National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Naloxegol for treating opioid induced constipation [ID674]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 29 January** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Definition of laxative inadequate response (LIR)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Naloxegol is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). The definition of inadequate response to laxatives that is within the products Summary of Product Characteristics and therefore accepted by the EMA is "*in the two weeks prior to first study visit patients had to have reported concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the pre study period*." It is factually incorrect to refer to the NICE definition of refractory constipation (*NICE definition indicates you would use two agents to be used at maximum dose for a sustained period (six months) before deciding that treatment had failed)* which forms part of the recommendation for lubiprostone and prucalopride in relation to naloxegol.	Reference to the NICE definition of refractory constipation should be deleted from the ERG report as it is inconsistent with the licensed indication for naloxegol and with the clinical evidence supporting the product. The NICE definition appears on pages 9 and 18.	The final scope for the naloxegol appraisal does not explicitly state the definition cited in the ERG report as a clinically appropriate population for naloxegol. In addition, the definition quoted is from previous appraisals for lubiprostone [TA318] and prucalopride [TA211] which are not listed in the final scope for the naloxegol appraisal as "Related NICE recommendations and NICE pathways"; indeed the lubiprostone STA cited is only for its appraisal within OIC. As a result, it is AstraZeneca's belief that NICE themselves neither mandated, nor recommended, the use of any past precedent for defining laxative inadequate response for the naloxegol STA. Naloxegol should be assessed in line with its licensed indication and this includes the LIR definition as defined in the SmPC. During the Scientific Advice procedure, CHMP advised that classification of patients according to baseline response to laxatives is clinically relevant and that stratification based on prior use of laxative and baseline laxative response is supported. As there is no precedent in the	**Not a factual error** The ERG quoted from the file 'Consolidated definition of laxative inadequate response' which was provided by the company.

		medical/scientific literature, professional society guidelines or in regulatory decisions for such classifications, AstraZeneca set out to construct definitions and a classification method by consulting an advisory board of 5 expert gastroenterologists and a palliative care nurse This advisory board was convened prior to protocol development and the final protocol definition was reached with the agreement of the EMA that it was acceptable. The consultants recommended a series of investigator-initiated questions to patients that would determine the patient's laxative-response status. The stool domain of the Patient Assessment of Constipation - Symptoms (PAC-SYM) questionnaire, a validated instrument for assessment of constipation symptoms, was used as the framework for forming the physician-initiated questions. The expert gastroenterologists advised the team that the stool symptoms incorporated in the PAC-SYM would be appropriate for querying treatment response to previous laxative use (incomplete bowel movements, hard stools, straining, and rectal urgency). Consistent with PAC-SYM, a 14-day recall period was chosen for the physician-initiated questions in order to minimise recall bias.	

		Unlike the PAC-SYM, the guided interview would not be a patient-reported outcome because the patient's responses are interpreted by a medical professional and because it is to be used as a baseline assessment and not as an outcome assessment. A copy of the Baseline Laxative Response Status Questionnaire (BLRSQ) was provided in Section 10.17 (Appendix 17: Guidelines for determination of laxative response status) of the naloxegol STA submission. Subsequent to these consultations, a definition of LIR was developed for use in the clinical trial programme, based on inadequate response to laxatives as recorded on the 14-day LIR questionnaire (see Figure 1). The classification and the approach used to designate and assign patients into 1 of the 3 LIR/LAR/LUR categories (14-day LIR assessment questionnaire) are used to stratify patients into treatment arms in the naloxegol pivotal trials. Treatment response among LIR patients was 1 of the key secondary endpoints The LIR definition used for KODIAC 4 and 5 therefore ensured that patients had trialled laxatives i.e. were inadequate responders, and were appropriate for a trial of naloxegol but without the need to persevere on standard laxatives for weeks or months.	

		Unlike functional constipation when the underlying cause is uncertain, opioid induced constipation has a very clear causal relationship to the initiation of opioid analgesia. It could therefore be considered illogical and indeed unethical to trial patients on conventional laxatives over several months when a medication with a mode of action that clearly acts to reverse the action on opioids in the gut is available.	

