

Naloxegol for treating opioid-induced constipation

Technology appraisal guidance

Published: 22 July 2015

www.nice.org.uk/guidance/ta345

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1 Recommendations

- 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.

2 The technology

- 2.1 Naloxegol (Moventig, AstraZeneca) is a form of naloxol which has been pegylated (that is, attached to a molecule of polyethylene glycol, or PEG). In this form, it selectively antagonises peripheral opioid receptors to relieve constipation. 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 severity while taking at least 1 laxative class for a minimum of 4 days during the last 2 weeks. The European public assessment report for naloxegol provides further clarification regarding the definition of an inadequate response to laxatives. It states that a person must have been taking 1 laxative class for a minimum of 4 days out of the 14 days prior to the screening visit and report moderate, severe, or very severe symptoms in at least 1 of the 4 stool symptom domains.
- 2.2 The most commonly reported adverse reactions to naloxegol are abdominal pain, diarrhoea, nausea, headache and flatulence. The majority of gastrointestinal adverse reactions are graded as mild to moderate, occur early in treatment and resolve with continued treatment. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 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.

3 The company's submission

The [Appraisal Committee](#) considered evidence submitted by AstraZeneca and a review of this submission by the [Evidence Review Group](#) (ERG).

Clinical effectiveness

- 3.1 The main clinical evidence for naloxegol came from the pivotal phase 3 trials KODIAC 4 (n=649) and KODIAC 5 (n=697). These were international, multicentre, randomised, double-blind, placebo-controlled trials comparing naloxegol with placebo in adults with non-cancer pain and opioid-induced constipation (OIC). Patients included in the trials had a stable maintenance opioid regimen for non-cancer related pain for a minimum of 4 weeks, and reported less than 3 spontaneous bowel movements (SBM) per week in the 2 weeks before screening. In addition, patients reported at least 1 of the following symptoms: Bristol Stool Scale stool type 1 or 2; moderate severe or very severe straining; incomplete bowel movement (BM), in at least 25% of BMs recorded in the patient's electronic diary during the OIC confirmation period. The 2 trials excluded patients having opioids for cancer-related pain.
- 3.2 In both trials, patients were randomised in a 1:1:1 ratio to either naloxegol 12.5 mg, naloxegol 25 mg or placebo once daily for 12 weeks. Patients were allowed to continue their baseline opioid pain control regimen with doses adjusted according to clinical need. They were also allowed to have bisacodyl rescue laxative if they had not had a bowel movement in 72 hours or more. The proportion of patients in the naloxegol 25 mg arm who used bisacodyl at least once was 54.7% (KODIAC 4) and 57.3% (KODIAC 5). In the placebo arm, these proportions were 72% and 70.7% respectively. No other laxatives were allowed in the trials.
- 3.3 Before the studies, the company defined several subgroups in terms of response to laxatives at baseline, using the baseline laxative response status questionnaire. The categories defined by the company were as follows:
- Laxative inadequate responder (LIR): people who were taking 1 or more laxative class for at least 4 days before screening and reported moderate,

severe or very severe symptoms in at least 1 of the 4 stool symptom domains (that is, incomplete BMs, hard stools, straining or false alarms). Around half of the clinical trial populations (54.6% in KODIAC 4 and 53.2% in KODIAC 5) were classified as laxative inadequate responders. This is the group covered by naloxegol's marketing authorisation.

- Laxative adequate responder (LAR): people whose constipation responded adequately to laxatives taken at least 4 days before screening and who reported mild or no symptoms.
- Laxative unknown responder (LUR): people who had not had laxatives in the last 2 weeks or had taken laxatives for less than 4 days in the last 2 weeks.

3.4 An additional subgroup was defined as the 2xLIR population. These were people who met the criteria for LIR but had at least 2 laxatives classes, or reported unsatisfactory relief from 1 or more additional laxative class taken during the 6 months before screening.

3.5 The company also conducted a post-hoc analysis of the LIR+step-3 opioids subgroup, comprising patients in the LIR population who had step-3 opioids (classified according to the World Health Organisation analgesic ladder). The company stated that this is a clinically valid subgroup of patients with OIC, because the more severe forms are more likely to be related to the use of step-3 opioids.

3.6 The primary outcome of the KODIAC 4 and 5 studies was response to treatment, defined as the proportion of patients with 3 or more SBMs per week, with improvement from baseline of 1 or more SBM per week for at least 9 of 12 weeks and 3 of the last 4 weeks of the study. SBM was defined as a bowel movement without using laxatives in the last 24 hours). The company stated that SBM frequency is a clinically meaningful measure commonly employed in clinical research to assess the efficacy of a treatment for chronic constipation.

3.7 The main secondary outcomes included:

- response to treatment (as defined for the primary outcome) in the LIR population only

- time to first post-dose SBM without the use of rescue medication in the last 24 hours
- mean number of days per week with at least 1 SBM.

