreting the results, it should be noted that the evidence base does not include a comparison of the *addition* of telotristat to SSAs with the *addition* of an active comparator to SSAs (that is, comparative studies included the active treatment SSAs in both arms, but compared the addition of telotristat with the addition of placebo.) People were also on varying doses of SSAs in placebo and telotristat arms of studies, which may disguise the true treatment effect of telotristat. No long-term follow-up data for the licensed dose of telotristat (250mg) are available, because all patients switched to 500mg dose after the 12 week primary outcome period (500mg is not a licensed therefore is not reported here). Finally, the small populations (n=10 to 135 all doses, n=3 to 45 for 250mg dose) should be taken into account when interpreting results, with the phase II studies not being powered to demonstrate efficacy (however, given the rare nature of the disease, it is not possible to have large trials in this disease area, and TELESTAR is one of the largest studies conducted to date in this area).

Clinical effectiveness

The primary outcome in TELESTAR addressed the most common symptom of CS, the mean number of BMs averaged over the 12-week double-blind study period for people with CS experiencing at least 4 BMs per day at baseline despite stable use of SSA therapy. A statistically significant reduction was observed for telotristat (-1.43 BMs) compared with placebo (-0.62 BMs) [Hodges-Lehman estimated treatment difference median = -0.81 BMs per day; 97.5% confidence interval (CI -1.26, -0.29), $p < 0.001$]. In TELESTAR, the number of participants achieving a durable treatment response (at least a 30% reduction in BMs per day for at least 50% of the time) was 20 (44%) for telotristat, compared with 9 (20%) for placebo [odds ratio = 3.49, (95%CI = 1.33, 9.16), $p = 0.01$]. The TELESTAR authors noted that a response rate for placebo (reported as 20%) was an unexpected finding. They stated that the 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. Given these potential confounders, which exist in both the placebo and telotristat arms, results should be interpreted with caution, because they may disguise the true treatment effect of telotristat.

The positive findings in BM frequency in TELESTAR were supported in the qualitative follow-up of TELESTAR (Anthony et al, 2017, see below). Statistically significant findings were also reported in TELECAST, which found mean reductions from baseline in BMs per day (-0.45) for people receiving telotristat 250mg compared with an increase in BMs per day (0.05) for people receiving placebo [Hodges-Lehman estimated treatment difference median = -0.45 BMs per day; (95%CI = -0.72, -0.17), $p = 0.004$]. and Pavel et al (2015) reported a statistically significant reduction in BMs per day (-2.57 per day; 43.5% difference; $p < 0.001$). Although statistical significance was not reported, reductions were also found in the Kulke et al (2014) when compared with placebo.

Secondary outcomes included patient reported symptom change. In the exit interview of TELESTAR (Anthony et al, 2017), patients stated they felt the 3 most important symptoms to treat were diarrhoea (n=17), BM frequency (n=9), and urgency to defecate (n=5), and 29 out of the 35 people (83%) completing the interview reported BM frequency as more important to treat than stool form. 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%). However, during the interview, 7 out of the 10 participants receiving telotristat compared with 4 out of 9 receiving placebo reported improvements in their CS symptoms. The most reported symptom improvement was in BM frequency with 7 for telotristat compared with 4 for placebo. Supportive evidence came from Kulke et al, 2014 which reported improvements in CS symptoms (and greatest reports of improvement in BM frequency) for people receiving telotristat and the exit interview of this phase II RCT (Gelhorn et al, 2016) with 82% reporting improvement in diarrhoea.

Other secondary outcomes included change in urinary 5-hydroxyindoleacetic Acid (u5-HIAA) levels over the 12-week double-blind study period, which is used to assess levels of serotonin in the body. TELECAST found statistically significant reductions (-33.16 %) for participants receiving telotristat compared with increases (97.72%) for placebo [Hodges-Lehman estimated treatment median = -53.95 % (95%CI = -85.0, -25.1) $p < 0.001$]. This finding -was supported by TELESTAR. Although Kulke et al, 2014 did not report change scores, 9 of 16 people receiving telotristat compared with 0 of 5 people receiving placebo achieved a biochemical response in u5-HIAA (greater than 50% decrease in 24-hour u5-HIAA levels from baseline, or normalisation of u5-HIAA in patients who had elevated baseline levels). The study authors noted that the clinical significance of this measure has not yet been fully established, although it is a commonly used marker of response in people with CS.

Other CS symptoms were also assessed in the evidence base:

Stool form and consistency was assessed daily using the Bristol Stool form Scale and a mean value was averaged over the 12 week double-blind period. Pavel et al, 2015 found a statistically significant improvement in the stool consistency from baseline. However results from TELESTAR and TELECAST found the change from baseline was not statistically significantly different, and Kulke et al, 2014

found no clear differences between telotristat and placebo (although it did not report values).

TELESTAR did not find a statistically significant difference in the mean proportion of days with a sense of urgency to defecate, or change in abdominal pain and discomfort, with similar findings reported by the results from TELECAST, Pavel et al, 2015 and Kulke et al, 2014. Although the results from TELESTAR and TELECAST found the change in number of flushing episodes was not statistically significant, the open label trial (Pavel et al, 2015) reported a statistically significant change from a baseline of flushing episodes per day by 27% ($p= 0.04$). Please note, because Pavel et al, 2015 did not compare treatment with telotristat to another therapy or placebo treatment, there may be some uncertainty interpreting results:

- Potential sources of bias were not controlled for, therefore there may have been factors other than treatment effectiveness influencing the results (that is, there may have been confounders).
- As there were no comparators, this trial cannot show that treatment with telotristat is any better or worse than any other treatment or placebo.