Issue 2 Quote in CS: OIC occurs in approximately 45-80% of patients receiving opioids for non cancer pain

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG believes that the quote *'OIC occurs in approximately 45–80% of patients receiving opioids for non-cancer pain'*[13-15], in Section 2.2, is misleading and the percentage should be 45-57%, according to the references quoted by the company and references identified by the ERG.[16] [13] Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. *Pain Med* 2009;10(1):35-42. [14] Cook SF, Lanza L, Zhou X, Sweeney CT, Goss D, Hollis K, et al. *Aliment Pharmacol Ther* 2008;27(12):1224-32. [15] Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. *Neurogastroenterol Motil* 2010;22(4):424-30, e96. .	The ERG belief that the data range is different to that presented by AstraZeneca should be deleted from the report.	The range given in the CS is valid and supported by the three references provided and AstraZeneca is uncertain how the ERG has arrived at its conclusion that the correct range is 45 to 57%. The upper end of the range is from the paper by Bell which gives a value of 81% of patients on opioids for non-cancer pain developing constipation. There is also a value of 45% of patients who report <3 bowel movements per week which is one definition of constipation but fails to consider the wider range of toher symptoms that contribute to constipation, see NICEs own definition. The other two references (Cook and Tuteja) both provide figures for the number of patients experiencing OIC of 57% and 47% respectively without any further clarification as to the definition of constipation nor any data on the number of weekly bowel movements. Tuteja reports 47% with constipation and again no information on <3BMs per week. It is therefore counterintuitive to accept the broadest constipation term from two papers but restrict it to	**No change needed.** The ERG believes that 45-57% is more likely to be correct based on a definition of less than 3 bowel movements per week.

		a tighter and limited definition for a third paper. Furthermore the reference used in the ERG report ([16] Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. *Neurogastroenterol Motil* 2014;26(10):1386-95) is not original research (unlike the references provided in the CS) but a review that refers to original research.	

Issue 3 LIR definition – unclear how this definition was developed

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 18 of the ERG report it states that the ERG, even after clarification was sought, was unclear as to how the definition of LIR used in the KODIAC 4 and 5 trials was arrived at. The ERG appear to challenge the fact that the definition that is within the naloxegol CS	The wording on page 18 "(even after clarification was sought)" should be deleted. The clarification questions received from ERG did not seek clarification on how the LIR definition was developed but did seek clarification as to why the NICE definition was not used (question 9). .	The development of the LIR definition used in the KODIAC 4 and 5 trials was explained in the original submission (see section 6.3.7). The following information should further aid the ERG's understanding of how the LIR definition was developed. The LIR definition used in the KODIAC 4 and 5 studies, and a tool for its assessment, was developed following consultation with an advisory board of external experts. This advisory board was convened prior to protocol development and the final protocol definition was reached with the agreement of the	**Not a factual error**

		EMA that it was acceptable. Unlike functional constipation when the underlying cause is uncertain, opioid induced constipation has a very clear causal relationship to the initiation of opioid analgesia. It could therefore be considered illogical and indeed unethical to trial patients on conventional laxatives over several months when a medication with a mode of action that clearly acts to reverse the action on opioids in the gut is available. The LIR definition used for KODIAC 4 and 5 therefore ensured that patients had trialled laxatives i.e. were inadequate responders, and were therefore appropriate for a trial of naloxegol but without the need to persevere on standard laxatives for weeks or months.	

Issue 4 Bisacodyl usage in OIC confirmation phase of KODIAC 4 and 5 trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 18 of the ERG report it states that clarification was sought from the company to identify what proportions of patients in the KODIAC trials were receiving high dose of bisacodyl. The report goes on to state that the majority of patients were	The text around the LIR definition should be separated from the text on bisacodyl usage in the KODIAC 4 and 5 trials as these two items are not directly related.	The bisacodyl dosage information provided in response to an ERG clarification question related to usage during the OIC confirmatory phase of the study (i.e. the two weeks between recruitment and randomisation). However this usage did not affect the LIR	**Not a factual error** From the information provided, the ERG believes that a proportion of patients were classified as non-responders based on a relatively low dose of bisacodyl.

receiving ≥15 mg/day rather than ≥30 mg/day and that based on all this evidence it would appear that the definition of LIR used by the company is a minimal definition of criteria for LIR. The reference to the bisacodyl dose being used is unclear as to whether it applies to the OIC confirmation phase of the study or when it is being used as rescue medication.		assessment which was documented for the two weeks prior to the recruitment visit. As currently written in the ERG report there is suggestion of a link between bisacodyl usage in the OIC confirmatory period and the assessment of a patient's LIR status when in fact no such link exists.	