- 3.8 In both KODIAC trials, treatment with naloxegol 25 mg (the recommended dose for all patients except those with renal insufficiency) resulted in significantly higher response rates than placebo in both the overall population (KODIAC 4: 44.4% compared with 29.4%, $p=0.001$; KODIAC 5: 29.3% compared with 39.7%, $p=0.021$) and the LIR population (KODIAC 4: 48.7% compared with 28.8%, $p=0.002$; KODIAC 5: 46.8% compared with 31.4%, $p=0.014$). In both studies, naloxegol showed consistent improvements in a range of secondary end points, including time to first post-dose SBM, total SBMs per week, number of days per week with at least 1 SBM and use of rescue medication at least once over the treatment period. The 3 instruments used by the company to measure quality of life (PAC-SYM, PAC-QoL and EQ-5D) also showed advantages with naloxegol compared with placebo.
- 3.9 There were no differences in adverse events between the overall and LIR populations. The most frequently reported adverse events were gastrointestinal in nature (predominantly diarrhoea, abdominal pain, nausea and flatulence); this is to be expected, considering the nature of OIC and naloxegol's pharmacological mechanism of action. Gastrointestinal adverse events were more frequent in the naloxegol 25 mg arms compared with naloxegol 12.5 mg and placebo. There were no notable differences in type or frequency of serious adverse events across the treatment arms of the studies. The incidence of discontinuations because of adverse events was dose-related, with a higher proportion of patients discontinuing in the naloxegol 25 mg arm compared with those having naloxegol 12.5 mg and placebo. The discontinuation rate with the longer-term use of naloxegol (52 weeks, as observed in KODIAC 8) was similar to that seen in the 12-week studies, KODIAC 4 and 5.

Mixed treatment comparison

- 3.10 The company conducted a mixed treatment comparison of naloxegol with methylnaltrexone and naloxone-oxycodone using data from KODIAC 4 and 5, 2

methylnaltrexone trials and 4 naloxone-oxycodone trials. All 8 trials compared the active treatments with placebo. The company stated that only the naloxegol trials were able to provide data in the specific patient populations of interest, namely the LIR (covered by the marketing authorisation) and the LIR+step-3 opioids subgroups. As none of the other studies reported data specifically for these 2 subgroups, the company used the main trial populations in these comparator studies to inform the mixed treatment comparison analyses.

Table 1 Summary of trials included in the mixed treatment comparison

Treatment, study, trial design and duration	Patient population	Treatment and dose	Outcomes used in the mixed treatment comparison
Naloxegol:	OIC patients with non-malignant pain. Only data from the LIR and LIR+step-3 opioid subgroups included in the mixed treatment comparison, n=349	Naloxegol 12.5 mg OD, n=114 Naloxegol 25 mg OD, n=117 Placebo OD, n=118	Mean change from baseline in SBMs per week SBM response (%) CSBM response DAEs (%) TEAEs (%)

Treatment, study, trial design and duration	Patient population	Treatment and dose	Outcomes used in the mixed treatment comparison
Naloxegol:	OIC patients with non-malignant pain. Only data from the LIR and LIR+step-3 opioid subgroups included in the mixed treatment comparison, n=372	Naloxegol 12.5 mg OD, n=122 Naloxegol 25 mg OD, n=121 Placebo OD, n=120	Mean change from baseline in SBMs per week SBM response (%) CSBM response DAEs (%) TEAEs (%)
Methylnaltrexone: Michna (2011):	OIC patients with non-malignant pain, n=469	Methylnaltrexone 12 mg, n=150 Methylnaltrexone 12 mg (once every other day), n=148 placebo, n=162	Mean change from baseline in SBMs per week SBM response (%) DAEs (%) TEAEs (%)

Treatment, study, trial design and duration	Patient population	Treatment and dose	Outcomes used in the mixed treatment comparison
Methylnaltrexone: Rauck (2012):	OIC patients with non-malignant pain, n=804	Methylnaltrexone 150 mg, n=201 Methylnaltrexone 300 mg, n=201 Methylnaltrexone 450 mg, n=201 placebo, n=201	Mean change from baseline in SBMs per week
Naloxone-oxycodone: Meissner et al. (2009): phase 2, double-blind RCT, 4 weeks	OIC patients, 2.9% with malignant and 97.1% with non-malignant pain, n=202	Naloxone 10 mg, n=51 Naloxone 20 mg, n=51 Naloxone 40 mg, n=50 Placebo, n=50	DAEs (%)
Naloxone-oxycodone: Lowenstein (2009): phase 3, double-blind RCT, 12 weeks	OIC patients with lower back pain, n=278	Naloxone-oxycodone, n=130 Placebo, n=135	CSBM response DAEs (%)
Naloxone-oxycodone: Simpson (2008): phase 3, double-blind RCT, 12 weeks	OIC patients with non-malignant pain, n=322	Naloxone-oxycodone, n=162 Placebo, n=160	CSBM response DAEs (%)
Naloxone-oxycodone: Arsenault (2014): randomised, double-blind, cross-over study, 5 weeks	OIC patients with chronic non-malignant pain, n=59	Naloxone-oxycodone Placebo	CSBM response

Note: treatments were given once daily unless otherwise stated.

Abbreviations: CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse event; NR, not reported; OD, once a day; OIC, opioid-induced constipation; RCT, randomised controlled trial; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.

- 3.11 The treatments evaluated in the mixed treatment comparison showed improved outcomes compared with placebo, which reflected the individual trial results. Generally, naloxegol 25 mg demonstrated improved outcomes when compared with methylnaltrexone, and naloxone-oxycodone. None of these analyses yielded statistically significant results.
- 3.12 The results of the mixed treatment comparison suggested that methylnaltrexone and naloxone-oxycodone as well as naloxegol were more likely than placebo to lead to discontinuations because of adverse events or treatment-emergent adverse events. Naloxegol 25 mg had a similar or lower rate of discontinuations because of adverse events compared with all methylnaltrexone and naloxone regimens evaluated, except when it was compared with naloxone-oxycodone. Treatment-related adverse effects were more likely with naloxegol 25 mg than with subcutaneous methylnaltrexone, but this was not statistically significant.

