

Reimbursement Review

Naloxegol

Requester: Public drug programs

Therapeutic area: Management of opioid-induced constipation

Summary

What Is Opioid-Induced Constipation?

- Opioid-induced constipation (OIC) is constipation that is triggered or aggravated by opioid therapy taken for pain control. Signs and symptoms of OIC include decreased ability to evacuate the bowels, changes in stool consistency, sense of incomplete rectal evacuation, bloating, abdominal distention and discomfort, and difficulty with digestion.
- Constipation is the most common adverse event (AE) in patients taking opioids, ranging from 40% to 90% of patients.

What Are the Treatment Goals and Current Treatment Options for Opioid-Induced Constipation?

- The goals of therapy for patients with OIC and cancer or noncancer pain include improved bowel function and improved health-related quality of life (HRQoL).
- Typically, the first line of treatment for OIC has been laxatives. However, more than 50% of patients do not respond to treatment with laxative(s).

What Is Naloxegol and Why Did We Conduct This Review?

- Naloxegol is a drug that is available as an oral tablet. Health Canada has approved naloxegol for the treatment of OIC in adult patients with noncancer pain who have had an inadequate response to laxative(s).
- At the request of the participating public drug programs, we reviewed naloxegol to inform a recommendation on whether it should be reimbursed for adult patients with noncancer or cancer pain who have had an inadequate response to laxative(s).

How Did We Evaluate Naloxegol?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of naloxegol versus other treatments used in Canada for OIC in adult patients with noncancer or cancer pain who have had an inadequate response to laxative(s).
- The clinical evidence was identified through systematic searches for available studies. The review was also informed by 2 clinical experts as part of the review process. We received input from drug plans, but not from patient groups, clinician groups, or industry.

Summary

What Did We Find?

Clinical Evidence

- We reviewed the following clinical evidence:
 - Two identical randomized controlled phase III trials (KODIAC-04 and KODIAC-05) comparing naloxegol with placebo for OIC in 720 adult patients with noncancer pain. Both trials included a subgroup of patients with an inadequate response to laxative(s).
 - One long-term extension study (KODIAC-08) comparing naloxegol with placebo for OIC in 245 adult patients with noncancer pain.
 - Three single-arm observational studies on naloxegol for OIC in 400 adult patients with cancer pain and an inadequate response to laxative(s).
- For the comparison of naloxegol 25 mg daily and naloxegol 12.5 mg daily versus placebo for OIC in adult patients with noncancer pain who had an inadequate response to laxative(s):
 - Naloxegol 12.5 mg and 25 mg resulted in a clinically important improvement in response compared to placebo. In KODIAC-05, the evidence for the 12.5 mg dose did not reach statistical significance.
 - Improvement in response was supported by shorter time to first postdose spontaneous bowel movement and number of days per week with a complete spontaneous bowel movement.
 - Limitations of the evidence included potential risk of bias due to missing outcome data and confidence intervals (CIs) that included effects that may not be considered clinically important.
 - Changes in constipation symptoms at 12 and 24 weeks were not considered large enough to be clinically important. Change from baseline in HRQoL did not appear to differ across groups, and no statistical testing was undertaken.
 - The overall rates of AEs and AEs leading to study discontinuation were increased with naloxegol 25 mg compared to placebo and the naloxegol 12.5 mg dose. AEs were primarily gastrointestinal in nature.
 - Few serious AEs and harms of special interest were observed in the trials and long-term extension study.
- The single-group observational studies in adult patients with cancer pain and an inadequate response to laxative(s) reported high response rates and improvement in constipation symptoms and HRQoL. However, such a design does not allow for causal conclusion about the effect of naloxegol in this population, and the studies were affected by several sources of bias. Although there was no evidence from randomized

Summary

controlled trials identified to inform how naloxegol compares with placebo for OIC in adult patients with cancer pain and an inadequate response to laxative(s), clinical experts suggested that the clinical efficacy or safety are not likely to differ in this population.

- There was no evidence to inform how naloxegol compares with osmotic laxatives, stimulant laxatives, or methylnaltrexone for OIC in adult patients with cancer or noncancer pain and an inadequate response to laxative(s).

Economic Evidence

- Naloxegol for the treatment of patients with OIC who have had an inadequate response to laxatives is generally expected to increase costs to the public drug programs.

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Abbreviations

AE	adverse event
CDA-AMC	Canada's Drug Agency
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention to treat
LIR	laxative inadequate response
OIC	opioid-induced constipation
PAC-QOL	Patient Assessment of Constipation – Quality of Life
PAC-SYM	Patient Assessment of Constipation – Symptoms
PAMORA	peripherally acting mu-opioid receptor antagonist
RCT	randomized controlled trial
SAE	serious adverse event
SBM	spontaneous bowel movement

Background

Introduction

The objective of this Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of naloxegol oral tablets, 25 mg and 12.5 mg, in the treatment of OIC in adult patients with an inadequate response to laxative(s) (laxative inadequate response [LIR]), irrespective of the cause of pain (i.e., for both noncancer and cancer pain). The focus will be placed on comparing naloxegol to relevant comparators and identifying gaps in the current evidence. The economic review consists of a cost comparison for naloxegol compared with relevant comparators for the same population. The comparators considered relevant to the reviews were placebo, osmotic laxatives, stimulant laxatives, and methylnaltrexone.

Naloxegol has not been previously reviewed by Canada's Drug Agency (CDA-AMC).

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Naloxegol, 12.5 mg and 25 mg, oral tablets
Relevant Health Canada indication	Treatment of OIC in adult patients with noncancer pain who have had an inadequate response to laxative(s)
Mechanism of action	Antagonizes opioid binding at the peripheral mu-opioid receptors
Recommended dosage	The recommended dosage is 25 mg once daily in the morning. If the patient is unable to tolerate this dosage, it should be reduced to 12.5 mg once daily.
Data protection status	Data protection end: June 2, 2023
Status of generic drugs or biosimilars	None marketed as of February 26, 2025 Report of 1 generic submission accepted for review in August 2021; name of generic manufacturer or review status not provided.
Information on the CDA-AMC review	
Requester	Formulary Working Group
Indication under consideration for reimbursement	Treatment of OIC in adult patients with an inadequate response to laxative(s), irrespective of the cause of pain (i.e., for both noncancer and cancer pain).

CDA-AMC = Canada's Drug Agency; OIC = opioid-induced constipation.

Sources of Information

The contents of the Clinical Review report are informed by studies identified through systematic literature searches and input received from interested parties.