Issue 5 Use of language such as "anticipated" or "intended" in relation to naloxegol's licensed indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 10 the ERG report states, "and anticipated licensed population", as well as similar language on page 28, "reflect the intended license". Though AstraZeneca recognise that at the time of original submission on November 7th 2014 this was factually accurate, the use of such anticipatory and conditional wording is no longer necessary given the EC approved an indication of naloxegol as of December 2014. As this report is dated completed 21/01/2015 all references to a license should be to an approved indication.	All references to "anticipated", "intended" or synonyms thereof should be removed and the license or indication referred to definitively rather than conditionally as "the licensed population" or "the license".	Though the ERG report highlights EC approval, e.g. page 17, the use of conditional, anticipatory language has the potential to mislead and cause readers to assume the patient population or the license of naloxegol is not final and may still be mutable. As EC approval has been granted in a clearly defined licensed population this is not the case and any potential for confusion can be avoided.	**Not a factual error** Quoted from the CS and the ERG report clearly states the EC approval (e.g. page 17).

Issue 6 Generalisability for the OIC Cancer patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg 11 and Pg 98 of the ERG report -the ERG thinks it is questionable to assume that efficacy (as demonstrated in previous studies of methylnaltrexone and naloxone-oxycodone, in Section 1.4 in the CS), safety and utility estimates (as they include a time and treatment effect interaction) could be kept similar for cancer pain patients. For simplicity reasons, the company maintained the efficacy, AE rates and all transition probabilities (A, B, C, D and E) the same as non-cancer population. Hence, the ERG does not believe that the current model is generalisable to cancer patients based on current model inputs & assumptions.	Suggest adding "However the CHMP has granted naloxegol a licensed indication to be used in cancer patients for there is no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in patients with cancer pain to those with non-cancer pain."	In the absence of data on the treatment of OIC in cancer pain patients, the CHMP asked AstraZeneca to justify the extrapolation of the available efficacy and safety data in OIC non-cancer patients to the treatment of OIC patients with cancer pain. In assessing the available evidence, the CHMP considered that AstraZeneca had attempted to conduct a Phase III, multicentre, global study dedicated to assessing the efficacy and safety of naloxegol in patients with cancer related pain and OIC (KODIAC 6). However, severe recruitment difficulties meant the study had to be terminated early with only 14 of the required 366 patients randomised. It was also discussed that there is no published evidence that opioid receptor pharmacology, density or location in cancer pain patients is substantially different from that of non-cancer pain patients. Thus, AstraZeneca presented their position that there is no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in patients with cancer pain to those with non-cancer	**Not a factual error** On page 98, the ERG made this remark in the context of the health economic model. While it is possible that the response rate for cancer patients is the same as for non-cancer patients, there might be important differences in for example the transitions between OIC and non-OIC (untreated) due to differences in mobility, activity level, diet and concomitant medications. In addition, it appears unreasonable to assume that the utility estimates for the various health states are the same in patients with and without cancer. Hence, the ERG maintains its view that the current model inputs cannot be generalised to cancer patients.

		pain. This is supported by data from other peripherally acting mu-opioid receptor antagonist (PAMORAs) which showed no decrease in efficacy in patients with OIC and cancer pain compared with patients with OIC and non-cancer pain: two Phase III studies using methylnaltrexone administered subcutaneously to treat patients with OIC and advanced illness (59% and 81% had cancer pain; (1, 2) and one Phase II study using oral oxycodone/naloxone prolonged-release to treat OIC patients with moderate/severe cancer pain (3). Furthermore, in one of the studies (2) a logistic regression analysis of methylnaltrexone-treated patients found that rescue-free laxation within 4 hours of the first dose did not vary according to diagnosis (cancer/non-cancer). In addition, there were no substantial differences in the safety profiles of these drugs in patients with cancer pain compared with patients with non-malignant pain (2, 3). 1. Slatkin N, Thomas J, Lipman AG, Wilson G, Boatwright ML, Wellman C, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol. 2009 Jan-Feb;7(1):39-46. 2. Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med. 2008 May 29;358(22):2332-43. 3. Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A	

		randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliat Med. 2012 Jan;26(1):50-60	

