**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Naloxegol for treating opioid-induced constipation**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)**

**Comment 1: the draft remit**

| Section | Consultees | Comments | Action |
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| Appropriateness | BSG/RCP | Appropriate remit | Comment noted. No action required. |
| | AstraZeneca UK | Opioid induced constipation is an area with no NICE recommended treatments and no specific guidelines. It is frequently confused with chronic idiopathic constipation although it is separate condition with different cause. A NICE recommended treatment in this condition should be a priority for NICE. | Comment noted. No action required. |
| | British Pain Society | Very appropriate for NICE appraisal | Comment noted. No action required. |
| Wording | BSG/RCP | Appropriate wording | Comment noted. No action required. |
| | British Pain Society | Yes | Comment noted. No action required. |
| Timing Issues | BSG/RCP | Non-urgent | Comment noted. No action required. |
| | British Pain Society | 'Desperate' - opioid induced constipation is a very big problem clinically | Comment noted. No action required. |

**Comment 2: the draft scope**

| Section | Consultees | Comments | Action |
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| Background information | BSG/RCP | Accurate | Comment noted. No action required. |
| | AstraZeneca UK | We would suggest to amend the wording for "opioids are widely used for the treatment of chronic severe pain" and amending the term "opioid induced bowel dysfunction" to reflect naloxegol's opioid-induced constipation (OIC) indication.<br>Physiological effects of opioids in the gastrointestinal tract are caused by binding at mu opioid receptors within the enteric nervous system and include decreased motility, decreased secretions, increased absorption of fluid from intestines and increased sphincter tone, which may cause or exacerbate constipation in 40-50% of individuals who take opioids. OIC is considered to be a condition that will impact a high proportion of all patients taking chronic opioid treatment and will persist unless opioid treatment is stopped or effective treatment is initiated.<br>Patients and people are used interchangeable. We suggest using one consistent term throughout the document.<br>3rd para – would recommend including on the final sentence that suppositories and enemas are not always effective and they can be uncomfortable and difficult to self-administer. | Comment noted. The first paragraph in the background section in the scope has been amended. The background section of the scope is only intended to provide a brief description of the condition and current treatment options. A detailed description of these aspects will be included in the manufacturer's evidence submission and will be considered during the appraisal. |
| | British Pain Society | The potential use of the product is greater than in patients with cancer pain. There are many more patients with chronic benign who take regular moderate or strong opioids for their pain and suffer with constipation. | Comment noted. No action required. |
| The technology/ intervention | BSG/RCP | Yes | Comment noted. No action required. |
| | AstraZeneca UK | We recommend including after the first sentence, the following statement:<br>*Pegylation renders the naloxol portion of the molecule as a PgP transport substrate. The PgP transporter is located, on the blood brain barrier and transports substrates out of the CNS.* | Comment noted. The technology section in the scope only includes information about the marketing authorisation of the technology, and a brief description of the clinical trials which will form the evidence base for the technology. |

| Section | Consultees | Comments | Action |
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| | | *Thus the PgP transporter minimizes naloxegol's ability to cross the blood brain barrier and interfere with analgesia, while not interfering with its ability to bind to GI tract opioid receptors*.<br>We recommend removing "cancer pain" from descriptions of studies. It has been studied in cancer pain patients but due to recruitment challenges, there is inadequate data to draw definitive conclusions on efficacy and safety in this population.<br>On the final sentence we believe it would be useful to clarify the clinical studies' definitions of inadequate responders:<br>Patients were classified as LIR at the screening visit.<br>— LIR: Self-reported moderate, severe, or very severe symptoms in ≥1 of the 4 stool symptom domains (incomplete BM, hard stools, straining, or false alarms) of the Baseline Laxative Response Status Questionnaire in patients taking ≥1 laxative class<br>for ≥4 days over a 14-day recall period immediately preceding screening<br>— 2X LIR: Inadequate response to ≥2 laxative classes as defined above or reported unsatisfactory relief from ≥1 additional laxative class in the 6 months before screening | Complete details about the technology and the clinical evidence will be included in the manufacturer's evidence submission and considered during the appraisal.<br>It is acknowledged that the evidence base for people with cancer pain is limited; therefore, consultees agreed that the population should not be divided into those with cancer pain and non-cancer pain. The description in the technology section of the scope serves to acknowledge that both groups have been included in the trials, albeit the cancer pain population is small. The manufacturer will be encouraged to describe the different patient characteristics in their trials as part of their evidence submission.<br>It was agreed at the scoping workshop that the definitions of an inadequate response to laxatives from the KODIAC trials do not necessarily follow the criteria for response seen and used in clinical practice; therefore they should not be used to define any subgroups in the scope. |
| | British Pain Society | Yes | Comment noted. No action required. |
| Population | BSG/RCP | Appropriate population | Comment noted. No action required. |
| | AstraZeneca UK | Naloxegol will be assessed specifically for patients with OIC who have had inadequate responses to at least two different classes of laxatives | Comment noted. It was agreed at the scoping workshop that the population in the scope should remain broad and should not be restricted to people in whom previous treatment with laxatives has failed to provide adequate relief. It was noted that naloxegol |

