East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	Naloxegol for treating opioid-induced constipation.
Requested by	

SUMMARY

Clinical Effectiveness

Naloxegol is a form of naloxol which has been pegylated (that is, attached to a molecule of polyethylene glycol, or PEG).
Naloxegol functions as a peripherally-acting mu-opioid receptor antagonist in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

Naloxegol has been reviewed by NICE (TA 345) which recommends that naloxegol should be available, within its marketing authorisation, as an option for treating opioid induced constipation in adults whose constipation has not adequately responded to laxatives.
The main clinical evidence for naloxegol came from the pivotal phase III 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.
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).

Safety

Naloxegol interacts with strong CYP3A4 inducers and inhibitors and so patients should be prescribed 12.5mg strength if taking these drugs.
Rare cases of GI perforation have been reported in post-marketing use of peripherally acting mu-opioid receptor antagonists in patients with advanced medical illness so caution should be exercised when considering use in patients with any condition which may result in impaired integrity of the GIT wall e.g. Crohn's disease,

peptic ulcer disease. Patients should stop treatment and notify physician immediately if they develop unusually severe or persistent abdominal pain.
Patients with clinically important disruptions to the blood-brain barrier (e.g. primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease etc.) were not included in clinical studies and may be at risk for naloxegol entry into the CNS.
Cases of opioid withdrawal syndrome have been reported in the naloxegol clinical programme (DSM-5).
The drug should be used with caution in patients who had had a recent CV event as these patients were excluded from the trials.

Patient factors

Constipation is one of the most common side effects experienced by patients taking opioids. Current laxatives available may now successfully treat opioid constipation and naloxegol may be an option in this group of patients.

It has been estimated that 50–80% of people taking laxatives for opioid-induced constipation report limited improvement in symptoms (Cook et al. 2008; Coyne et al. 2014). However, the proportion of people who have moderately severe opioid-induced constipation (as defined in the guidance) after treatment with laxatives for at least 4 days is uncertain.

Cost implications

The cost to treat a patient with naloxegol for one year is £669.76.
Current guidelines recommend the use of either senna or bisacodyl with or without docusate or macrogol.

Table 1- Estimated drug cost

Drug	**Usual treatment dose**	**Approx £/year**
Senna tablets	2 ON	42.10
Docusate	2ON	50.72
Bisacodyl	2OD	27.79
Laxido® (current preferred macrogol brand)	2 sachets ON	103.62
Methylnaltrexone (4 months of treatment)	Subcutaneous injection, every 2 days.	1,284.05
Targinact® (oxycodone+ naloxone) (NB this drug is classified black in Surrey)	Usually 1 BD	5mg/2.5mg=£551.67 10mg/5mg=£551.67 20mg/10mg=£2206.16 40mg/20mg=£4413.37

Table 2 Potential costs for treatment of opioid-induced constipation

PbR tariff-2015/16	Cost (£)
PA26A Other Gastrointestinal Disorders with CC – elective admission	1,455
PA26A Other Gastrointestinal Disorders with CC – non-elective admission	1,031
PA26B Other Gastrointestinal Disorders without CC – elective admission	817
PA26B Other Gastrointestinal Disorders without CC – non-elective admission	576
Gastroenterology - outpatient first-attendance	181
Gastroenterology - outpatient follow-up attendance	107

Relevant guidance / reviews

NICE TA 345

Likely place in therapy relative to current treatments

To be used for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).
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.

Recommendation to PCN

Naloxegol to be available in primary care (green) for patients with OIC, who have had inadequate response to other laxatives indicated for the treatment of OIC e.g. senna, docusate, bisacodyl and macrogol. When naloxegol is initiated all other laxative treatment should be stopped and the effectiveness of naloxegol should be assessed after a maximum of 7 days. Patients should be advised that if they develop and sudden severe abdominal pain they should stop taking naloxegol and let the GP know. They should also be warned of the potential of opioid withdrawal symptoms which should alos be reported to their GP immediately.

