NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA345; Naloxegol for treating opioid induced constipation

Original publication date:	22 July 2015
Review date	July 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA345, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

No new evidence has been identified that is likely to change the recommendations in TA345.

No relevant head-to-head trials of naloxegol with placebo or other comparators (that is, methylnaltrexone or naloxone-oxycodone) were identified that would change the recommendation in TA345. A new network meta-analysis (Sridharan 2018) shows that subcutaneous methylnaltrexone may be more clinically effective compared with naloxegol, but this was based on low or very low quality evidence with differences across the trial populations and did not include the results from the 12 week extension of KODIAC 4 (KODIAC 7). Therefore the new evidence is unlikely to be considered relevant to TA345 and change the original recommendations.

The company has confirmed that no changes are anticipated in the marketing authorisation or costs. Based on this information a review of the guidance would not provide value for the NHS.

3. Summary of new evidence and implications for review

Naloxegol is recommended as an option for the treatment of opioid induced constipation in adults whose constipation has not adequately responded to laxatives. KODIAC 4 (Chey 2014) was included as part of TA345 and since its publication in 2015, a 12 week extension study has also been published (Webster 2016, KODIAC 7). KODIAC 7 showed naloxegol was still clinically effective (no changes in pain scores or opioid dose and improvements in quality of life) compared with placebo

and no new important adverse events were observed in people with non-cancer pain and opioid-induced constipation (OIC). These results are similar to KODIAC 4 and 5 (included as part of TA345) and are unlikely to change the original recommendations.

A new network meta-analysis (Sridharan, 2018) shows that subcutaneous methylnaltrexone may be more clinically effective compared with naloxegol, but this was based on low or very low quality evidence, the trial populations were different and did not include a direct head-to-head trial of naloxegol compared with methylnaltrexone. The network also included oral methylnaltrexone, however, only subcutaneous methylnaltrexone is licensed in the UK. In addition, TA345 highlighted some challenges with administration of the subcutaneous methylnaltrexone. Based on the above the results of the network meta-analysis should be treated with caution.

Has there been any change to the price of the technology since the guidance was published?
The company has confirmed that no changes to the prices are anticipated.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
The company confirmed there has been no change to the marketing authorisation since the publication of the original guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
In TA345 the committee was uncertain about using 2 different populations (miTT and laxative inadequate responders (LIR) subgroup) in the company's mixed treatment analyses. It also understood that the mixed treatment comparison of naloxegol compared with other active treatments (subcutaneous methylnaltrexone and naloxone-oxycodone) showed no statistically significant differences across outcomes. The new network meta-analysis (Sridharan, 2017) shows subcutaneous methyl naltrexone is associated with significantly improved rescue-free bowel movements (RFBM) compared with naloxegol and other treatment options (that is, lubriprostone, prucalopride and naloxegol) in people with opioid-induced constipation. However, the results may not be relevant to TA345 because: • There were substantial differences in the inclusion criteria of clinical trials used in the company's mix treatment comparison and the new meta-analysis described by Sridharan. For example KODIAC 4 included adults with chronic non-malignant pain and opioid-induced constipation (defined by as bowel movements less than 3 per week and one or more of the following symptoms: hard or lumpy stools, straining, incomplete evacuation, or anorectal obstruction) while studies used in the new meta-analysis included adults patients who underwent orthopaedic procedures with prior 4 to 10 days constipation and no bowel movement for at least 48h with difficulty in spontaneous bowel movement.

• The network included oral methylnaltrexone (only subcutaneous methylnaltrexone is licensed in the UK). • Not everybody can have methylnaltrexone because of its subcutaneous route of administration, monitoring and X‑ray requirements, and adverse effects. • The network meta-analysis was based on low and very low quality of evidence. • The network meta-analysis did not include results from the12 week extension study KODIAC 7. Therefore the results of the new network meta-analysis are unlikely to be relevant to TA345 or lead to a change the original recommendations.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None

The search strategy from the original ERG report was adapted and re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2015 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues were raised during the committee meeting.