Calls for patient group, clinician group, and industry input are issued for each Non-Sponsored Reimbursement Review. We did not receive any patient group submissions, clinician group submissions, or submissions from industry.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

Each review team includes at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two clinicians (1 medical oncologist and 1 gastroenterologist) with expertise in the diagnosis and management of OIC participated as part of this review team, with representation from Alberta and Manitoba.

Disease Background

OIC is constipation that is triggered or aggravated by opioid therapy taken for pain control. The binding of opioid agonists to mu-opioid receptors in the enteric nervous system leads to increased nonpropulsive contractions and inhibited water and electrolyte excretion.¹ This results in decreased ability to evacuate the bowels, a change in stool consistency, a sense of incomplete rectal evacuation, bloating, abdominal distention and discomfort, and difficulty with digestion.² Although there are no data on the exact prevalence or frequency of OIC in Canada, constipation is the most common AE in patients taking opioids,^{1,3} ranging from 40% to 90% of patients.¹ OIC also has a negative impact on HRQoL.¹ OIC has traditionally been treated pharmacologically with osmotic and stimulant laxatives.⁴ However, these laxatives fail to effectively treat OIC in more than 50% of patients.⁵ These patients require alternative therapy, which may include peripherally acting mu-opioid receptor antagonists (PAMORAs), such as naloxegol.⁴

Current Management

Treatment Goals

The clinical experts consulted for this review indicated that the goals of therapy for patients with OIC were to improve bowel function, reduce associated symptoms (e.g., vomiting, nausea, discomfort), minimize adverse effects of opioids, improve HRQoL, and maintain independence. In patients with advanced cancer, treatment goals also include increased comfort, pain reduction, and reduced dependence on pain and other medications.

Current Treatment Options

The clinical experts consulted for this review indicated that the current treatment options for patients with OIC include nonpharmacological interventions, such as increased fluid intake, increased physical activity, reduction of offending medications (e.g., 5-HT₃ antagonists, antidepressants), and increased consumption of foods that improve stool output. Pharmacological interventions included traditional laxatives (e.g., polyethylene glycol, lactulose, magnesium citrate, magnesium hydroxide) for first-line treatment, and PAMORAs (e.g., naloxegol, methylnaltrexone) for second-line treatment. The clinical experts referenced the guideline by the American Gastroenterological Association on the medical management of OIC in patients with noncancer pain published in 2019.⁴ The American Gastroenterological Association recommendations are implemented in clinical practice by the clinical experts.

The clinical expert in oncology was unable to identify a current clinical practice guideline for OIC in patients with cancer pain, but did reference the 2010 Canadian consensus recommendations and algorithm for the management of constipation in patients with advanced progressive illness.⁶

In the noncancer pain population, there have been many more agents available on the market for OIC in the past 10 years. However, the treatment offered to a patient in clinical practice is often dependent on cost. Some patients combine treatment with an over-the-counter medication to offset the cost.

Key characteristics of naloxegol are summarized in the Key Characteristics table in Appendix 1 of the Supplemental Material.

Unmet Needs and Existing Challenges

The clinical experts explained that not all patients respond to available treatments despite proper and regular use. Patients may become refractory to current treatment options. Rectal bleeding, neutropenia, and the risk of infection prevent ongoing use of laxative suppositories. In some patients (e.g., with anorexia, undergoing chemotherapy), the taste or side effects of laxatives (e.g., lactulose is very sweet and can induce bloating) may be problematic. Some laxatives require a certain amount of fluid intake to work effectively; this may be very difficult for patients with advanced cancer and other conditions. Treatments are needed that are better tolerated and more convenient to administer. The clinical experts also added that sometimes PAMORAs are not initiated soon enough due to cost and access. There is a need to understand the efficacy and safety of naloxegol compared to osmotic laxatives, stimulant laxatives (both types of laxatives available over the counter), and methylnaltrexone for OIC in patients with LIR and noncancer or cancer pain.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review. The following has been summarized by the review team.

Place in Therapy

According to the clinical experts, naloxegol would fit into the current treatment paradigm as second-line treatment following an adequate trial of traditional laxatives.

Patient Population

The clinical experts indicated that patients taking a stable dose of opioids, requiring medication for a regular bowel movement, and not responding to traditional laxatives were best suited for treatment with naloxegol. However, it was not possible to identify in advance which patients were most likely to exhibit a response to treatment.

The clinical experts informed us that diagnosis of OIC was based on clinical assessment and directed medical history. Patients are asked about frequency and consistency of bowel movements before and after the initiation of opioids, associated symptoms during a bowel movement (e.g., pain, straining, bleeding), oral fluid intake and associated difficulties, activity level, and medication history. When making a diagnosis, the clinical experts would also look for “red flags,” such as rectal bleeding, anemia, and weight loss, to decide if further assessments were required, such as an abdominal X-ray or colonoscopy. The clinical experts

indicated that when starting patients on opioids for pain, clinicians will almost always also start them on a laxative, typically a sennoside and sometimes polyethylene glycol 3350 or lactulose.

The reduced dose of naloxegol (12.5 mg) should be given to patients with OIC and renal dysfunction. Naloxegol should not be used by patients with bowel obstruction, severe liver dysfunction, specific types of cancer (e.g., gastrointestinal, gynecological, urothelial), and strictures. Sometimes, the dosage must be adjusted on a regular (e.g., weekly) basis.

Assessing the Response to Treatment

The clinical experts indicated that they would assess frequency of bowel movements, tolerance of medication, and HRQoL to determine whether a patient is responding to treatment in clinical practice. Tools such as the Edmonton Symptom Assessment System⁷ is used regularly in both oncology and in palliative care to assess HRQoL. However, this tool has not been validated in patients with OIC. The Bristol Stool Scale⁸ is often used by clinicians as an assessment of the type of stool. The clinical experts also assessed symptoms associated with OIC, such as abdominal pain, discomfort, pain, nausea, and early satiety. Patient willingness to continue and remain on treatment would indicate a clinically meaningful response.

Discontinuing Treatment

The clinical experts indicated that the following factors should be considered when deciding to discontinue treatment with naloxegol: disease progression, inability to take oral medications, reduction or stopping of opioids, progressive diarrhea, abdominal pain, and nonresponse to treatment.

Prescribing Considerations

The clinical experts pointed out that there was no reason that administration of naloxegol treatment should be restricted to specialists. It was reasonable that all physicians be given access to prescribe naloxegol. Both outpatient and inpatient settings are appropriate for treatment with naloxegol.

Clinical Review

Methods

We conducted a systematic review to identify evidence for naloxegol for the treatment of OIC in adult patients with LIR. Studies were selected according to the eligibility criteria in [Table 2](#). To be included, studies needed to have enrolled at least 50% of LIR or reported relevant outcomes specifically for the LIR subgroup. We also included long-term extension studies of included randomized controlled trials (RCTs), indirect treatment comparisons (ITCs) that adhered to the eligibility criteria except for the study design criteria, and studies addressing gaps that did not meet the eligibility criteria but were considered to address important gaps in the systematic review evidence.