Quality of life

Quality of life outcomes were reported in TELESTAR and Gelhorn et al (2015). Both studies used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), and Gelhorn et al. (2015) additionally reported results using GI.NET.21. The EORTC QLQ-C30 is a 30-item questionnaire which assesses quality of life of people with cancer. It uses a seven point rating scale to measure global (overall) health status and quality of life and a four point rating scale to measure functional status (focusing on physical, role, cognitive, emotional, and social outcomes); and symptom outcomes (focusing on fatigue, pain, and nausea and vomiting). Changes from baseline were assessed in these studies, whereby a higher global health scores represented better overall quality of life and higher scores on the functional scale represented higher levels of functioning; whereas conversely higher scores on the symptom scales represent more symptoms. The GI.NET-21 is a supplemental

module of the EORTC-QLQ-C30, which has been specifically devised for people with gastro intestinal-related NETs, at varying stages of disease or treatment options. It contains 21 questions which assess disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality.

TELESTAR reported the mean change from baseline on the EORTC-QLQ-C30 in points (on a 0 to 100 point scale averaged over the 12 week treatment period, with higher points representing a better quality of life score). Although the study reported a small improvement in the global health status subscale score (1.7 points) at 12 weeks end-point for people receiving telotristat, compared with a worsened global health status subscale score (-2.0 points) from the original average baseline rating for people receiving placebo, this was not statistically significant. A statistically significant improvement in the diarrhoea subscale score of the EORTC-QLQ-C30 was observed, which showed a mean improvement of 19.2 points for people receiving telotristat 250mg compared with a mean improvement of 8.5 points for people receiving placebo ($p=0.039$). However, there was no difference in the reduction on the nausea and vomiting subscale score for treatment at 250mg compared with placebo (both reported an improvement of 2.4 points). 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. However, they noted that minimal changes in global health scores were observed in previous studies of patients with NETs who received SSAs, which suggests the tool may not be sensitive for this domain. 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.

Gelhorn et al. (2015), which used both the EORTC-QLQ-C30 and the GI.NET-21, described the impact of diarrhoea on patients. It affects social functioning (e.g. difficulty with travel) and sleep (e.g. waking up at night to have a bowel movement), and it can be related to fatigue or tiredness. It stated that high bowel movement frequency is a central issue for patients, and it directly affects the ability of patients to enjoy life and participate in social and physical activities. Gelhorn et al (2015) stated that results suggest telotristat may improve key aspects of CS that

are important to patients (participants self-reported feeling improvements in diarrhoea (82%), abdominal pain (45%), abdominal cramping (36%) and flushing (36%) over the telotristat trial they were involved in). It also reported results for GI.NET-21, where higher scores represented worse symptoms, where, in general, participants reported scores below a mean value of 50 across all subscale scores (out of a maximum of 100). However, it stated there were limitations in both the EORTC QLQ-C30 and GI.NET21 in assessing people with CS. In EORTC QLQ-C30, BM frequency, which it stated is the highest priority for patients, is captured in only 1 domain (out of 30, all of which have equal weight) and some of the domains are not necessarily related to treatment (e.g. financial worries). It stated this may impact the ability of the tool to show statistically significant differences. There were further limitations to this study, including the small patient numbers (n=11) and because only 2 of the 7 centres that enrolled patients onto the phase II trial (Kulke et al. 2014) that this exit interview was based on participated in the questionnaire.

Safety

The results suggest telotristat was generally well-tolerated.

In TELESTAR 37 participants (82.2%) receiving telotristat reported any treatment emergent adverse event (TEAE) during the double blind study period compared with 39 participants (86.7%) for placebo. Of these, 3 (6.7%) receiving telotristat discontinued treatment due to a TEAE compared with 6 (13.3%) for placebo.

The most commonly reported GI symptom related adverse event was abdominal pain. In TELESTAR, 5 (11%) of participants receiving telotristat and 8 (17.8%) of participants receiving placebo reported this.

TELESTAR reported that depressive symptoms were experienced in 3 (6.7%) of people receiving telotristat and 3 (6.7%) of people receiving placebo during the study. In TELESTAR 1 death was reported in a patient with advanced disease receiving telotristat 250mg and 3 deaths of advance disease were reported in the placebo group. In the TELECAST trial (Pavel et al, 2018) there were no treatment emergent adverse events resulting in death.

8 Proposed Criteria for Commissioning

Not applicable as not for routine clinical commissioning policy.

9 Proposed Patient Pathway

Patients would follow the current pathway for treatment of SSA diarrhoea.

10 Proposed Governance Arrangements

Not applicable as not for routine clinical commissioning policy.

11 Proposed Mechanism for Funding

Not applicable as not for routine clinical commissioning policy.

12 Proposed Audit Requirements

Not applicable as not for routine clinical commissioning policy.

13 Documents That Have Informed This Policy Proposition

The documents that have informed this policy include a review of the clinical evidence available for telotristat. Additional evidence sources are listed in the references below.

14 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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