GE paper sign off: **Helen Knight, 21/06/2018**

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of naloxegol within its licensed indication for treating opioid-induced constipation.

6. Current guidance

1.1 Naloxegol is recommended, within its marketing authorisation, as an option for treating opioid induced constipation in adults whose constipation has not adequately responded to laxatives.

An inadequate response is defined as opioid-induced constipation symptoms of at least moderate severity in at least 1 of the 4 stool symptom domains (that is, incomplete bowel movement, hard stools, straining or false alarms) while taking at least 1 laxative class for at least 4 days during the prior 2 weeks.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

"The list price for naloxegol, which has been agreed by the Department of Health, is £55.20 per 30-tablet pack of 12.5-mg or 25-mg film-coated tablets. The recommended dose is 25 mg taken orally once daily (or 12.5 mg for people with renal insufficiency). Costs may vary in different settings because of negotiated procurement discounts."

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specific trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Constipation (2018) NICE pathway

Suspended/terminated

Methylnaltrexone bromide for treating opioid-induced constipation (terminated appraisal) (2017) NICE technology appraisal guidance TA468.

Methylnaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care (terminated appraisal) (2013) NICE technology appraisal guidance TA277.

Constipation (opioid induced) - lubiprostone NICE technology appraisal guidance. Publication date to be confirmed. *4 April 2014: This appraisal has now been suspended.*

Naldemedine for treating opioid-induced constipation NICE technology appraisal guidance. Publication date to be confirmed. *23 February 2018: "We have been informed by the company of a delay to the licensing application, therefore, NICE will suspend and reschedule this appraisal in line with the new timings."*

2. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"The list price for naloxegol, which has been agreed by the Department of Health, is £55.20 per 30‑tablet pack of 12.5‑mg or 25‑mg film‑coated tablets. The recommended dose is 25 mg taken orally once daily (or 12.5 mg for people with renal insufficiency)." "It has a marketing authorisation for treating opioid‑induced constipation (OIC) in adults whose constipation has had an inadequate response to laxative(s). The summary of product characteristics defines an inadequate response to laxatives as concurrent symptoms of OIC of at least moderate	The indication and price remains the same (eBNF accessed 26 April 2018).

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
severity while taking at least 1 laxative class for a minimum of 4 days during the last 2 weeks."	

3. Registered and unpublished trials

Trial name and registration number	Details
A Phase II, Randomized, Single Center, Pilot Feasibility Study to Evaluate Naloxegol for Opioid-Induced Constipation in Cancer Patients NCT02745353	Phase II, currently recruiting. Estimated enrolment: 60 Start date: May 2016 Estimated primary completion date: April 2020. "The purpose of this study is to compare the effect of naloxegol versus the patient's usual care in treating opioid-induced constipation, as well as the effect on the patient's quality of life and how much pain is experienced. Also, the purpose of this study is to compare whether treatment with naloxegol versus usual care has any impact on the number of hospital or clinic visits or telephone calls to the patient's physician that are related to constipation, and to determine the patient's preference for continuing to receive naloxegol as treatment for opioid-induced constipation."
A Study to Assess the Tolerability, Safety, and Feasibility of Naloxegol in Patients With Cancer and Opioid-Induced Constipation NCT02839889	Phase IV, ongoing not recruiting. Estimated enrolment: 12 Start date: September 2016 Estimated primary completion date: March 2018. "The purpose of this study is to determine if naloxegol can be used in the treatment of opioid-induced constipation in patients with cancer and pain. This phase 4 study consists of a two week randomized double blind period followed by a two week open-label period.

Appendix D – References

1. Chey, W (2014) Naloxegol for opioid-induced constipation in patients with noncancer pain. *The New England journal of medicine* 370 (25): 2387-96.

2. Sridharan, K (2018) Drugs for treating opioid-induced constipation: A mixed treatment comparison network meta-analysis of randomised controlled clinical trials. *Journal of pain and symptom management* 55 (2): 468-479.

3. Webster, L (2016) A 12-week extension study to assess the safety and tolerability of naloxegol in patients with noncancer pain and opioid-induced constipation. *Journal of opioid management* 12 (6): 405-419.