Issue 7 Description of NICE Clinical Knowledge Summaries as recommendations

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 17 the ERG report states, "there are online recommendations by NICE for treatment of opioid induced constipation and palliative care constipation". Referring to these both as recommendations, in addition to the suggestion of bespoke recommendations is erroneous. Though AstraZeneca recognise that a Clinical Knowledge Summary for Constipation exists, per the NICE website these are: "…the NICE CKS service which provides primary care practitioners with a readily accessible summary of the current evidence base and practical guidance on best practice in respect of over 330 common and/or significant primary care presentations. Given this, it is misleading to refer to the CKS as a "recommendation".	There is a NICE Clinical Knowledge Summary (CKS) online for Constipation, which contains a section focussed on opioid-induced constipation" and contained in CG140: Opioids in palliative care, there is section entitled "Management of Constipation" which provides recommendations.	The existing wording of the ERG report has the potential to mislead and cause readers to believe that NICE has issued bespoke Clinical Guidelines for opioid-induced constipation both broadly and in palliative care. As this is not the case, the wording of the report should more accurately reflect that one reference is a Clinical Knowledge Summary of Constipation with a section relating to opioid-induced constipation, and this is not the same as a "recommendation" given the remit of the CKS, and that the other reference is to a broader Clinical Guideline relating to the use of opioids in palliative care. AstraZeneca consider this to be of particular importance owing to feedback during market research, advisory boards and meetings with external scientific experts, as well as literature searches, which point to the lack of clear recommendations	**Not a factual error.** Source clearly referenced.

Moreover, the CKS should be appropriately described as it is for Constipation and contains a brief section on opioid-induced constipation particularly given that NICE's own scoping for the naloxegol HTA defined opioid-induced constipation as suitably distinct from chronic idiopathic constipation to not warrant an MTA. Additionally, though referred to as "palliative care constipation" this relates to CG140 Opioids in palliative care" and should be referenced accordingly.		for opioid-induced constipation in the UK. Indeed, given the ERG accept on page 16 that the "lack of consensus on a definition of OIC appears to be correct", this would appear to reinforce the lack of clear recommendations and guidelines for OIC.	

Issue 8 Reference to the bowel function diary as an outcome in the final scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 20 the ERG report states that "compared to the final scope some outcomes were not clearly considered and/or reported in the CS, eg...bowel function diary". The bowel function diary referenced is not listed in the NICE final scope for naloxegol: https://www.nice.org.uk/guidance/gid-tag458/documents/constipation-opioidinduced-naloxegol-final-scope-2 Moreover, this is statement is not	Deletion of "and bowel function diary" so that the statement on page 20 reads "...not clearly considered and/or reported in the CS, eg effects on analgesic efficacy and PAC-SYM."	The existing statement in the ERG report suggests AstraZeneca has not reported data in-line with the final scope, which the ERG highlight on page 24 not to be the case. The creates an erroneous impression of both the final scope, the AstraZeneca submission as well as the KODIAC trial programme because the bowel function diary was not utilised during the studies referenced in the CS.	**Not a factual error** a) Bowel function diary is a way of measuring "symptoms of constipation" (which is an outcome defined in the final scope). b) The statement on page 24 was not cited in full and reads: "The outcomes in the CS match the outcomes

internally consistent with the ERG's report as on page 24 section 3.4 states the "outcomes in the CS match the outcomes described in the final scope".		Though AstraZeneca accept the relevance of reporting the instrument exists it would be more appropriate to highlight that it was not used in the KODIAC trials and so data from it is unavailable only.	described in the final scope ('frequency of spontaneous bowel movements; symptoms of constipation; use of rescue medication or interventions; response rate; upper gastrointestinal symptoms including nausea; effects on analgesic efficacy; adverse effects of treatment; health-related quality of life'). However, as detailed in Section 2.2 of this report, some outcomes were not considered or discussed in the CS."