| Section | Consultees | Comments | Action |
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| | | | may be an appropriate first-line treatment option for some patients (such as those with severe opioid-induced constipation) if first line use is permitted in the marketing authorisation. It was acknowledged during the scoping workshop that the Committee can only make recommendations on the use of the technology for the population in line with the marketing authorisation. |
| | British Pain Society | Yes for cancer pain, but chronic benign pain also needs to be understood as cause of opioid induced constipation. | Comment noted. Naloxegol will be appraised within the boundaries of its marketing authorisation for opioid-induced constipation. Consultees agreed that the patient population should not be divided into those with cancer pain and non-cancer pain. |
| Comparators | BSG/RCP | In addition to the standard comparators also targinact (naloxone-oxycodone);relistor (methylnaltrexone) are both u-opioid antagonists available on the NHS for opioid induced constipation. Additionally prucalopride and linaclotide are both available on the NHS and have been used in opioid induced constipation. | Comment noted. The comparators in the scope should constitute established clinical practice. In some instances comparators may include treatments which are used off-label for an indication (please see Guide to the methods of technology appraisal 2013, sections 6.2.1-4 for further information). Peripheral mu-opioids antagonists (methylnaltrexone and naloxone-oxycodone) have been listed as appropriate comparators for naloxegol for people in whom oral laxatives have provided inadequate relief, following advice from clnical experts at the scoping workshop. It was agreed at the scoping workshop that prucalopride and linaclotide (currently used after after peripheral mu-opioid antagonists) were not appropriate comparators because they are used later in |

| Section | Consultees | Comments | Action |
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| | | | the treatment pathway to where naloxegol is likely to be positioned. |
| | AstraZeneca UK | We are not aware of best alternative care due to lack of national guidance for the treatment of OIC with NICE making no recommendations for the treatment for OIC in its HTA or Clinical Guideline work programme.<br>oral laxative treatment without naloxegol<br>rectal interventions (e.g. suppositories and enemas)<br>manual evacuation – the treatment to treat pharmacologically has already been made and we would question whether manual evacuation is an appropriate comparator for naloxegol<br>Prucalopride – currently licensed for chronic idiopathic constipation, however there has been some use in OIC due to the high unmet need.<br>Lubiprostone – included in NICE's work programme for OIC with guidance expected in October 2014<br>Methylnaltrexone – was on NICE's work programme (ID2) and the appraisal is now terminated and therefore would not be an appropriate comparator. | Comment noted. It was agreed at the scoping workshop that there is no clear treatment pathway for constipation. A request for a clinical guideline on constipation was noted in the report to the Department of Health.<br>Comparators in the scope should constitute established clinical practice. In some instances comparators may include treatments which are used off-label for an indication (please see Guide to the methods of technology appraisal 2013, sections 6.2.1-4 for further information).<br>Peripheral mu-opioids antagonists (methylnaltrexone and naloxone-oxycodone) have been listed as appropriate comparators for naloxegol for people in whom oral laxatives have provided inadequate relief, following advice from clnical experts at the scoping workshop. It was agreed at the scoping workshop that prucalopride and linaclotide (currently used after after peripheral mu-opioid antagonists) were not appropriate comparators because they are used later in the treatment pathway to where naloxegol is likely to be positioned. |
| | British Pain Society | A simple comparison of Naloxegol alone with standard oral laxatives without Naloxegol may not reveal the full potential cost effectivenes of the new medication (assuming it is relatively expensive). This is because there is likely to be a relatively high incidence of non-opioid induced constipation in any study population and these patients would not be expected | Comment noted. Technology appraisals make recommendations on the use of new and existing medicines and treatments within the NHS and these recommendations are based on a review of clinical and economic evidence. No clinical trials are carried out as part of a |