Relevant comparators included treatments used in clinical practice in Canada in the patient population under review. We selected outcomes (and follow-up times) for review considering clinical expert input. Selected outcomes are those considered relevant to expert committee deliberations. Detailed methods

for literature search, study selection, data extraction, and risk-of-bias appraisal are in Appendix 2 of the Supplemental Material.

Table 2: Systematic Review Eligibility Criteria

Criteria	Inclusion
Population	Adult patients (≥ 18 years of age) with opioid-induced constipation and inadequate response to laxative(s) ^a Subgroups • Type of pain (i.e., noncancer pain versus cancer pain)
Intervention	Naloxegol, 12.5 mg and 25 mg tablets, administered orally, once daily
Comparators	• Placebo • Osmotic laxatives (e.g., polyethylene glycol, lactulose, sorbitol, magnesium citrate, magnesium hydroxide, milk of magnesium) • Stimulant laxatives (e.g., senna, bisacodyl, sodium picosulfate) • Methylnaltrexone
Outcomes	Efficacy outcomes: • Response rate • Time to first postdose SBM • Days per week with ≥ 1 SBM • HRQoL Harms outcomes: • AEs, SAEs, WDAEs • AEs of special interest: ◦ Major cardiovascular events, opioid withdrawal syndrome, orthostatic hypotension, hypertension
Study design	Published phase III and IV RCTs

AE = adverse event; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SBM = spontaneous bowel movement; WDAE = withdrawal due to adverse event.

^aTo ensure a systematic approach to study inclusion, for studies to be included, at least 50% of patients enrolled had to have an inadequate response to laxatives or include a subgroup analysis so that the treatment effect among patients with an inadequate response to laxatives could be isolated.

Clinical Evidence

From the search for primary studies, we identified 235 unique records via the searches of databases and trial registers, of which 215 were excluded by title and abstract. We screened 20 records by full text and included 4 reports^{1,9-11} of 2 RCTs. This included the KODIAC-04 and KODIAC-05 trials¹ comparing naloxegol with placebo for OIC in adult patients with noncancer pain, as well as pooled analyses of the LIR population in these trials.¹⁰ Another publication reported the pooled analyses of the overall population in each trial (no results specific to LIR).¹¹ Additionally, 1 long-term extension of the KODIAC-04 trial was included (KODIAC-07),⁹ which presented HRQoL and harms outcomes for the treatment period and long-term extension period for the overall population (no results specific to LIR).

We did not identify any completed comparative studies on the effect of naloxegol in adult patients with cancer pain. KODIAC-06^{12,13} was a double-blind, international, multicentre, randomized phase III trial in adult patients with OIC and cancer pain. The primary objective was to assess efficacy of naloxegol 12.5 mg and 25 mg doses compared to placebo. Due to recruitment challenges, the KODIAC-06 study was stopped

early.^{12,13} Another study¹³ assessed the feasibility of a multicentre, randomized phase III trial of naloxegol versus placebo in adult patients with OIC and advanced cancer. Patient recruitment across 3 sites in the US was challenging and the study was stopped early. Although potentially eligible patients were identified, 98% did not enrol in the trial.¹³

From the search for ITCs, we identified 17 unique records via the searches of databases and trial registers. No ITCs relevant to the report were identified. We identified 3 reports¹⁴⁻¹⁶ of 3 observational studies addressing gaps in the systematic review evidence.

Systematic Review

Description of Studies

Study Characteristics of KODIAC-04 and KODIAC-05

The KODIAC-04 and KODIAC-05 trials¹ are 2 identical double-blind, multicentre, international, randomized phase III trials. The KODIAC-04 trial was conducted in 115 outpatient centres in Australia, Germany, Slovakia, and the US. The KODIAC-05 trial was conducted in 142 outpatient centres in Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden, the UK, and the US. There were no study sites in Canada. The source of support was the manufacturer, AstraZeneca. The purpose of the 2 trials was to investigate the efficacy and safety of naloxegol for the treatment of OIC in adult patients with noncancer pain. The trials were conducted from March 2011 to August 2012 (KODIAC-04) and to September 2012 (KODIAC-05).

Adult patients who had been taking a stable dose of oral opioids for noncancer pain and reported symptoms of active OIC (defined as < 3 SBMs per week, with ≥ 1 of the following symptoms: hard or lumpy stools, straining, and sensation of incomplete evacuation or anorectal obstruction in at least 25% of bowel movements during the 4 weeks before screening) were eligible for inclusion. Patients were not eligible for the studies if they had uncontrolled pain, cancer in the past 5 years, conditions or use of medications associated with diarrhea or constipation, and patients with gastrointestinal obstruction or at risk of bowel perforation. Each study planned to ensure that at least 50% of patients had an inadequate response to laxatives at baseline. Following a 2-week screening period and a 2-week OIC confirmation period, eligible patients were stratified by prescreening laxative response status (LIR, laxative adequate response, laxative unknown response) randomized in a 1:1:1 ratio to receive 25 mg of oral naloxegol, 12.5 mg of naloxegol, or placebo once daily for 12 weeks.

Other laxatives and bowel treatments were not allowed, except for bisacodyl rescue treatment for patients without a bowel movement for a period of 72 hours. If treatment with bisacodyl was unsuccessful, an enema could be used; if that was not successful, the patient was discontinued from the study. The baseline opioid regimen was encouraged to remain stable throughout the study but could be adjusted according to clinical judgment. Concomitant nonopioid analgesics and drugs that prolong the QT interval were not permitted.

The primary end point was response rate during the 12-week treatment period, defined as 3 or more spontaneous bowel movements (SBMs) (bowel movements without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of 1 or more SBMs over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks. The key secondary end point was response

rate at 12 weeks in the subpopulation of patients with LIR before study enrolment. The LIR population was defined as patients who took medication from 1 or more laxative classes for a minimum of 4 days within the 2 weeks before screening and whose symptoms were rated as moderate, severe, or very severe in at least 1 of the 4 questions in the laxative response questionnaire which explore frequency of laxative use, constipation symptom severity, and laxative side effects. Additional key secondary end points were time to first postdose SBM, mean number of days per week with 1 or more SBMs, constipation symptoms (measured using Patient Assessment of Constipation – Symptoms [PAC-SYM]), and HRQoL (measured using Patient Assessment of Constipation – Quality of Life [PAC-QOL]). Details regarding the relevant outcome measures are in Appendix 3 of the Supplemental Material.