Issue 9 Clarification of KODIAC data used in MTC/indirect comparisons

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG correctly identifies an inconsistency between the data provided and the data used in the MTC analysis and indirect comparisons. The MTC analyses were conducted with LIR subgroup data from the KODIAC data, as intended. However, Table 45 of the CS incorrectly provides the ITT data from the KODIAC trials.	The submission should be revised to reflect the accurate KODIAC data used in the MTC analyses (Revised Table 45 provided below).	The clarification regarding what data is used is important to the interpretation of the MTC and indirect comparisons. This will allow the ERG to replicate these analyses.	**Not a factual error** The ERG has rerun the MTC analyses using the corrected data for LIR populations from Kodiac 4 and 5 as provided in Revised Table 1. We were able to confirm the results for the following outcomes: SBM response, CSBM response and DAEs. However, we were unable to confirm the results for mean change in SBMs per week as Table 1 does not provide the standard deviation or standard error to accompany

			the reported mean. We could also not confirm results for TEAEs as the results table in the CS (table 50) contains results for Methylnalterxone versus placebo, however, the revised data in Table 1 does not contain the raw data for these comparisons. It only gives results for Naloxegol versus placebo. The ERG was previously unable to check the MTC results as the original company's submission provided data for the wrong populations (ITT only, not the LIR subgroups from Kodiac 4 and 5). However, the value of the MTC is undermined by the comparison of two different populations, i.e. the LIR subpopulation for the naloxegol trials vs. the whole population for the other trials.

Issue 10 CS criteria match the scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 5 states that the outcomes analyzed in MTC/indirect analyses do not match the broader criteria of the scope.	An accurate statement is that it "Partially" matches the criteria for the scope.	Several of the outcomes listed were analyzed. Inclusion of the word 'partially' may provide further transparency as to the outcomes included within the scope and meeting the criteria.	**Not a factual error**

Issue 11 Inclusion of active-controlled trials in the MTC/indirect comparisons

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on pages 33, 43, and 106 that active-controlled trials (non-placebo controlled trials) were excluded from the review and analysis. The full inclusion criteria were any studies reporting on an intervention/comparator, that compare to any of those interventions/comparators, placebo, or best supportive care. Active-controlled trials were not included in analysis, because none were identified by the search.	Statements that the MTC analyses are missing potential indirect trial connections should be removed.	Need to clarify that all studies eligible for the evidence network were searched for and would have been included, if they existed.	**Not a factual error.** It was unclear in the CS.

Issue 12 Clarification of excluded study (CLB FNB naloxone PR study) from MTC/indirect comparisons

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 33 that CLB FNB naloxone PR study was incorrectly excluded for not having outcomes of interest; the report states that DAE and TEAE data were eligible. However, the DAE and TEAE data from that study were not eligible, as they were not specific to the OIC population. The CLB Naloxone study enrolled a pain population, with only a subset of	This statement should be removed.	Need to clarify that this study was not eligible for analysis.	**Not a factual error.** The response to the clarification letter stated that this study was excluded for “not having outcomes of interest” while the company now states that outcomes of interest were reported but for the wrong population.

patients having OIC (BFI ≥ 50 at visit 4). The DAE and TEAE data reported in the paper refers to the overall pain population and not the OIC subgroup population.			

Issue 13 Type of analysis provided in forest plots

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 38 that "no details were given of the actual method used in the indirect comparison" for the results presented in the forest plots. Both the appendix title and information within the plots indicate that these results are MTC analyses.	This statement should be removed.	Need to clarify that the forest plots are clear in the analysis type presented.	**Not a factual error.** Statement was not referring to forest plots. Note: Results for the Bucher indirect comparison method (table 60 to 63) are incompatible with the reported analysis method and seem to have been obtained from a Bayesian MTC model (use of credible intervals).

Issue 14 Type of indirect analyses conducted

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report implies on page 38 that Bucher analyses should be conducted. These analyses were conducted (these are the "indirect" analyses the ERG report refers to). For clarification, the MTC was utilized as this was the	This statement should be removed.	Need to clarify that Bucher analyses were conducted, as recommended by the ERG.	**Not a factual error.** See comment on issue 13.

decision made a priori for the base case. The Bucher analyses were also conducted as a sensitivity analysis given the simplistic nature of the network, as the ERG indicates.			