| Section | Consultees | Comments | Action |
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| | | to respond to Naloxegol without standard laxatives - the sensitivity of the study would thus be reduced.<br>Also, a proportion of patients who take strong opioids do not develop constipation and these patients would be exposed to the treatment and cost of the treatment without benefit and with the risk of side effects.<br>An alternative pragmatic study that assessed the benefit of Naloxegol as second line to an agreed first line regime of simple laxatives would avoid these limitations.<br>Early thought should be given to blinding - assuming that RCT is proposed - because simple laxatives may be bulky (sachets and powders) and one of the advantages of the new technology will be that it is a small tablet or capsule.<br>Subcutaneous methylnaltrexone could also be considered as a comparator. | technology appraisal. For further details please see Guide to the methods of technology appraisal 2013.<br>Peripheral mu-opioids antagonists (methylnaltrexone and naloxone-oxycodone) have been listed as comparators for naloxegol in the scope. |
| Outcomes | BSG/RCP | Under adverse outcomes this might include reduced analgesic efficacy and any systemic opioid withdrawal side effects | Comment noted. Following comments from consultation and agreement at the scoping workshop, the outcomes section in the scope has been expanded and the following outcomes have been included: response rate, upper gastrointestinal symptoms including nausea, and effects on analgesia. |
| | AstraZeneca UK | We would recommend including the following additional outcomes<br>• Responder rates<br>• Time to first post dose laxation<br>• Discontinuation rates<br>Modify adverse effects to adverse events to accurately reflect outcomes being collected. | Comment noted. Following comments from consultation and agreement at the scoping workshop, the outcomes section in the scope has been expanded and the following outcomes have been included: response rate, upper gastrointestinal symptoms including nausea, and effects on analgesia. It was agreed at the scoping workshop that time to first post-dose laxation is not a clinically relevant outcome for naloxegol and |

| Section | Consultees | Comments | Action |
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| | | | discontinuation rates is already covered by use of rescue medication or interventions in the scope. |
| | British Pain Society | Yes. Hospitalisation for faecal impaction is a definitive indicator of the most severe constipation and is an expensive and inconvenient occurance that could be reduced by an effective treatment. | Comment noted. It was agreed at the scoping workshop that hospitalisation for faecal impaction would be covered in the evidence submission through resource use and should not be listed as an outcome in the scope. |
| Economic analysis | BSG/RCP | Appropriate | Comment noted. No action required. |
| | AstraZeneca UK | We are currently modelling a 1,3,5 year time horizon would be appropriate | Comment noted. No action required. |
| | British Pain Society | A suitable study duration should be agreed. It would need to be 3-6 months for cancer pain but longer if chronic benign pain is studied separately. | Comment noted. No action required. |
| Equality and Diversity | BSG/RCP | No concerns | Comment noted. No action required. |
| | British Pain Society | No issues | Comment noted. No action required. |
| Innovation | BSG/RCP | yes | Comment noted. No action required. |
| | AstraZeneca UK | Naloxegol is a first in class Peripheral Acting Mu Opioid Receptor Antagonist (PAMORA). Pegylation renders the naloxol portion of the molecule as a PgP transport substrate. The PgP transporter is located, on the blood brain barrier and transports substrates out of the CNS. Thus the PgP transporter minimizes naloxegol's ability to cross the blood brain barrier and interfere with analgesia, while not interfering with its ability to bind to GI tract opioid receptors. This novel mechanism of action will allow patient's pain relief provided by opioids not to be affected by the administration of naloxegol. | Comment noted. No action required. |
| | British Pain | Yes | Comment noted. No action required. |