A later publication by Tack et al. (2015)¹⁰ presented the findings of pooled data from the LIR populations of the KODIAC-04 and KODIAC-05 trials. This pooled analysis was prespecified in the study protocol and presented the same end points of interest as were presented in the separate KODIAC trials.

Study Characteristics of KODIAC-07

The KODIAC-07 study⁹ is a double-blind, multicentre, randomized phase III extension study that compared the long-term safety and tolerability of naloxegol with placebo after 24 weeks of treatment (i.e., 12 weeks in KODIAC-04 trial and 12 weeks in KODIAC-07) in patients with who had completed the KODIAC-04 trial (patients completing KODIAC-05 were not included).

Patients who entered the extension study continued treatment with the same regimen received in the KODIAC-04 trial. The use of rescue treatment was allowed as per the KODIAC-04 trial, and the dose of opioids for pain could be adjusted based on clinical judgment. Outcomes of interest included PAC-SYM, PAC-QOL, and harms at up to week 24.

Statistical Testing and Analysis Populations

KODIAC-04 and KODIAC-05

The sample size calculation was based on data from a 4-week phase IIb trial. With a 2-sided alpha level of 2.5%, 105 patients in each treatment group were required to achieve an overall 90% power to reject the null hypothesis for the primary outcome.

Efficacy analyses were performed in the intention-to-treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug and had at least 1 postbaseline assessment. The Bonferroni-Holm correction method, with fixed-sequence testing of the primary and key secondary end points within groups, was used to control the type I error rate at 5%. Statistical testing of the key secondary end points occurred in the following order: response rate in the LIR subpopulation, time to first postdose SBM, and number of days per week with at least 1 SBM. Each dose group was assigned 2.5% alpha. If all primary and key secondary end points were significant for 1 dose group, the alpha could be propagated to the other dose group. Safety analyses were conducted for patients in the safety population, defined as all randomized patients who had received 1 or more doses of the study drug.

For the pooled data analysis in the LIR population, analyses were not adjusted for multiplicity.

KODIAC-07

There was no formal sample size calculation. The ITT population included all patients randomly assigned to treatment in the KODIAC-04 trial who gave informed consent to continue into the extension study; this was used for baseline characteristics only. Safety analyses were conducted in the safety population, which included all patients in the ITT population who received at least 1 dose of the study drug in the extension study. HRQoL end points were presented for the modified ITT population and included patients in the safety population with at least PAC-SYM or PAC-QOL assessment at 12 weeks (end of KODIAC-04 treatment period) or 24 weeks (end of KODIAC-07 treatment period).

Patient Disposition

Details of the patient disposition for the pivotal trials and extension study are presented in Appendix 4 of the Supplemental Material.

KODIAC-04

Of the 1,750 patients screened in the KODIAC-04 trial (1,712 patients in the US and 38 patients in other countries), 652 underwent randomization: 217 to the placebo arm, 217 to the naloxegol 12.5 mg arm, and 218 to the naloxegol 25 mg arm.

Three randomized patients did not receive the study treatment (1 in the placebo group and 2 in the naloxegol 12.5 mg group). Patients who were randomized and discontinued study participation included 36 (16.6%) in the placebo group, 37 (17.1%) in the 12.5 mg group, and 44 (20.0%) in the 25 mg group. The most common reasons for study discontinuation were patient decision, AE, and loss to follow-up. For patients who were randomized and received treatment, 11 patients were found before database lock and unblinding to have participated in the program multiple times at different centres and were excluded from the ITT analysis population (3 in the placebo group, 4 in the naloxegol 12.5 mg group, and 4 in the naloxegol 25 mg group).

KODIAC-05

In the KODIAC-05 trial, 1,969 patients were screened (1,827 patients in the US and 142 patients in other countries) and 700 underwent randomization: 233 to the placebo arm, 233 to the naloxegol 12.5 mg arm, and 234 to the naloxegol 25 mg arm.

Of the patients who were randomized, 44 (18.9%) in the placebo group, 53 (22.8%) in the 12.5 mg group, and 59 (25.2%) in the 25 mg group discontinued study participation. The most common reasons for study discontinuation were patient decision, AE, and loss to follow-up. For randomized patients who received treatment, 4 patients were found before database lock and unblinding to have participated in the program multiple times at different centres and were excluded from the ITT analysis population (1 in the placebo group, 1 in the naloxegol 12.5 mg group, and 2 in the naloxegol 25 mg group).

KODIAC-07

In the KODIAC-07 study, 302 of 524 (57.6%) patients who completed KODIAC-04 were enrolled: 106 patients in the placebo arm, 97 in the naloxegol 12.5 mg arm, and 99 in the naloxegol 25 mg arm.

Five randomized patients did not receive treatment (3 patients in the placebo group, 1 patient in the 12.5 mg group, and 1 in the 25 mg group). Six patients (3 in the placebo group, 2 in the naloxegol 12.5 mg group, and 1 in the naloxegol 25 mg group) were excluded from the safety analysis population because they had previously received naloxegol at a different centre. Of the patients who were randomized, 14 (13.2%) in the placebo group, 17 (17.5%) in the 12.5 mg group, and 15 (15.2%) in the 25 mg group discontinued study participation. The most common reasons for study discontinuation were patient decision and AE.

Baseline Characteristics

Patients' baseline characteristics for full population in each trial are presented in [Table 3](#).

Patients' baseline characteristics for the LIR population in each trial are presented in Appendix 3 of the Supplemental Material. Patients' baseline characteristics for the overall population in the extension study are also presented in Appendix 3 of the Supplemental Material.

KODIAC-04 and KODIAC-05

More than 50% of patients in each trial (54.6% in KODIAC-04 and 53.2% in KODIAC-05) were classified as having an LIR. There were no important differences in baseline characteristics between the overall population and the LIR subpopulation.

KODIAC-07

In the extension study, 45% of patients had an LIR. Baseline characteristics were not reported for the subgroup with LIR.

In the overall population, 61% were female, 23.3% were Black, and 74.7% were white. The most common reason for opioid therapy was back pain (53.4%), followed by arthritis (11.5%) and fibromyalgia (6.0%). The most commonly used maintenance opioid medications were morphine, hydrocodone plus paracetamol, and oxycodone.