Evidence Review Group comments

- 3.13 The ERG commented that some studies that were potentially relevant may have been omitted from the mixed treatment comparison because of how the company defined and adhered to the criteria in its literature search. For example, the difference in population specification between the scope and the company's submission (that is, limiting the naloxegol studies in the submission to the LIR subgroup) is likely to have reduced the number of studies included.
- 3.14 The ERG stated that insufficient details were presented for comparator study design, quality and data. It stated that the definition of rescue treatment varied between trials and there was not enough information to judge the similarity of the rescue treatments used. It also noted that the company did not present details of the baseline characteristics for the comparator studies, thereby preventing any further assessment of their similarities. The ERG felt that these limitations prevented further analyses based on baseline characteristics (for pain intensity, opioid dose, duration of opioid use, duration of OIC and previous laxative use).
- 3.15 The ERG questioned the reliability of the mixed treatment comparison because it compared the LIR population only from KODIAC 4 and 5 with the overall population from the comparator studies. The ERG conducted its own exploratory

analyses using the overall populations from all trials, including KODIAC 4 and 5. The results of these analyses were similar to the company's results, which the ERG felt suggested there were unlikely to be any major differences between the LIR and intention-to-treat populations. However, it questioned whether combining the 2 populations in a mixed treatment comparison as the company had, could be clinically justified. The ERG stated that overall there was no robust evidence to distinguish the relative efficacy and safety between naloxegol and the comparators of interest.

Cost effectiveness

- 3.16 The company constructed a decision-analytic model comparing the cost effectiveness of naloxegol 25 mg with several comparators for OIC that has responded inadequately to laxatives (that is, the population covered by the marketing authorisation). The comparator for the base-case analysis was placebo (as in the pivotal clinical trials KODIAC 4 and 5), whereas methylnaltrexone was used in a scenario analysis. The company also presented an analysis of the LIR+step-3 opioids subgroup, in which the comparators were placebo, methylnaltrexone and naloxone-oxycodone.
- 3.17 The company presented 2 additional analyses which it considered to be the most clinically relevant comparisons (based on clinical guidance from an advisory board and company-sponsored research):
- Naloxegol compared with placebo plus bisacodyl (where bisacodyl was a proxy for using stimulant laxatives as needed).
 - Naloxegol plus bisacodyl compared with placebo plus bisacodyl (to demonstrate the cost effectiveness of naloxegol when used with a stimulant laxative).
- 3.18 The company's economic model comprised a decision-tree structure for the first 4 weeks of treatment, followed by a Markov structure. All patients entered the model with OIC and were treated with naloxegol or a comparator. Response to treatment was assessed after 4 weeks, with people being classified as responders if they achieved constipation relief and as non-responders if they did

not.

3.19 The Markov model consisted of 4 health states: opioid-induced constipation (OIC), non-OIC (on treatment), non-OIC (untreated) and death. OIC and non-OIC were defined as follows:

- OIC: less than 3 SBMs per week in at least 2 of the last 4 weeks.
- Non-OIC: 3 or more SBMs per week in at least 3 of the last 4 weeks.

The company justified this change from the clinical definition of OIC because it corresponds with internationally accepted definitions of constipation (although these were not specified) and helped to simplify the model by allowing utility and resource to be estimated as a function of constipation status, rather than a change in that status. People whose constipation responded to treatment after 4 weeks entered the Markov phase of the model in the non-OIC (on treatment) health state, whereas those who did not respond to treatment by week 4 entered in the OIC health state. People may move between the OIC and non-OIC state in the model even in the absence of effective treatment. The company stated that clinical expert opinion and trial data suggested that patients in the placebo arm moved between the OIC and non-OIC states.

3.20 The time horizon in the company's base case was 5 years. The company felt this reflected the upper end of a period of opioid use and the model suggested that it reaches a steady state within that period. Scenario analyses were done using several other time horizons to test the effect on cost effectiveness. The cycle length was 4 weeks and a half-cycle correction was applied. The company applied a discount of 3.5% for costs and benefits and adopted an NHS/personal social services perspective.

3.21 The proportion of people in the non-OIC (on treatment) state of the model was estimated based on response rates derived from the KODIAC 4 and 5 trials. For the comparisons with methylnaltrexone and naloxone-oxycodone, the outcomes of the mixed treatment comparison were used. To estimate transitions from the non-OIC (on treatment) state to the OIC state, the company conducted parametric survival analyses based on data from the KODIAC trials; this informed the prediction of how many patients remained in the non-OIC (treated) health

state for 5 years. The exponential distribution was used for both arms in the base case. For the comparisons with methylnaltrexone and naloxone-oxycodone, the curves were estimated based on the naloxegol curve, assuming proportional hazards and using the hazard ratios estimated from the mixed treatment comparison. The company also did a scenario analysis in which the hazard ratio for methylnaltrexone compared with naloxegol was set to 1 (assuming equal treatment effect for both treatments).

