SPECIALISED COMMISSIONING - CLINICAL EVIDENCE EVALUATION CRITERIA FOR A PROPOSITION FOR A CLINICAL COMMISSIONING POLICY FOR ROUTINE COMMISSIONING

URN: 1745
TITLE: Telotristat for treating carcinoid syndrome diarrhoea

CRG: Specialised Endocrinology
NPOC: Internal Medicine
[redacted]
Date: 18/04/18

This policy is being considered for:	For routine commissioning	X	Not for routine commissioning	
Is the population described in the policy the same as that in the evidence review including subgroups?	Yes. However, the Panel was concerned that the selection criteria did not appear to identify only those patients most severely affected. The criteria reflect those in the pivotal trial (a minimum of 4 bowel movements per day) but this alone may not be a sufficient measure of severity.			
Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review?	Yes.			
Is the comparator in the policy the same as that in the evidence review? Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development?	Panel noted that the studies compared telotristat with placebo or had no comparator. This may not reflect plausible comparators used in the NHS which may include octreotide or lanreotide.			
Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy?	There are clinical benefits demonstrated in the trial but the Panel were not convinced that the benefits demonstrated in the trial were clinically substantial. The modest net reduction in average number of bowel movement per day of 0.81 reported in the pivotal trial, combined with no statistically significant changes in; urgency, stool consistency and abdominal pain and discomfort were disappointing. The panel recognised that even a moderate improvement for these patients could be important. Change in the global health status subscale score of the EORTC-QLQ-C30 is reported, although it is not clear whether the 1.7 score			

Are the clinical harms demonstrated in the evidence review reflected in the eligible and /or ineligible population and/or subgroups presented in the policy?	improvement in the telotristat group compared with a 2.0 deterioration score in the control group is clinically meaningful. Yes.		
Rationale Is the rationale clearly linked to the evidence?	It is partly demonstrated, see advice		
<u>Advice</u> The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover: • Uncertainty in the evidence base • Challenges in the clinical interpretation and applicability of policy in clinical practice • Challenges in ensuring policy is applied appropriately • Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review.	The panel considered that there are two potential options for the PWG to consider and to bring back to panel: 1. Reverse the policy proposition to become a not for routine commissioning policy because the degree of clinical benefit is too small to be meaningful and because the degree of certainty regarding this benefit is low due to limitations in the research. . 2. The policy working group may choose to substantially rewrite the criteria for commissioning to identify those patients who may have the greatest ability to benefit from treatment. The policy proposition should be clearer in the stopping criteria. These need to be specific about the degree of benefit that needs to be demonstrated to justify continuation of treatment. The Panel noted that this is a complex syndrome and would like to know if there are wider benefits of the drug on other symptoms. The evidence review may have been too restrictive if other benefits are thought to be significant.		
Overall conclusion	This is a proposition for routine commissioning and	Should proceed for routine commissioning	
		Should reversed and proceed as not for routine commissioning	X or rewritten as advised above.
	This is a proposition for not routine	Should proceed for	

	commissioning and	not routine commissioning	
		Should be reconsidered by the PWG	

Overall conclusions of the panel
Report approved by:
David Black
Clinical Panel Co-Chair
4th May 2018

Post meeting note:

1. Panel asked us to consider amending the starting criteria to better identify those who will be most severely affected.
    a. CSP have added in additional criteria for severity:
        i. stool form as follows: "Bristol stool chart types 5 to 7"
        ii. urgency as follows: "severe urgency related to diarrhoea (for example, difficulty controlling bowels, or bowel-related accidents)".
    b. CSP have clarified that the patient should have "severe symptoms of CS diarrhoea" despite previous treatment
2. Panel asked us to be clearer in the stopping criteria.
    a. CSP have added that "at least one" of the outcomes should be achieved.
    b. CSP have added in more detail to existing stopping criteria to make them more objectively measurable:
        i. Reduction in BM frequency changed to "<4 BMs per day"
        ii. Improvement in urgency to defecate changed to "a reduction from baseline in number of days with urgency to defecate"
        iii. Improvement in stool form and consistency changed to "type 3 or 4 stool consistency using the Bristol stool chart"
    c. CSP have added additional stopping criteria:
        i. "a reduction from baseline in frequency of rescue short-acting SSA therapy to treat bowel-related symptoms associated with CS"
        ii. "a 30% reduction from baseline in u5-HIAA levels"
        iii. "Reduced urgency related to diarrhoea compared with baseline (for example, control of bowels)"

3. Panel queried whether the comparators in the evidence review reflected those used in NHS practice (because the trials had placebo arms, whereas treatments such as SSAs are available in NHS practice)
    a. CSP would like to note that this point is broadly correct although the inclusion of background therapy means that the comparator **wasn't purely a placebo arm**. The main study (TELESTAR) included people receiving SSA plus telotristat vs SSA plus placebo i.e. SSA was in both telotristat and placebo arms. We have made some tracks to both the CER and DPP to clarify this e.g. we have added to p.12 of the DPP the following text: "(…comparative studies included the active treatment

SSAs in both arms, but compared the addition of telotristat with the addition of placebo)...".

4. Panel stated that it was "not convinced that the benefits demonstrated in the trial were clinically substantial". It also requested further clarity on whether the quality of life benefits were clinically meaningful, and whether there were any wider benefits of the drug.

    a. We asked the chair to comment on Panel's statement that the 0.81 reduction in the average number of bowl movements per day was "modest", and the chair responded "It is modest but 'meaningful' for patients especially for example if patients have bowel urgency and incontinence".
    b. We have provided more detail about BMs, patient reports of symptoms and additional detail relating to flushing episodes to the CER and DPP e.g. pp.13-14 of the DPP.
    c. We have added more detail about the quality of life benefit to the CER and DPP e.g. pp14-16 of the DPP.