Table 3: Summary of Baseline Characteristics in Overall Population From Studies Included in the Systematic Review

Characteristic	KODIAC-04			KODIAC-05		
	Placebo (n = 214)	Naloxegol 12.5 mg (n = 213)	Naloxegol 25 mg (n = 214)	Placebo (n = 232)	Naloxegol 12.5 mg (n = 232)	Naloxegol 25 mg (n = 232)
Age (years), mean (SD)	52.9 (10.0)	51.9 (10.4)	52.2 (10.3)	52.3 (11.6)	52.0 (11.0)	51.9 (12.1)
Female, n (%)	140 (65.4)	135 (63.4)	118 (55.1)	145 (62.5)	149 (64.2)	147 (63.4)
Race, n (%)						
Asian	4 (1.9)	5 (2.3)	1 (0.5)	0	1 (0.4)	0
Black	44 (20.6)	42 (19.7)	38 (17.8)	44 (19.0)	41 (17.7)	40 (17.2)
White	160 (74.8)	164 (77.0)	173 (80.8)	183 (78.9)	187 (80.6)	189 (81.5)
Other	6 (2.8)	2 (0.9)	2 (0.9)	5 (2.2)	3 (1.3)	3 (1.3)

Characteristic	KODIAC-04			KODIAC-05		
	Placebo (n = 214)	Naloxegol 12.5 mg (n = 213)	Naloxegol 25 mg (n = 214)	Placebo (n = 232)	Naloxegol 12.5 mg (n = 232)	Naloxegol 25 mg (n = 232)
Opioid use (mg/day), mean (SD)	135.6 (145.8)	139.7 (167.4)	143.2 (150.1)	119.9 (103.8)	151.7 (153.0)	136.4 (134.3)
Most common maintenance opioid medications (in > 5% patients overall)						
Hydrocodone + acetaminophen	59 (27.6)	65 (30.5)	52 (24.3)	58 (25.0)	44 (19.0)	59 (25.4)
Oxycodone	49 (22.9)	48 (22.5)	57 (26.6)	54 (23.3)	70 (30.2)	65 (28.0)
Morphine	53 (24.8)	57 (26.8)	47 (22.0)	61 (26.3)	55 (23.7)	55 (23.7)
Oxycodone + acetaminophen	28 (13.1)	40 (18.8)	27 (12.6)	30 (12.9)	31 (13.4)	37 (15.9)
Tramadol	25 (11.7)	18 (8.5)	26 (12.1)	34 (14.7)	31 (13.4)	37 (15.9)
Fentanyl	17 (7.9)	15 (7.0)	14 (6.5)	18 (7.8)	29 (12.5)	16 (6.9)
Hydrocodone	18 (8.4)	14 (6.6)	11 (5.1)	17 (7.3)	17 (7.3)	13 (5.6)
Methadone	12 (5.6)	9 (4.2)	17 (7.9)	17 (7.3)	10 (4.3)	13 (5.6)
Primary reason for opioid use, %						
Back pain	56.0			56.8		
Arthritis, joint pain, or fibromyalgia	18.5			21.6		
Headache, migraine, neuralgia, or other pain syndrome	5.9			4.5		
Other ^a	19.7			17.1		
Duration of opioid use (months), mean (SD)	39.5 (39.4)	44.4 (47.3)	44.5 (47.8)	43.0 (51.4)	48.5 (48.7)	40.9 (41.6)
Characteristics of OIC, mean (SD)						
SBMs per week	1.4 (0.89)	1.4 (0.85)	1.3 (1.11)	1.5 (0.95)	1.6 (1.05)	1.3 (0.85)
Score for severity of Straining ^b	3.3 (0.78)	3.1 (0.79)	3.2 (0.84)	3.3 (0.81)	3.1 (0.82)	3.2 (0.82)
Score for stool consistency ^c	2.8 (1.22)	2.9 (1.20)	2.9 (1.16)	3.0 (1.29)	3.0 (1.32)	2.8 (1.26)
Laxative use, n (%)						
Within previous 6 months	177 (82.7)	184 (86.4)	181 (84.6)	197 (84.9)	189 (81.5)	194 (83.6)
Within previous 2 weeks	151 (70.6)	140 (65.7)	166 (77.6)	173 (74.6)	156 (67.2)	166 (71.6)

Characteristic	KODIAC-04			KODIAC-05		
	Placebo (n = 214)	Naloxegol 12.5 mg (n = 213)	Naloxegol 25 mg (n = 214)	Placebo (n = 232)	Naloxegol 12.5 mg (n = 232)	Naloxegol 25 mg (n = 232)
Laxative response status						
Inadequate, n (%) ^d	118 (55.1)	115 (54.0)	117 (54.7)	121 (52.2)	125 (53.9)	124 (53.4)
Unknown, % ^e	44.6%					
Adequate, % ^f	1.6%					

ITT = intention to treat; OIC = opioid-induced constipation; SD = standard deviation; SBM = spontaneous bowel movement.

^aOther conditions causing pain, primarily musculoskeletal disorder.

^bSeverity of straining was measured on the following scale: 1 = not at all; 2 = a little bit; 3 = a moderate amount; 4 = a great deal; and 5 = an extreme amount.

^cStool consistency was assessed on the Bristol Stool Scale (types 1 to 7, with 1 = small, hard, lumpy stool and 7 = watery stool).

^dPatients with LIR were those who took laxatives in 1 or more laxative classes for a minimum of 4 days within 2 weeks before screening and had ratings of moderate, severe, or very severe on 1 or more of the 4 stool symptom domains in the baseline laxative response questionnaire.

^ePatients with LUR were those who reported no or infrequent (< 4 days) use of laxatives in the 2 weeks before study screening.¹⁰

^fPatients with LAR were those who had no symptoms or very mild symptoms associated with laxative use.¹⁰

Source: Chey et al. (2014).¹

Treatment Exposure and Concomitant Medications

The duration of study drug exposure in the pivotal trials and extension study are summarized in Appendix 4 of the Supplemental Material.

KODIAC-04 and KODIAC-05

The mean durations of study exposure were 77.5 days (KODIAC-04) and 76.1 days (KODIAC-05) for the placebo groups, 77.4 days (KODIAC-04) and 75.9 days (KODIAC-05) for the naloxegol 12.5 mg groups, and 74.3 days (KODIAC-04) and 72.4 days (KODIAC-05) for the naloxegol 25 mg groups. Information on concomitant medications was not reported.

KODIAC-07

The mean duration of cumulative exposure from the first dose in KODIAC-04 to the last dose in KODIAC-07 was 163.2 days for the placebo group, 163.5 days for the naloxegol 12.5 mg group, and 166.8 days for the naloxegol 25 mg group.

In the extension study, 93.2% of the full patient population took at least 1 concomitant medication (other than opioids). The most common concomitant medications were gabapentin (17.9%), omeprazole (14.9%), lisinopril (14.2%), alprazolam (11.8%), simvastatin (12.5%), vitamins (11.8%), and Aspirin (11.1%). The proportion of patients taking concomitant medications was not reported in the LIR subpopulation or by study treatment group.