- 3.22 The company's estimates for transitions from the OIC health state to the non-OIC (untreated) health state and from the non-OIC (untreated) health state to the OIC health state were generated from an analysis of the LIR population in the placebo arms of KODIAC 4 and 5. The company analysed the placebo data because the model assumed that patients are not on treatment in the OIC and non-OIC (untreated) health states. This same transition estimate was assumed for all comparators in the model.
- 3.23 For the transition to death, the company applied the same mortality rate to all health states (based on the UK general population). Mortality was calculated based on the UK life table for 2008 to 2010. The company used the exponential function to calculate cycle probability of mortality.
- 3.24 Utility estimates in the economic model were derived from an analysis of KODIAC 4 and 5 EQ-5D data, collected at 0, 4 and 12 weeks. These data were used with the Dolan algorithm to derive utility scores. Based on the results of a regression analysis, the company applied time- and treatment-specific utilities in the base case for the comparison with placebo. The company also presented scenario analyses applying treatment-specific utilities only and health state-specific utilities only. Only health state-specific utilities were used for the comparisons with methylnaltrexone and naloxone-oxycodone. No direct estimates of the effect of adverse events on utility were included in the model. The company stated that its clinicians advised that adverse events were unlikely to make a difference to health-related quality of life.
- 3.25 Costs incorporated in the company's model included drug costs, administration costs for methylnaltrexone, laxative costs, adverse events costs, opioid costs for the naloxegol arm of the comparison with naloxone-oxycodone, and other costs for managing constipation (including inpatient care, outpatient care, emergency

care, GP visit and consultation, nurse visits, rescue therapy and medical tests). The company assumed that patients having naloxone-oxycodone did not incur additional opioid costs (because of the presence of oxycodone). Therefore, the company presented 2 separate scenarios applying opioid costs to the naloxegol arm of the comparison with naloxone-oxycodone. The first scenario used morphine (the most commonly prescribed step-3 opioid) and the second used oxycodone. The company's estimates of resource use associated with managing constipation and adverse events were based on a survey of clinicians. Costs were based on the BNF, NHS reference costs and the Payment by Results tariff.

Company's base-case results and sensitivity analyses (naloxegol compared with placebo)

3.26 In the company's base-case analysis (based on KODIAC 4 and 5 data), the incremental cost-effectiveness ratio (ICER) for naloxegol compared with placebo was £10,849 per quality-adjusted life year (QALY) gained. However, the company stated that the most clinically relevant comparisons are as follows:

- Naloxegol compared with placebo plus bisacodyl (ICER of £12,639 per QALY gained).
- Naloxegol plus bisacodyl compared with placebo plus bisacodyl (ICER of £11,175 per QALY gained).

3.27 The company conducted a number of 1-way sensitivity analyses to demonstrate the model's robustness to changes in parameters and assumptions. In nearly all of the sensitivity analyses, naloxegol produced an ICER of less than £20,000 per QALY gained. The company also conducted several scenario analyses including: using alternative utility input assumptions; using the burden of illness data for resource use costs of managing constipation; assuming no extrapolation beyond the trial period (that is, using a time horizon of 12 weeks); and using alternative functions to estimate the transitions in the model. Of these, only 2 scenarios produced an ICER for naloxegol that was over £20,000 per QALY gained. Using a 12-week time horizon resulted in ICERs of £20,020 per QALY gained for naloxegol compared with placebo and £33,708 per QALY gained for naloxegol compared with placebo plus bisacodyl. When a health state-specific utility input was

employed, the ICER for naloxegol compared with placebo increased to £38,921 per QALY gained, and the ICER for naloxegol compared with placebo plus bisacodyl increased to £63,423 per QALY gained. The company did not present results of these 2 scenario analyses for naloxegol plus bisacodyl compared with placebo plus bisacodyl.

- 3.28 For the analysis comparing naloxegol with subcutaneous methylnaltrexone every other day, the results showed that naloxegol dominated methylnaltrexone (that is, naloxegol was more effective and cost less than methylnaltrexone).
- 3.29 For the analysis of the LIR+step-3 opioids subgroup, naloxegol dominated methylnaltrexone and naloxone-oxycodone (when oral morphine was added to the naloxegol arm). For the different placebo comparisons (with and without bisacodyl), the ICERs were less than £7,000 per QALY gained. The ICER increased to £34,054 per QALY gained for naloxegol compared with naloxone-oxycodone when oxycodone was added to the naloxegol arm.
- 3.30 The company did not do a subgroup analysis on patients with cancer who have OIC. However, it stated that there is no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in this patient population, because the underlying physiology of pain is the same regardless of the underlying cause. The company stated that pain medications act on the same target receptors regardless of whether the trigger for the pain is cancer or non-cancer. Because of this, extrapolating the available data to the treatment of OIC in patients with cancer pain was justified. The company also stated that patients with cancer and OIC would fit in the acceptable range for the key model variables which resulted in ICERs of less than £20,000 per QALY gained for naloxegol compared with each comparator.

ERG comments

- 3.31 The ERG indicated that the company's model was generally well presented and reported. It noted that the model structure was based on a revised definition of response (3 or more SBMs per week in at least 3 out of the last 4 weeks) compared with that used in the clinical studies (which also included an improvement of 1 or more SBM per week for 9 weeks out of 12). Because of this,

the model was able to use absolute health states rather than health states relative to a baseline. The ERG considered the 5-year time horizon to be acceptable.

