NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Naloxegol for treating opioid induced constipation [ID674]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Andrew Davies

Name of your organisation: Royal Surrey County Hospital NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Currently, most patients with opioid-induced constipation (OIC) are managed with conventional laxatives (and usually a combination of a softener and a stimulant laxative). However, there is no evidence base to support the use of these drugs in the management of OIC, and the clinical experience is that these drugs are relatively ineffective in many patients. Thus, many patients require other interventions to manage their OIC (e.g. suppositories, enema, manual evacuations).

In the UK, the only drug licensed for the management of OIC is methylnaltrexone (Relistor®). There is a good evidence base to support the use of Relistor® in the management of OIC. However Relistor® is only available as a subcutaneous injection, and is associated with rapid onset of defecation (which is often accompanied by abdominal discomfort / pain). Furthermore Relistor® has been associated with some cases of intestinal perforation, which may be related to its pharmacokinetic / pharmacodynamic profile, i.e. very acute onset of action.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Naloxegol® would be beneficial to any / all patients with OIC (irrespective of their condition / prognosis).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Naloxegol® could be used in primary and secondary care.

The introduction of Naloxegol® should reduce the need for rectal interventions for OIC (i.e. suppositories, enemas, manual evacuations), and so free up nursing time for other activities. In addition, it would reduce the expenditure on conventional laxatives. [The introduction of Naloxegol® should also reduce the need for outpatient reviews and inpatient admissions for OIC, and so free up resources for other activities].

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If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Currently, Naloxegol® is not available in the UK.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The guidelines that are most relevant to my practice are:

1. European Association of Palliative Care endorsed guidelines on the management of constipation
Larkin P et al. The management of constipation in palliative care: clinical practice recommendations. Palliative Medicine 2008; 22: 796-807.
Systematic review of literature / expert group recommendations (reasonable methodology) – recommend peripherally acting mu opioid receptor antagonist (PAMORAs) as second line treatment for OIC

2. Cochrane systematic review
Candy B et al. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. Cochrane Database of Systematic Reviews 2011.
Updated Cochrane review of literature (robust methodology) – conclude subcutaneous methylnaltrexone (PAMORA) "is effective in inducing laxation in palliative care patients with opioid-induced constipation and where conventional laxatives have failed". [Review pre-dates publication of Naloxegol data].

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Naloxegol® should prove to be more effective than conventional laxatives, and as easy to use as conventional laxatives. There should be no practical barriers to its introduction into the UK.

Naloxegol® should prove to be as effective as Relistor®, but easier to use then Relistor® (oral preparation vs subcutaneous preparation).

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If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

I would suggest that initially Naloxegol® is used as second line treatment for OIC (after conventional laxatives) but that there is no minimum time limit on switching from conventional laxatives to Naloxegol®. Patients on Naloxegol® would not need more intensive monitoring than patients on conventional laxatives (with OIC).

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The phase III studies involved patients with non cancer pain, but the results are applicable to all patients with OIC (i.e. patients with non cancer pain and patients with cancer pain).

The phase III studies compared Naloxegol® with a placebo, (with a conventional laxative as 'rescue medication') and it would be useful to have further studies comparing Naloxegol® with conventional laxatives.

The outcome measures in the phase III studies were appropriate, and the results are relevant to clinical practice in the UK.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The adverse events / side effects are similar to those seen with other PAMORAs (and similar to the symptoms seen in untreated patients with OIC); 10.3% patients were withdrawn from the phase III studies due to adverse events in the active arm (compared to 5.4% in the placebo arm).

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

The phase III studies involved patients with non-cancer pain, but there are a significant number of patients with cancer pain and OIC – it is important that this group has access to Naloxegol®. OIC in cancer pain patients is the same entity as OIC in non-cancer pain patients, i.e. the problem relates to the opioid, and not the underlying disease (requiring the opioid).

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

N/A

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The introduction of Naloxegol® should significantly improve the management / improve the quality of life of many patients with non-cancer / cancer pain and OIC

NHS staff would need some education / training re use of the drug (similar to other "new" drugs).

No additional resources would be required. Indeed, the introduction of Naloxegol® should reduce the need for rectal interventions for OIC (i.e. suppositories, enemas, manual evacuations), and so free up nursing time for other activities. In addition, it would reduce the expenditure on conventional laxatives. [The introduction of Naloxegol® should also reduce the need for outpatient reviews and inpatient admissions for OIC, and so again free up resources for other activities].