Critical Appraisal

Internal Validity

KODIAC-04 and KODIAC-05

The risk of bias in the randomization process was low. The randomization schedule was generated using a computer software program (an interactive voice response system). The balanced block randomization was stratified by response to laxatives (i.e., LIR, laxative adequate response, and laxative unknown response); this ensured prognostic balance in the LIR subpopulation of interest to this review. The randomization seemed to be effective; there were no notable imbalances across treatment groups regarding baseline demographic and disease characteristics.

Patients and investigators were blind to treatment assignment. The active and placebo tablets were identical in size and colour and packaged and labelled in a manner to ensure blinding throughout the study. However, there is some risk that the higher rate of AEs reported in the naloxegol 25 mg group compared to the other 2 treatment groups may have led to unblinding. If this were the case, there would be a potential for the reporting of subjective outcomes to be biased, but it is not possible to ascertain whether this occurred.

There is likely low risk of bias due to deviations from the assigned intervention and nonadherence to the study interventions. The mean dose of opioids remained stable throughout the studies, and the mean duration of exposure to naloxegol or placebo was similar across groups. Concomitant treatments were not reported, and the protocol disallowed treatments that would likely affected efficacy.

Efficacy analyses were conducted in the ITT population which is appropriate to assess the effect of assignment to the intervention. Patients who were found to have participated in a naloxegol program at other centres were not included in the ITT population. This number was low ($n = 11$ in KODIAC-04 and $n = 4$ in KODIAC-05) and unrelated to prognosis so would not have introduced bias.

Limited information was provided in the study publication to inform a robust assessment of the risk of bias due to missing outcome data. There was a high proportion of study discontinuations (17.5% in KODIAC-04 and 22.3% in KODIAC-05). There were more discontinuations due to AEs in the naloxegol 25 mg group, and several reasons for discontinuation were nonspecific (e.g., patient decision, loss to follow-up). The risk of bias due to missing outcome data would affect the efficacy outcomes in the following ways:

- **Response rate:** The response end point relied on reporting of SBM by the patient in electronic diaries. If at least 4 days each week were reported, data were imputed such that the frequency of SBMs over the recorded days would be consistent with days that electronic diaries were not completed. This assumed that unreported days were missing completely at random, an assumption that cannot be validated. Patients were considered as nonresponders in any given week if they did not complete electronic diaries for at least 4 days or discontinued the study. This approach assumed that all reasons for noncompletion and discontinuation were compatible with lack of efficacy. Reasons for discontinuation do not suggest that this was the case. The extent of potential bias introduced cannot be quantified because the completeness of electronic diaries and extent of imputation was not reported.

- **Change from baseline in proportion of days with at least 1 complete SBM:** Similar assumptions were made to assess the change from baseline in proportion of days per week with complete SBM, except for weeks with fewer than 4 days of reporting or patients who dropped out were considered “missing.” The mixed model for repeated measures used in the analysis implicitly handles the missing data under a missing-at-random assumption, which is unverifiable and may not be compatible with the reasons for dropout. The extent of potential bias introduced cannot be quantified because the completeness of electronic diaries and extent of imputation was not reported in the publication.
- **Time to first postdose SBM:** The number of patients censored and the reasons for censoring were not reported so it is not possible to assess the potential for bias or draw conclusions on the potential for bias due to informative censoring.

There were no sensitivity analyses to understand the robustness of the findings to different plausible assumptions about the missing data.

It is likely there was low risk of bias due to measurement of study outcomes.

The trials were adequately powered to detect a 25% difference in treatment response in naloxegol compared to placebo. The statistical analysis plan in the pivotal trials included a provision for correcting for multiplicity when conducting tests for primary and key secondary end points to control the overall type I error rate. In the KODIAC-05 trial, the primary end point was nonsignificant in the 12.5 mg naloxegol group. Subsequent end points tested in that group should be considered to be at increased risk of type I error.

Interpretation of results for the time to first postdose SBM was limited by incomplete reporting. The median time to first postdose SBM and 95% CI were reported for each study group in the full and LIR populations, as well as the P values to determine between-group statistical significance. However, estimated between-group differences with CIs were not reported, precluding judgments about the precision of the differences.

Outcomes based on the PAC instruments were only assessed using the pooled data in the LIR population, and analyses were unadjusted for multiplicity. Additionally, there is a risk of bias due to missing outcome data in these analyses due to a high proportion of missing data and reliance on a mixed model for repeated measures that implicitly handles missing data under a missing-at-random assumption. The reasons for missing data suggest that this assumption may not be valid, and no sensitivity analyses were provided to assess the robustness of the results to different plausible assumptions about the missing data.

KODIAC-07

The KODIAC-07 study was double-blinded, which protects against biased reporting of subjective HRQoL outcomes and harms.

There is a risk of selection bias; many patients from the KODIAC-04 study did not enrol in the KODIAC-07 study. Because this is not the initial randomized population, we cannot consider the groups to still be prognostically balanced.

Analysis of HRQoL outcomes are descriptive; therefore, estimated between-group differences with CIs were not reported, which precludes judgments about the effect and precision of the differences.

The rate of study discontinuations was also high, with 81% of enrolled patients completing the study; there were similar rates of completion in each study group. There is a risk bias due to missing data. Complete cases (i.e., 1 or more PAC-SYM or PAC-QOL assessments beyond the initial assessment at enrolment) were reported and would be valid only if the data are missing completely at random, which is unlikely to be a valid assumption.

External Validity

KODIAC-04 and KODIAC-05

The KODIAC-04 and KODIAC-05 trials took place in Australia, Europe, and the US. Most participants were enrolled in the US. There were no study sites in Canada. The clinical experts did not express any concerns that differences in clinical practice, general medical care, reporting of AEs, and access to health care resources among the countries. The clinical experts also confirmed that determination of OIC by symptomology in the pivotal trials was similar to clinical practice in Canada. The dosing (25 mg per day) and administration (orally) of naloxegol was consistent with the Health Canada–approved product monograph. The trials included a 12.5 mg daily dose to explore the threshold for the minimally effective dose; this reflected clinical practice because the clinical experts might often start patients on the lower dose. The clinical experts on the review team confirmed that the baseline demographic and disease characteristics were representative of the patients with OIC and noncancer pain seen in clinical practice.

The reported efficacy outcomes were appropriate. Treatment response was identified in this review as a goal of therapy.