- 3.32 The ERG noted that the modelled population was based on the marketing authorisation for naloxegol (that is, people who constipation has had an inadequate response to laxatives). However, it questioned whether the trial definition of inadequate response to laxatives (see section 3.3) reflected clinical practice. It argued that although the effectiveness of some types of laxative can be reasonably assessed after 4 days (for example bisacodyl), others – such as lactulose – may need to be used for slightly longer before their effectiveness can be fully assessed.
- 3.33 The ERG stated that the main weakness of the cost-effectiveness analysis was the definition of intervention and comparator. It noted that the cost-effectiveness analysis compared naloxegol with placebo based on SBM in the base case, and naloxegol plus bisacodyl with placebo plus bisacodyl based on bowel movement in a scenario analysis. However, the ERG considered the base-case analysis (that is, naloxegol without bisacodyl) to be neither clinically relevant nor consistent with the KODIAC 4 and 5 trials in which rescue medication was permitted in all arms. The ERG argued that the use of naloxegol without rescue medication in clinical practice is implausible considering that the rates of SBM in the trial may have been affected by the use of rescue medication.
- 3.34 The ERG stated that EQ-5D data were available from the clinical studies to inform the utilities used in the model, thus providing good quality evidence for the cost-effectiveness analysis. However, the ERG stated that it would have been preferable for the company to use health state-specific utilities in its base case for the comparison of naloxegol with placebo rather than treatment-specific utilities because there was insufficient evidence to suggest an independent treatment effect of naloxegol on health-related quality of life. The ERG also commented with regards to the health-related quality of life analysis that the non-OIC health state is too broad to be homogeneous. Using the company's definition of response, any patient with at least 9 SBMs over a 28-day period would be classified as a responder (and so move to the non-OIC on treatment state). However, patients with 28 or more SBMs over this period would be considered to be in the same health state and have the same quality of life as

patients who had only 9 SBMs, which the ERG considered to be unlikely. The ERG stated that the model should have included more discrete health states which were more reflective of patient experience and this would have allowed the company to apply health-state specific utilities.

3.35 The ERG performed an exploratory base-case analysis comparing naloxegol plus bisacodyl with placebo plus bisacodyl. The outcome was SBM, rather than bowel movement as the company had used in its own analysis. The ERG commented that this was the only accurate comparison that could be made using the data from KODIAC 4 and 5. The analysis increased the ICER for naloxegol compared with placebo to £10,864 per QALY gained.

3.36 The ERG conducted an exploratory sensitivity analysis on response rate as a proxy for the 2xLIR population (see section 3.4). The ERG extracted the response rates at 4 weeks for the LIR and 2xLIR populations from KODIAC 4 and 5. Using these data, it calculated a pooled response rate for the 2xLIR population using an adjusted response rate as a proxy for that population. The ERG noted that there was a marked difference in response rates in the naloxegol arm compared with the placebo arm between the LIR and 2xLIR populations. The response rate for the LIR subgroup was 20.4% better in the naloxegol arm than the placebo arm, and the response rate in the 2xLIR population was 13.5 % better in the naloxegol arm than in the placebo arm. The ERG assumed that all other input parameters would be the same as the company's base case, because there were no 2xLIR data to inform the various transition probabilities in the model. This analysis increased the ICER for naloxegol compared with placebo from £10,849 per QALY gained (in the company's base case) to £11,406 per QALY gained. The ERG also conducted a sensitivity analysis exploring the impact of changing the parametric distribution of the time-to-event curve used to estimate the transition probability from non-OIC (on treatment) to opioid-induced constipation. The ERG noted that in its analyses, the company used the same parametric function for both placebo and naloxegol. Instead, the ERG used different combinations of the following distributions: exponential, Weibull, lognormal and loglogistic. The ERG compared naloxegol plus bisacodyl with placebo plus bisacodyl and most cases, the ICER was similar to or lower than the company's base case ICER. The ICERs only increased beyond £13,000 per QALY gained when the exponential distribution was used for naloxegol and either the lognormal or loglogistic distribution was used for placebo.

3.37 The ERG conducted threshold analyses on the hazard ratio for the transition from the non-OIC (on treatment) state to the OIC state for methylnaltrexone and naloxone-oxycodone. In the company's model, the hazard ratios for this transition were calculated using the ratio between the 4-week response rates for methylnaltrexone and naloxone-oxycodone and the response rate of naloxegol 25 mg. None of the additional economic analysis by the ERG resulted in ICERs that differed from the company's results in any meaningful way. For this reason the ERG considered that the company's cost-effectiveness results were generally robust. However, given that the company did not perform a full mixed treatment comparison, the ERG cautioned that the results of the comparisons with methylnaltrexone and naloxone-oxycodone should be interpreted with care.

3.38 Full details of all the evidence are in the [committee papers](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of naloxegol, having considered evidence on the nature of opioid-induced constipation (OIC) and the value placed on the benefits of naloxegol by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.1 The Committee considered the experience of people with OIC and the clinical need for treatment options for people with this condition. The Committee heard from clinical experts that most people taking opioids experience constipation and that constipation is a painful and uncomfortable condition that can lead to other physical and psychological problems. It heard from the patient expert that constipation has a substantial impact on quality of life, including increased time spent on bowel care and reliance on help from others. The Committee also heard that frequency of bowel movements is less important to people than ease of bowel movements in terms of impact on quality of life. The clinical experts stated that in some people taking opioids, constipation does not respond adequately to conventional laxatives because they do not specifically target OIC. The Committee also heard from clinical experts that in an attempt to relieve their constipation some people reduce their opioids, but this tends to reduce the effect of the opioid on the pain without relieving the constipation. Therefore, alternative treatment options for treating OIC are needed in clinical practice. The Committee accepted that naloxegol was a new treatment option for OIC that has not responded adequately to laxatives.
- 4.2 The Committee considered the treatment pathway for people with opioid-induced constipation. The Committee heard from the clinical experts that people with OIC would use a stimulant laxative and an osmotic laxative before moving on to other treatments such as methylnaltrexone. The clinical experts stated that the decision to move on to other treatments will depend on the severity of constipation symptoms and the person's own quality of life after using laxatives. The Committee understood that there is no formal treatment pathway for people with OIC. It noted that there was currently limited evidence on which to base any clinical guidelines for OIC, and that what guidance exists is based on clinical consensus rather than study evidence.