Medicine details	
Name and brand name	Naloxegol oxalate (Moventig®) 12.5mg and 25mg tablets
Licensed indication, formulation and usual dosage	Indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). 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. The recommended dose of Moventig® is 25 mg once daily. When naloxegol therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of naloxegol is determined. No dose adjustment is recommended based on age. The starting dose for patients with moderate or severe renal insufficiency is 12.5 mg. If side effects impacting tolerability occur, naloxegol should be discontinued. Naloxegol is not licensed for use in children.
Summary of mechanism of action, and relevant pharmacokinetics	Naloxegol 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. Naloxegol functions as a peripherally-acting mu-opioid receptor antagonist in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.
Important drug interactions	*Interaction with strong CYP3A4 inhibitors* In an open-label, non-randomized, fixed-sequence, 3-period, 3-treatment, crossover study to evaluate the effect of multiple doses of ketoconazole on the single dose PK of naloxegol, co-administration of ketoconazole and naloxegol resulted in a 12.9-fold (90% CI: 11.3-14.6) increase in naloxegol AUC and a 9.6-fold increase in naloxegol C_{max} (90% CI: 8.1-11.3), compared to when naloxegol was administered alone. Therefore, concomitant use with strong CYP3A4 inhibitors is contraindicated (see section 4.3). Grapefruit juice has been classified as a potent CYP3A4 inhibitor when consumed in large quantities. No data are available on the concomitant use of naloxegol with grapefruit juice. Concomitant consumption of grapefruit juice while taking naloxegol should generally be avoided and considered only in consultation with a healthcare

	provider. *Interaction with moderate CYP3A4 inhibitors* In an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, crossover study to evaluate the effect of multiple doses of diltiazem on the single dose PK of naloxegol, co-administration of diltiazem and naloxegol resulted in a 3.4-fold (90% CI: 3.2-3.7) increase in naloxegol AUC and a 2.9-fold increase in naloxegol C_{max} (90% CI: 2.6-3.1), compared to when naloxegol was administered alone. Therefore, a dose adjustment of naloxegol is recommended when co-administered with diltiazem and other moderate CYP3A4 inhibitors (see section 4.2). The starting dose for patients taking moderate CYP3A4 inhibitors is 12.5 mg once daily and the dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient . No dosage adjustment is required for patients taking weak CYP3A4 inhibitors. *Interaction with strong CYP3A4 inducers* In an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, single-dose, crossover study to evaluate the effect of multiple doses of rifampin on the single dose PK of naloxegol, co-administration of rifampin and naloxegol resulted in a 89% (90% CI: 88%-90%) decrease in naloxegol AUC and a 76% decrease in naloxegol C_{max} (90% CI: 69%-80%), compared to when naloxegol was administered alone. Therefore, naloxegol is not recommended in patients who are taking strong CYP3A4 inducers. *Interaction with P-gp inhibitors* A double-blind, randomized, 2-part, crossover, single centre study was conducted to evaluate the effect of quinidine on the pharmacokinetics of naloxegol and the effect of the co-administration of naloxegol and quinidine on morphine-induced miosis in healthy volunteers. Co-administration of the P-gp inhibitor quinidine resulted in a 1.4 fold increase in the AUC (90% CI: 1.3-1.5) and a 2.4 fold increase in the C_{max} (90% CI: 2.2-2.8) of naloxegol. Co-administration of naloxegol and quinidine did not antagonize the morphine-induced miosis effect, suggesting that P-gp inhibition does not meaningfully change the capacity of naloxegol to cross the blood-brain barrier at therapeutic doses. As the effects of P-gp inhibitors on the PK of naloxegol were small relative to the effects CYP3A4 inhibitors, the dosing recommendations for naloxegol when co-administered with medicinal products causing both P-gp and CYP3A4 inhibition should be based on CYP3A4 inhibitor status - strong, moderate or weak.
Monitoring requirements	Conditions with increased potential for gastrointestinal perforation