The clinical experts noted that the primary outcome of response rate was clinically relevant, and the timing of assessment used in the pivotal trials was consistent with clinical practice. Response was assessed at 12 weeks, which may align with the frequency of visits in clinical practice. The clinical experts on the review team indicated that most clinicians feel the first 2 weeks of treatment are the pivotal time to know if the drug is effective or not; however, patient visits occur at longer intervals. An assessment at 12 weeks may provide insight into maintenance of the efficacy over time. In practice, the treatment dosage (e.g., as needed rather than daily) and duration would then be tailored to the individual patient's needs rather than remain constant over time.

The key secondary outcomes were also clinically relevant. The clinical experts informed us that they asked patients about their number of bowel movements per week rather than ascertaining the frequency of SBMs as an outcome of treatment as reported in the literature, although they did not use the term “spontaneous” with patients. The clinical experts on the review team also did not use the validated PAC instruments in clinical practice, but did ask individual questions about abdominal pain, physical discomfort, rectal symptoms (incomplete versus complete evacuation, tenesmus, urgency), unexpected pain, physical discomfort, tolerability, and functionality. For context, the PAC instruments are not often used in clinical practice outside of academic centres or research trials.

Although there may be a few limitations to generalizability, as discussed, the results of the pivotal trials appear to be generalizable to Canadian clinical practice for treating patients with OIC and noncancer pain.

KODIAC-07

The study population for the analysis of the KODIAC-07 trial consisted of patients who took part in the KODIAC-04 trial; therefore, it is reasonable to expect that its same strengths and limitations related to generalizability also apply to KODIAC-07. Because patients needed to complete the KODIAC-04 study before enrolling, the KODIAC-07 population introduces some selection bias for patients who chose to continue the study drugs and to those with a potentially lower risk of harms; therefore, the findings may not be generalizable to the population of patients who are taking naloxegol. Although KODIAC-04 was an international trial, all participants in the extension study were from the US.

Results

Efficacy

Results for efficacy outcomes important to this review from the KODIAC-04 and KODIAC-05 trials in the overall population and LIR subpopulation are presented in [Table 4](#) and [Table 5](#), respectively.

KODIAC-04 and KODIAC-05

Key results include the following:

- In the LIR subpopulation, point estimates for response rate favoured naloxegol over placebo. The between-group differences compared to placebo of naloxegol at both doses exceeded the clinical minimally important threshold of 10% for clinical significance. The results were similar in the overall population, but the magnitude of each effect estimate appeared larger in the LIR population.
- Because the primary end point (response rate in the overall population) was not statistically significantly different (or clinically important) in the KODIAC-05 trial, statistical testing in the 12.5 mg naloxegol group stopped. The key secondary end points (including response rate in the LIR subpopulation) can be considered to be at increased risk of type I error.
- In the LIR subpopulation, median times to first postdose SBM favoured naloxegol over placebo. However, between-group differences with CIs for the full population, pooled LIR subpopulation, and the LIR subpopulation in the individual studies were not reported. In the overall population, the median time to first postdose SBM in the naloxegol groups was shorter compared to placebo.
- In the pooled LIR subpopulation, the absolute between-group differences in days per week with 1 or more complete SBMs favoured both naloxegol groups over placebo. The results were similar in the overall population and individual LIR subpopulations in each study.
- In the pooled LIR subpopulation, the between-group differences in PAC-SYM total score at 12 weeks compared to baseline favoured naloxegol over placebo, but did not meet the clinical minimally important threshold of 1.0 for clinical significance. No formal analyses were performed in the overall population.

Table 4: Summary of Key Efficacy Results From Studies Included in the Systematic Review

Variable	KODIAC-04			KODIAC-05		
	Placebo (n = 214)	Naloxegol 12.5 mg (n = 213)	Naloxegol 25 mg (n = 214)	Placebo (n = 232)	Naloxegol 12.5 mg (n = 232)	Naloxegol 25 mg (n = 232)
Response rate^a (overall population)¹						
Response rate, %	29.4	40.8	44.4	29.3	34.9	39.7
Absolute group difference versus placebo, % (95% CI)	Reference	11.4 (2.4 to 20.4)	15.0 (5.9 to 24.0)	Reference	5.6 (-2.9 to 14.1)	10.3 (1.7 to 18.9)
P value	Reference	0.02	0.001	Reference	0.20	0.02
Response rate^a (LIR population)¹						
Number of patients in LIR population, n	118	115	117	121	125	124
Response rate, %	28.8	42.6	48.7	31.4	42.4	46.8
Absolute group difference versus placebo, % (95% CI)	Reference	13.8 (1.6 to 26.0)	19.9 (7.7 to 32.1)	Reference	11.0 (-1.0 to 23.0)	15.4 (3.3 to 27.4)
P value	Reference	0.03	0.002	Reference	0.07 ^a	0.01
Time to first postdose SBM^b (LIR population)¹⁰						
Number of patients in analysis, n	118	115	117	121	125	124
Time to first postdose SBM (hours), median (95% CI)	43.4 (25.2 to 48.2)	20.6 (8.1 to 23.5)	5.4 (3.9 to 10.7)	38.2 (28.9 to 57.4)	12.8 (6.4 to 21.9)	18.1 (6.5 to 22.8)
P value	Reference	< 0.002	< 0.001	Reference	< 0.001 ^c	< 0.002
Days per week with ≥ 1 complete SBM^d (LIR population)¹⁰						
Number of patients in analysis, n	118	114	117	120	122	121
Change from baseline (days), LS mean (SEM)	1.59 (0.18)	2.21 (0.18)	2.51 (0.18)	1.76 (0.17)	2.36 (0.17)	2.69 (0.18)
Groups mean difference versus placebo (95% CI)	Reference	0.61 (0.18 to 1.05)	0.92 (0.48 to 1.35)	Reference	0.60 (0.17 to 1.03)	0.92 (0.49 to 1.35)
P value	Reference	0.006	< 0.001	Reference	0.006 ^c	< 0.001
PAC-SYM total score^{e,f} (overall population)⁹						
Number of patients at baseline, n	99	91	91	NR	NR	NR
Baseline score, mean (SD)	1.8 (0.70)	1.8 (0.69)	1.8 (0.70)	NR	NR	NR
Number of patients at week 24, ^g n	91	78	85	NR	NR	NR
Score at week 24, mean (SD)	1.0 (0.74)	0.9 (0.67)	0.9 (0.78)	NR	NR	NR
PAC-QOL total score^{e,f} (overall population)⁹						
Number of patients at baseline, n	98	91	90	NR	NR	NR
Baseline score, mean (SD)	1.9 (0.73)	2.1 (0.81)	2.0 (0.74)	NR	NR	NR

Variable	KODIAC-04			KODIAC-05		
	Placebo (n = 214)	Naloxegol 12.5 mg (n = 213)	Naloxegol 25 mg (n = 214)	Placebo (n = 232)	Naloxegol 12.5 mg (n = 232)	Naloxegol 25 mg (n = 232)
Number of patients at week 12, ^h n	97	89	89	NR	NR	NR
Score at week 12, mean (SD)	1.1 (0.77)	1.1 (0.76)	1.1 (0.82)	NR	NR	NR
Number of patients at week 24, ^g n	91	78	85	NR	NR	NR
Score at week 24, mean (SD)	1.1 (0.79)	1.2 (0.74)	1.0 (0.84)	NR	NR	NR

CI = confidence interval; ITT = intention to treat; LIR = laxative inadequate response; LS = least square; NR = not reported; PAC-QOL = Patient Assessment of Constipation – Quality of Life; PAC-SYM = Patient Assessment of Constipation – Symptoms; SBM = spontaneous bowel movement; SEM = standard error of the mean; SD = standard deviation.