- 4.3 The Committee noted that the marketing authorisation for naloxegol is for the treatment of OIC in adult patients who have had an inadequate response to laxative(s) and that the trials and summary of product characteristics for naloxegol defines an inadequate response to laxative(s) as moderate, severe or very severe symptoms of opioid induced constipation 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 and took this into consideration in its decision making.
- 4.4 The Committee discussed the relevant comparators for this appraisal. The Committee was aware that in its evidence submission, the company compared naloxegol with methylnaltrexone, naloxone-oxycodone and placebo with and without bisacodyl. The clinical experts observed that in clinical practice bisacodyl is not usually given as a laxative but as a rescue medication. The Committee heard from the clinical experts that naloxone-oxycodone is not used frequently in UK clinical practice because it is produced as a fixed-ratio combination of a laxative and an opioid in which the opioid, oxycodone, cannot be titrated without also having to titrate the naloxone. Because of this, some people would not be able to take it. The Committee heard from the clinical experts that methylnaltrexone is effective in this group of people and would be the most relevant of the comparators assessed in the company's evidence submission. However, the clinical experts also indicated that not everybody can have methylnaltrexone because of its subcutaneous route of administration, monitoring and X-ray requirements, and adverse effects. The Committee heard that naloxegol would be an alternative to methylnaltrexone and would be similarly positioned in the treatment pathway after treatment with a stimulant and osmotic laxative had failed. The Committee agreed that it would consider analyses for all the comparators presented in the company's submission, but concluded that methylnaltrexone was the most relevant comparator for this appraisal.

Clinical effectiveness

- 4.5 The Committee considered the clinical effectiveness of naloxegol as seen in the KODIAC 4 and 5 trials, which compared naloxegol with placebo in people with OIC. It was aware that the marketing authorisation for naloxegol covers only people whose constipation had not adequately responded to laxatives and that

an inadequate response to laxatives was defined in the trials and in the summary of product characteristics (see section 4.3). It noted the Evidence Review Group's (ERG's) concerns that it may take more than 4 days to assess the effectiveness of some laxatives. The company stated that most patients in the trial had used the laxatives for more than 4 days before being classed as inadequate responders, and that 4 days was the minimum duration of use. The clinical experts stated that although some laxatives will take longer than 4 days for their effectiveness to be established, the majority will work within this time. The Committee questioned whether the trial definition of laxative-inadequate response was relevant in clinical practice in England. It heard from the clinical experts that the definition of laxative-inadequate response is subjective in clinical practice, and that the company's definition was reasonable. The clinical experts also stated that the decision to consider alternative treatments in practice would depend on a person's quality of life after using laxatives. The Committee accepted the definition of inadequate response to laxatives used in the clinical trials and in the summary of product characteristics for naloxegol.

- 4.6 The Committee discussed the generalisability of the KODIAC 4 and 5 studies to the population in England with OIC. It was aware that the trials were mainly done in the USA and that some of the baseline characteristics of the trial population differed from the population of England with OIC. It noted that the proportion of people who were obese in the studies was higher than the proportion of people who are obese in England. In addition, the average age of the patients included in the studies was 52.2 years, whereas the population in England who take opioids is likely to be older, particularly in people with cancer pain. The Committee heard from the clinical experts that although these baseline characteristics differed between the trial population and the population in England with OIC, the efficacy of naloxegol was not expected to be affected by age or weight and that the results of the trials would be generalisable to people with OIC in England. The Committee also heard from the company that its post-hoc subgroup analyses reported in the [European Public Assessment report for naloxegol](#), showed naloxegol to be effective compared with placebo regardless of age or weight. The Committee concluded that the KODIAC 4 and 5 trials could be generalised to the population seen in clinical practice in England and that it could use those results in its decision making.
- 4.7 The Committee also considered the generalisability of the results of the KODIAC

4 and 5 studies to people with cancer pain who have OIC. The Committee noted that both KODIAC 4 and 5 specifically excluded people with cancer. The Committee heard from the company that a separate study which included people with cancer was started, but was stopped due to extreme difficulties of enrolment for this group of people. The Committee heard from the company and clinical experts that it was difficult to enrol patients with cancer mainly because of short life-expectancy. The Committee heard from the clinical experts that naloxegol was likely to be effective in people with cancer because naloxegol targets the OIC, rather than the underlying condition causing the pain. The Committee noted that the marketing authorisation for naloxegol did not exclude people taking opioids for cancer pain. However, it was aware that the summary of product characteristics includes some special warnings about the lack of clinical trial evidence in people with cancer and the contraindications for certain patients who are at heightened risk of gastrointestinal perforation (including people with cancer pain). Having heard from the clinical experts and considering the marketing authorisation, the Committee was persuaded that naloxegol would be equally effective in people with cancer pain who have OIC taking into account the special warnings highlighted in the summary of product characteristics. It therefore concluded that its recommendations regarding the use of naloxegol in clinical practice also applies to people with cancer pain who have OIC.

- 4.8 The Committee considered the results of KODIAC 4 and 5 presented by the company. It noted that the results suggested a statistically significant improvement over weeks 1 to 12 in the proportion of laxative-inadequate responders who had spontaneous bowel movements (SBMs) in the naloxegol arm compared with the placebo arm (see section 3.8). The Committee heard that although the number of SBMs during the trial was important, the most clinically relevant outcome measure was the mean difference from baseline in SBMs. This is because there are large differences in the number of SBMs normally experienced by people without OIC. The Committee also noted that naloxegol was associated with statistically significant improvements in secondary outcomes, including health-related quality of life compared with placebo in the KODIAC 4 and 5 studies (see section 3.8). Therefore, the Committee concluded that naloxegol was effective compared with placebo as shown by the data on SBM frequency in the KODIAC 4 and 5 studies in people with OIC that has not responded adequately to laxatives.