Issue 15 Inclusion of KODAIC 16 in MTC/indirect comparisons

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 39 that the non-randomized KODIAC 16 trial was included in the MTC. This is an error, as only KODIAC 4 and KODIAC 5 were included, among the naloxegol trials.	This statement should be removed.	Important to clarify the studies included in analysis, especially as it would not be appropriate to include a non-randomized study in an MTC analysis.	**Not a factual error**

Issue 16 Pooling of treatments in MTC/indirect comparisons

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 39 that subcutaneous and oral methylnaltrexone treatments were pooled in the MTC analysis. This may be a misinterpretation of the network diagram included in the original submission as every dose and route of administration was analyzed separately. A revised network diagram clarifying this	This statement should be removed.	Important to clarify the dosages of analyzed treatments and analysis approach.	**Not a factual error**

approach was provided in question 31 in the “AstraZeneca Response to Naloxegol Clarification Questions” document.			

Issue 17 Availability of SCBM response data from KODIAC 4 & 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 44 that an incompatible definition of SCBM response was used in the MTC analysis. . Post-hoc analyses of SCBM response were conducted in order to match with the definition in the comparator studies. The definition used was >=3 CSBM per week during weeks 1−4. (However the ITT data is incorrectly provided in the submission instead of the LIR data)	This statement should be removed.	Important to clarify that the definitions for this outcome were compatible.	**Not a factual error** It was reported incorrectly in the CS, see reply to issue 9.

Issue 18 Availability of 4 week TEAE data from KODIAC 4 & 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 44 that TEAE data from KODIAC 4 and 5 were not provided. Post-hoc analyses of KODIAC data were conducted to provide TEAE data at 4 weeks, as this timepoint was needed for the economic model (however the ITT data is	This statement should be removed.	Important to clarify that the timepoints for this outcome were compatible.	**Not a factual error.** Data and newly provided information were not available for the ERG.

incorrectly provided in Table 45 instead of the LIR data)			

Issue 19 MTC model choice

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 44 that the choice of random or fixed models for the MTC was based on the DIC and that the choice of model was inappropriate. Our response to question 34 in the "AstraZeneca Response to Naloxegol Clarification Questions" document indicated that model choice was not based on DIC alone. Furthermore, the ERG claimed that the difference between model choice was shown only for comparisons versus placebo, precludes interpretation for comparisons of the treatments against each other. As the comparisons are directly related, any changes in the placebo comparisons, would be reflected proportionately in the naloxegol comparisons, so a sense of that difference between models can be interpreted.	This statement should be removed. The statements that the model was chosen based on the DIC should be removed from the submission.	Important to clarify the justification for model choice.	**Not a factual error.** Methods and results are not described in sufficient detail in the CS and the response to the clarification letter.

Issue 20 Extraction of TEAE data from Meissner 2009

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 49 that TEAE data was available from Meissner 2009, but that extraction was not performed. This data was intentionally not included in the MTC, as adverse events reported in this paper were not specified to be treatment emergent. Furthermore, because only the 4 week data was utilized for analysis, the 12 week data would not have been provided.	This statement should be removed.	Important to clarify the data eligible for MTC analysis.	**Not a factual error** It is reported in table 11 of the ERG report which data are available.

Issue 21 Extraction of TEAE data from Lowenstein 2009

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report indicates on page 49 that TEAE data was available from Lowenstein 2009, but that extraction was not performed. This data was intentionally not included in the MTC. The TEAE data from this paper was not provided as the 12 week data did not contribute to the 4 week TEAE analyses.	This statement should be removed.	Important to clarify the data eligible for MTC analysis.	**Not a factual error** It is reported in table 11 of the ERG report which data are available.

Issue 22 Exclusion of treatments in the MTC

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg 33 of the ERG report states "This illustrates that 11 studies were excluded because the comparator was not of interest (ALKS 37, alvimopan, bevenopran, TD-1211, lubiprostone and prucalopride). The first three of these drugs are mu-opioid receptor inhibitors and should not have been excluded according to the scope."	Suggest removal of this comment	ALKS 37, alvimopan, bevenopran, TD-1211 are not available in the UK and therefore not relevant to the scope of this UK appraisal. In addition, NICE STA recommendations for lubiprostone and prucalopride were not listed within the scope as related recommendations.	**Not a factual error** To the knowledge of the ERG, availability of drugs in the UK is not considered to be valid exclusion criteria according to NICE.