| Section | Consultees | Comments | Action |
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| | Society | | |
| Other considerations | BSG/RCP | Effects on analgesic efficacy, upper gut/small bowel motility, & nausea might also be considered | Comment noted. Following comments from consultation and agreement at the scoping workshop, the outcomes section in the scope has been expanded and the following outcomes have been included: response rate, upper gastrointestinal symptoms including nausea, and effects on analgesia. |
| | AstraZeneca UK | We recommend expanding the definition of subgroups from the KODIAC study programme<br><br>— **LIR**: Self-reported moderate, severe, or very severe symptoms in ≥1 of the 4 stool symptom domains (incomplete BM, hard stools, straining, or false alarms) of the Baseline Laxative Response Status Questionnaire in patients taking ≥1 laxative class<br>for ≥4 days over a 14-day recall period immediately preceding screening<br>— **2X LIR**: Inadequate response to ≥2 laxative classes as defined above or reported unsatisfactory relief from ≥1 additional laxative class in the 6 months before screening | Comment noted. No action required. It was agreed at the scoping workshop that these definitions of people in whom laxatives have not provided adequate relief are not in line with the criteria for treatment response seen and used in clinical practice; therefore it was concluded by consultees that the subgroup in the scope should remain unchanged. |
| | British Pain Society | None | Comment noted. No action required. |
| Questions for consultation | BSG/RCP | Please see comparators section<br>Naloxegol most likely to be considered for patients failing to respond to standard laxatives | Comment noted. Naloxegol will be appraised within its marketing authorisation for opioid-induced constipation. |
| | AstraZeneca UK | We support naloxegol to be appraised under the STA process and this should enable the NHS to access naloxegol in a timely fashion. | Comment noted. No action required. |
| | British Pain | None | Comment noted. No action required. |

| Section | Consultees | Comments | Action |
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| | Society | | |
| Additional comments on the draft scope. | British Pain Society | No | Comment noted. No action required. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Healthcare Improvement Scotland
Department of Health

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

**Single Technology Appraisal (STA)**

**Naloxegol for treating opioid induced constipation**

**Response to consultee and commentator comments on the provisional matrix of consultees and commentators**

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| **Version of matrix of consultees and commentators reviewed:**<br>Provisional matrix of consultees and commentators sent for consultation | | | | | |
| **Summary of comments, action taken, and justification of action:** | | | | | |
| | Proposal: | Proposal made by: | | Action taken:<br>Removed/Added/Not included/Noted | Justification: |
| 1. | Remove Commissioning Support Appraisals Service | NICE Secretariat | | Removed | This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria Commissioning Support Appraisals Service has not been included in the matrix of consultees and commentators. |

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| 2 | Remove British Association for services to the Elderly | NICE Secretariat | | Removed | This organisation ceased to exist July 2012, therefore British Association for Services to the Elderly have been removed from the matrix of consultees and commentators. |
| 3 | Remove Research institute of the Care of Older People | NICE Secretariat | | Removed | This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Research Institute of the Care of Older People has not been included in the matrix of consultees and commentators. |
| 4. | Add Chatfield Pharmaceuticals | NICE Secretariat | | Added | Chatfield Pharmaceuticals has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |

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| 5. | Add Chelonia Healthcare | NICE Secretariat | | Added | Chelonia Healthcare has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |
| 6. | Chemidex Pharma | NICE Secretariat | | Added | Chemidex Pharma has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |
| 7. | L.C.M. | NICE Secretariat | | Added | L.C.M. has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |

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| 8. | Medreich | NICE Secretariat | | Added | Medreich has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |
| 9. | Napp Pharmaceuticals | NICE Secretariat | | Added | Napp Pharmaceuticals has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |
| 10. | Novartis Consumer Health | NICE Secretariat | | Added | Novartis Consumer Health has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |

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| 11. | Orbis Consumer Products | NICE Secretariat | | Added | Orbis Consumer Products has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |
| 12. | The Boots Company | NICE Secretariat | | Added | The Boots Company has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |
| 13. | TMC Pharma Services | NICE Secretariat | | Added | TMC Pharma Services has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators |

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| 14. | Remove Potter's Herbal Medicines UK | NICE Secretariat | | Removed | This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Potter's Herbal Medicines UK has not been included in the matrix of consultees and commentators |
| 15. | Remove Perrigo | NICE Secretariat | | Removed | This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Perrigo has not been included in the matrix of consultees and commentators |
| 16. | Remove Manx healthcare | NICE Secretariat | | Removed | This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Manx healthcare has not been included in the matrix of consultees and commentators |

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| 17. | Remove J M Loveridge | NICE Secretariat | | Removed | This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; J M Loveridge has not been included in the matrix of consultees and commentators |