- 4.9 The Committee considered evidence on the company's mixed treatment comparison of naloxegol, methylnaltrexone and naloxone-oxycodone. The Committee was aware that in the mixed treatment comparison, the company had used response rates from the laxative-inadequate responder population in the naloxegol KODIAC 4 and 5 studies, and conversely, rates for the overall population from the methylnaltrexone and naloxone-oxycodone studies. The Committee noted that the results from the ERG's exploratory mixed treatment comparison, in which it used data for the overall population from the KODIAC trials, did not differ substantially from the company's estimate. Nevertheless, the Committee considered that using 2 different populations introduced uncertainty in the company's analyses. The Committee also noted that none of the results from the mixed treatment comparison for naloxegol compared with methylnaltrexone and naloxone-oxycodone were statistically significant, indicating that there was also uncertainty regarding its relative efficacy in the mixed treatment comparison. The Committee concluded that there was insufficient evidence that naloxegol's clinical effectiveness differed from that of methylnaltrexone and naloxone-oxycodone, and that it was not unreasonable to use the mixed treatment comparison analysis in its decision-making.

Cost effectiveness

- 4.10 The Committee discussed the company's cost-effectiveness analysis. It considered all the comparisons provided by the company, including naloxegol compared with placebo (with and without bisacodyl), methylnaltrexone and naloxone-oxycodone, noting that methylnaltrexone was the most appropriate comparator for this appraisal (see section 4.4). The Committee noted that the company's comparison of naloxegol with placebo included analyses with and without bisacodyl. However, it was aware that most patients in KODIAC 4 and 5 had bisacodyl as a rescue medication. It also noted the ERG's comments that the use of the rescue medication may have positively affected the SBM rates in the trial. The Committee concluded that the analysis without bisacodyl was neither clinically relevant nor consistent with the KODIAC 4 and 5 trials. Therefore, for the comparison with placebo, it did not consider the analysis without bisacodyl for both groups any further.
- 4.11 The Committee considered the company's economic model and the ERG's

critique of the model. The Committee noted that the company's base case ICER for naloxegol plus bisacodyl compared with placebo plus bisacodyl was £11,200 per QALY gained. The Committee noted that for the analyses comparing naloxegol with placebo, the company designed its model to include time-specific and treatment-specific utilities. The Committee heard from the ERG that it would have been more appropriate to use health state-dependent utility values only, rather than assuming different utilities for the treatment arms. The Committee noted that the company's base case ICER increased to £38,900 per QALY gained when the company used health state-dependent utility values for naloxegol compared with placebo (without bisacodyl in both treatment groups). Similar analysis was not presented for the comparison that included bisacodyl in both treatment groups. The Committee understood from the ERG that the large increase in the ICER was a result of the model structure, in that the non-OIC (on treatment) state in the model was too broad, that is, it included a heterogeneous group of patients with different number of SBMs during the same period (see section 3.34), and that applying a single utility value to that health state would not accurately reflect patient experience in that state. The ERG stated that the model should have included more discrete health states which were more reflective of patient experience and this would have allowed the company to apply health-state specific utilities. However, the Committee understood from the ERG that taking this approach may not necessarily have changed the model results.

- 4.12 The Committee noted that there was less uncertainty when comparing naloxegol with methylnaltrexone and naloxone-oxycodone, because health state-specific utilities were used for these comparisons rather than treatment-specific utilities. It noted that when compared with methylnaltrexone and naloxone-oxycodone, naloxegol dominated (that is, naloxegol was both more effective and cheaper than) these treatments in almost every scenario (see sections 3.28 and 3.29), except when naloxegol was given with oxycodone compared with naloxone-oxycodone (which produced an ICER of £34,100 per QALY gained). It also noted that the comparison of naloxegol with naloxone-oxycodone was for the subgroup of people taking a step 3 opioid and not the full population covered by the marketing authorisation. In addition, the Committee had previously decided that naloxone-oxycodone was not the most relevant comparator for this appraisal because it is not used frequently in UK clinical practice (see section 4.4). The Committee concluded that although the company's model had

some limitations, overall it was acceptable for modelling treatment in this population.

- 4.13 The Committee considered the assumptions used by the company to model the duration of treatment response – that is, transition from the non-OIC (on treatment) health state to the OIC health state. The Committee noted that for its base case, the company had chosen the exponential function for both naloxegol and placebo because it was the most conservative of the available functions. However, the Committee observed that after only 2 years nearly all patients having naloxegol transitioned from the non-OIC (treated) health state to the OIC health state, which suggested that naloxegol lost its treatment effect over time. The Committee queried whether this was clinically plausible, and heard from clinical experts that if a patient were having opioids and naloxegol, there was no reason to expect that the treatment effect of naloxegol would lessen over time. The Committee also heard from the company that the discontinuation rates in the KODIAC 8 trial were very small, even though the trial lasted for 1 year. The Committee noted that in the ERG's exploratory analyses, the ICERs for naloxegol plus bisacodyl compared with placebo plus bisacodyl were mostly less than £13,000 per quality-adjusted life year (QALY) gained (see sections 3.35 and 3.36). The Committee concluded that the ERG's exploratory analyses had little impact on the cost-effectiveness results presented by the company.
- 4.14 The Committee considered the effect of the company's not conducting a fully incremental analysis (that is, calculating the incremental QALY gains and costs for all treatment options and ordered by increasing costs). The company stated that an incremental analysis was not possible, because the definition of response from the KODIAC trials as used in the placebo comparisons differed from the definition used for the mixed treatment comparison for the active comparators. The mixed treatment comparison analyses did not include all the comparators in the economic model (as requested by NICE during clarification) and therefore no comparable ICERs or incremental analysis was available from the mixed treatment comparison either. The Committee stated that it would have preferred to see a fully incremental analysis as described in the [guide to the methods of technology appraisal](#). However, the Committee considered methylnaltrexone to be the most relevant comparator, and because naloxegol dominated methylnaltrexone in the pairwise analysis (that is, naloxegol was both more effective and cheaper); it would also dominate it in an incremental analysis. The Committee concluded that