Revised Table 1: Summary of results from studies used to conduct the comparisons

Outcome	Naloxegol		Methylnaltrexone		Naloxone-oxycodone			
	KODIAC 4 (LIR subgroup)	**KODIAC 5 (LIR subgroup)**	**Michna 2011 (36)**	**Rauck 2012 (40)**	**Meissner 2009 (37)**	**Lowenstein 2009 (38)**	**Simpson 2008 (39)**	**Arsenault 2014 (24)**
Mean change from baseline in SBMs/week (4–12 weeks)	Naloxegol 12.5 mg, OD, n=114: 2.6 Naloxegol 25 mg OD, n=117: 3.5 Placebo, n=118: 2.0	Naloxegol 12.5 mg, OD, n=122: 2.7 Naloxegol 25 mg OD, n=121: 3.6 Placebo, n=120: 2.2	MNTX 12 mg OD, n=150: 3.1 MNTX 12 mg QAD, n=148: 2.1 Placebo, n=162: 1.5	MNTX 150 mg OD, n=201: 1.88 MNTX 300 mg OD, n=201: 2.39 MNTX 450 mg, n=200: 2.4	-	-	-	-
SBM response† over 4 weeks (%)	Naloxegol 12.5 mg, OD, n=114: 45.22% Naloxegol 25 mg OD, n=117,: 45.30% Placebo, n=118: 27.97%	Naloxegol 12.5 mg, OD, n=122: 37.60% Naloxegol 25 mg OD, n=121: 34.68% Placebo, n=120: 24.79%	MNTX 12 mg OD, n=150: 58.7% MNTX 12 mg QAD, n=148: 45.3% Placebo, n=162: 38.3%	-	-	-	-	-
CSBM response‡ at 4 weeks (%)	Naloxegol 25 mg OD, n=117,: 35.04% Placebo, n=118: 22.03%	Naloxegol 25 mg OD, n=121: 41.32% Placebo, n=120: 18.33%	-	-	-	Naloxone PR/Oxycodone PR FRC OD, n=130: 51% Placebo, n=135: 26%	Naloxone PR/Oxycodone PR FRC OD, n=162: 65% Placebo, n=160: 39%	Naloxone /Oxycodone PR 60 or 80 mg BD, 29.5% Placebo, 15.6%
DAEs, 4-12 weeks (%)	Naloxegol 12.5 mg, OD, n=114: 4.4% Naloxegol 25 mg OD, n=117,: 9.4% Placebo, n=118: 4.2%	Naloxegol 12.5 mg, OD, n=123: 2.4% Naloxegol 25 mg OD, n=124: 10.5% Placebo, n=120: 5.8%	MNTX 12 mg OD, n=150: 6.7% MNTX 12 mg QAD, n=148: 8.8% Placebo, n=162: 2.5%	-	Naloxone 10 mg BD, n=51: 9.8% Naloxone 20 mg BD, n=51: 11.8% Naloxone 40 mg BD, n=50: 18%	Naloxone PR/Oxycodone PR FRC OD, n=130: 5.4% Placebo, n=135: 3%	Naloxone PR/Oxycodone PR FRC OD, n=162: 4.9% Placebo, n=160: 11.3%	-
TEAEs, 4 weeks (%)	Naloxegol 12.5 mg, OD, n=114: 30.7% Naloxegol 25 mg, OD, n=117: 47% Placebo, n=118: 32.2%	Naloxegol 12.5 mg, OD, n=123: 40.7% Naloxegol 25 mg, OD, n=124: 54% Placebo, n=120: 36.7%	-	-	-	-	-	-

Abbreviations: BD, twice daily; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse event; FRC, fixed ratio combination; MNTX, methylnaltrexone; OD, once daily; PR, prolonged release; QAD, every other day; SBM, spontaneous bowel movement;
† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period. ‡ Defined as the proportion of patients with ≥3 CSBMs/week at four weeks