	Rare cases of gastrointestinal perforation have been reported in the post-marketed use of peripherally acting mu-opioid receptor antagonists in patients with advanced medical illness. Caution with regards to the use of naloxegol should be exercised in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall (e.g. severe peptic ulcer disease, Crohn's Disease, active or recurrent diverticulitis, infiltrative gastrointestinal tract malignancies or peritoneal metastases). The overall benefit-risk profile for each patient should be taken into account. Patients are advised to discontinue therapy with naloxegol and promptly notify their physician if they develop unusually severe or persistent abdominal pain. Clinically important disruptions of the blood-brain barrier Naloxegol is a peripherally acting mu-opioid receptor antagonist with restricted access to the central nervous system (CNS). The blood brain barrier integrity is important for minimizing naloxegol uptake into the CNS. Patients with clinically important disruptions to the blood-brain barrier (e.g. primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease etc.) were not included in clinical studies and may be at risk for naloxegol entry into the CNS. Naloxegol should be prescribed with caution in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of opioid withdrawal and/or interference with opioid-mediated analgesia. If evidence for opioid-mediated interference with analgesia or opioid withdrawal syndrome occurs, patients should be instructed to discontinue naloxegol and contact their physician. Cases of opioid withdrawal syndrome have been reported in the naloxegol clinical programme (DSM-5). Opioid withdrawal syndrome is a cluster of three or more of the following signs or symptoms: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinnorrhea, pupillary dilation or piloerection or sweating, diarrhoea, yawning, fever or insomnia. Opioid withdrawal syndrome typically develops within minutes to several days following administration of an opioid antagonist. If opioid withdrawal syndrome is suspected the patient should discontinue Moventig® and contact their physician.
Prescribing considerations	When naloxegol therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of naloxegol is determined. The patient 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.
Other considerations	

Potential patient group (if appropriate to include)	
Brief description of disease	Opioids are effective pain relievers, but have a very common side effect of constipation which will be experienced for the duration of treatment with opioids. These medicines affect the gastrointestinal tract in a variety of ways. Opioids increase the amount of time it takes stool to move through the gastric system. They increase non-propulsive contractions in the middle of the small intestine (jejunum) and decrease longitudinal propulsive peristalsis - motions critical to moving food through the intestines. This results in food that fails to travel through the digestive tract. Opioids are also able to partially paralyze the stomach (gastroparesis) so that food remains in the digestive organ for a longer period of time. Opioids can also cause a reduction in digestive secretions and decrease the urge to defecate.
Potential patient numbers per 100,000	Unknown
Outcomes required	

Summary of current treatment pathway

Evidence review

The main clinical evidence for naloxegol came from the pivotal phase III 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.

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.

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.

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.

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.

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.

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.

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.

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 wasdose-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.

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.

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.

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.

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	Mid Essex CCG has added it to the pathway for treating OIC Hounslow CCG have added to formulary for use by all prescribers
Recommendations from national / regional decision making groups	NICE technology appraisal guidance 345 recommends naloxegol for use within its marketing authorisation, as an option for treating opioid induced constipation in adults whose constipation has not adequately responded to laxatives
Stakeholder views	
CCG priorities	
Health economic considerations	
Cost per year per patient	£669.76

Alternative treatments cost per patient per year

Current guidelines recommend the use of either senna or bisacodyl with or without docusate or macrogol.

Table 1- Estimated drug cost

Drug	Usual treatment dose	Approx £/year
Senna tablets	2 ON	42.10
Docusate	2ON	50.72
Bisacodyl	2OD	27.79
Laxido® (current preferred macrogol brand)	2 sachets ON	103.62
Methylnaltrexone (4 months of treatment)	Subcutaneous injection, every 2 days.	1,284.05
Targinact® (oxycodone+naloxone) (NB this drug is classified black in Surrey)	Usually 1 BD	5mg/2.5mg=£551.67 10mg/5mg=£551.67 20mg/10mg=£2206.16 40mg/20mg=£4413.37

Table 2 Potential costs for treatment of opioid-induced constipation

PbR tariff-2015/16	Cost (£)
PA26A Other Gastrointestinal Disorders with CC – elective admission	1,455
PA26A Other Gastrointestinal Disorders with CC – non-elective admission	1,031
PA26B Other Gastrointestinal Disorders without CC – elective admission	817
PA26B Other Gastrointestinal Disorders without CC – non-elective admission	576
Gastroenterology - outpatient first-attendance	181
Gastroenterology - outpatient follow-up attendance	107

Other financial considerations (if relevant)

Where current laxatives do not work, patients may have to access urgent care due to severe constipation caused by the opioids

Health economic data (if available)

References

1. https://www.nice.org.uk/guidance/ta345
2. http://www.medicines.org.uk/emc/medicine/30483
3. http://www.drugtariff.nhsbsa.nhs.uk/#/00241786-FA/FA00241341/Home

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Declaration of interest:
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