the ICERs presented in the pairwise analyses were sufficient evidence on which to base its decisions.

- 4.15 The Committee considered whether naloxegol was a cost-effective use of NHS resources compared with the comparators. The Committee noted that for all comparisons, the company's base-case results and most of the company's sensitivity analyses resulted in ICERs below £20,000 per QALY gained (see section 3.27). It was aware that all sensitivity analyses by both the company and the ERG showed that the model was stable and the ICERs robust to most model changes (see section 3.37). The Committee noted that the ICERs were above £20,000 per QALY gained only when health state-specific utilities were used and when the outcomes were not extrapolated beyond the trial period for naloxegol compared with placebo, and also when naloxegol was given with oxycodone compared with naloxone-oxycodone (see sections 4.11 and 4.12). The Committee concluded that in light of the robustness of the company's model, the ICERs being mostly below £20,000 per QALY gained for the comparison of naloxegol plus bisacodyl with placebo plus bisacodyl, and naloxegol mostly dominating methylnaltrexone and naloxone-oxycodone, naloxegol was considered a cost-effective use of NHS resources. The Committee therefore recommended naloxegol as an option within its marketing authorisation for people with OIC that has not responded adequately to laxatives.
- 4.16 The Committee considered whether naloxegol could be considered innovative in its potential to make a substantial effect on health-related benefits for people with opioid-induced constipation and whether it could be considered a step-change in the management of opioid-induced constipation. The Committee heard from the company that the innovativeness of naloxegol was in the combination of its mode of action and formulation, because it offers more flexibility in dosing than naloxone-oxycodone and can be used independently of the opioid being prescribed. The Committee heard from the clinical specialists that naloxegol would be a useful option for treating opioid-induced constipation. It noted that naloxone has been in use for many years and that the only innovation it could discern was the attachment of a polyethylene glycol molecule to naloxone in order to prevent it from crossing the blood-brain barrier. The Committee considered that although this addition was novel, there were no additional gains in health-related quality of life over those already included in the QALY calculations.

- 4.17 The Appraisal Committee considered whether it should take into account the consequences of PPRS 2014, and in particular the PPRS Payment Mechanism, when appraising naloxegol. The Appraisal Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of naloxegol. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of cost effectiveness of naloxegol.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has opioid-induced constipation and the healthcare professional responsible for their care thinks that naloxegol is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each Appraisal Committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Eugene Milne

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel

Institute of Brain and Behaviour Mental Health, University of Manchester

David Chandler

Lay member

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Dept of Primary Care and Population Health, University College London

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Claire McKenna

Research Fellow in Health Economics, University of York

Dr Iain Miller

Founder and CEO, Health Strategies Group

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing & Healthcare School and Senior Clinical University Teacher, University of Glasgow

Dr John Radford

General Practitioner, NHS Sheffield

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Dr Judith Wardle

Lay member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Richard Diaz

Technical Lead

Nwamaka Umeweni

Technical Adviser

Lori Farrar

Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews Ltd:

- Wolff R, Al M, Zaim R, Lang S, Leunis A, Noake C, Ryder S, Worthy G, Stirk L, Armstrong N, Riemsma R, Severens JL, Kleijnen J. Naloxegol for treating opioid-induced constipation: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd, 2015

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Companies were also invited to make written submissions. Professional or expert and patient or carer groups, and other consultees, had the opportunity to make written submissions. Companies, professional or expert and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company:

- AstraZeneca

Professional or expert and patient or carer groups:

- PromoCon
- The IBS Network
- Association of Cancer Physicians
- Association of Coloproctology of Great Britain and Ireland
- Cancer Research UK
- Royal College of Physicians

Other consultees:

- Department of Health
- NHS England
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Boehringer Ingelheim (bisacodyl, docusate, macrogol, sodium picosulphate)
- Napp Pharmaceuticals Limited (naloxone-oxycodone)
- Norgine Pharmaceuticals (sterculia/frangula, macrogol, docusate sodium enema)
- TMC Pharma Services (methylnaltrexone bromide)
- National Cancer Research Institute
- Kleijnen Systematic Reviews
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on naloxegol for treating opioid-induced constipation by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Andrew Davies, Clinical Director Supportive & Palliative Care, nominated by AstraZeneca – clinical expert
- Dr Paul Farquhar-Smith, Consultant in Anaesthesia and Pain Management, nominated by AstraZeneca – clinical expert
- Karen Irwin, Services Manager and Specialist Nurse, nominated by Promocon – patient expert

Representatives from the following company attended Committee meetings. They

contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- AstraZeneca

ISBN: 978-1-4731-1309-1