^aAnalysis method for response rate: Cochran-Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, laxative adequate response, laxative unknown response). Not stratified for LIR population.¹

^bAnalysis method for time to first postdose SBM: Statistical model not reported, appears that medians are estimated with the Kaplan-Meier method; difference between groups tested with a log-rank test stratified by response to laxatives at baseline (LIR, laxative adequate response, laxative unknown response).¹ Not stratified for LIR population.¹⁰

^cTested after failure of the statistical hierarchy. There is an increased risk of type I error (i.e., erroneously rejecting the null hypothesis).¹

^dAnalysis method for days per week with complete SBM: Mixed-model repeated measures was used with fixed effects of treatment, baseline value of the dependent variable, week, treatment-by-week interaction, and prescreening laxative response status, with centre and patient as random effects.¹

^ePossible values range from 0 to 4, with higher scores indicating worse outcomes.⁹

^fAnalysis method for PAC-SYM and PAC-QOL: descriptive statistics, no between-group differences or statistical testing.⁹

^gWeek 24 = week 12 of KODIAC-7 extension study.⁹

^hWeek 12 = end of treatment period in KODIAC-4 study.⁹

Sources: Chey et al. (2014),¹ Tack et al. (2015),¹⁰ and Webster et al. (2016).⁹

Table 5: Summary of Pooled Key Efficacy Results in the LIR Subpopulation

Variable	Pooled KODIAC-04 and KODIAC-05		
	Placebo (n = 239)	Naloxegol 12.5 mg (n = 240)	Naloxegol 25 mg (n = 241)
Response rate^a			
Number of pooled patients in analysis, n	239	240	241
Response rate, %	30.1	42.5	47.7
P value ^b	Reference	< 0.05	< 0.01
Time to first postdose SBM^c			
Response rate, %	239	240	241
Absolute group difference versus placebo, % (95% CI)	41.1 (30.9 to 47.7)	19.2 (9.3 to 21.8)	7.6 (5.2 to 18.9)
P value ^b	Reference	< 0.001	< 0.001
Days per week with ≥ 1 complete SBM^d			
Number of pooled patients in analysis, n	238	236	238
Change from baseline (days), LS mean (SEM)	1.69 (0.12)	2.29 (0.13)	2.60 (0.13)
LS mean group difference versus placebo, % (95% CI)	Reference	0.61 (0.30 to 0.91)	0.91 (0.61 to 1.22)

Variable	Pooled KODIAC-04 and KODIAC-05		
	Placebo (n = 239)	Naloxegol 12.5 mg (n = 240)	Naloxegol 25 mg (n = 241)
P value ^b	Reference	< 0.001	< 0.001
PAC-SYM total score^{d,e}			
Number of pooled patients in analysis, n	191	189	177
Change from baseline (score), LS mean (SEM)	-0.56 (0.05)	-0.83 (0.05)	-0.82 (0.05)
LS mean group difference versus placebo, % (95% CI)	Reference	-0.27 (-0.40 to -0.13)	-0.26 (-0.39 to -0.12)
P value ^b	Reference	< 0.001	< 0.001

CI = confidence interval; LIR = laxative inadequate response; LS = least square; PAC-SYM = Patient Assessment of Constipation – Symptoms; SBM = spontaneous bowel movement; SEM = standard error of the mean.

^aAnalysis method for response rate: Cochran-Mantel-Haenszel test stratified by study.

^bStatistical testing was not adjusted for multiplicity. There is an increased risk of type I error (i.e., erroneously rejecting the null hypothesis).

^cAnalysis method for time to first postdose SBM: Medians estimated using the Kaplan-Meier method; between-group difference tested using the log-rank test.

^dAnalysis method for change from baseline in days per week with 1 SBM and PAC-SYM: Mixed model for repeated measures with fixed effects for the baseline, treatment and treatment-time interaction; random effect of study centre.

^ePossible values range from 0 to 4, with lower scores indicating better outcomes.⁹

Source: Tack et al. (2015).¹⁰

KODIAC-07

The mean PAC-SYM and PAC-QOL total scores at 24 weeks for the overall population were reported but no formal analyses were performed.

Harms

Details of the patient disposition for the pivotal trials and extension study are presented in Appendix 4 of the Supplemental Material.

KODIAC-04 and KODIAC-05

Detailed results for harms in the full population of the KODIAC-04 and KODIAC-05 studies are available in Chey et al. (2014).¹

Detailed results for harms in the pooled LIR population from the KODIAC-4 and KODIAC-5 studies are available in Tack et al. (2015).¹⁰ Herein, the focus is on results for the LIR population to align with the reimbursement request, with supplemental information from the full population for context. The following are the results at 12 weeks of follow-up.

- In the pooled LIR subpopulation, 152 of 241 patients (63.1%) in the naloxegol 25 mg group and 120 of 237 (50.6%) in the naloxegol 12.5 mg group reported 1 or more AEs compared to 119 of 238 patients (50.0%) in the placebo group at 12 weeks. The most common treatment-emergent AEs in the naloxegol groups included abdominal pain, diarrhea, nausea, and flatulence. These findings are aligned with those reported in the overall population.

- In the pooled LIR subpopulation, 7 of 237 patients (3.0%) in the naloxegol 12.5 mg group and 8 of 241 patients (3.3%) in the 25 mg naloxegol group versus 13 of 238 patients (5.5%) in the placebo group reported 1 or more serious adverse events (SAEs). Details on the specific SAEs were not reported; however, based on results from the full population, it was apparent that no single SAE was reported in more than 2 patients per group.
- In the pooled LIR subpopulation, 24 of 241 of patients (10%) in the 25 mg group reported an AE that led to permanent discontinuation of the study drug compared to 8 of 237 (3.4%) in the naloxegol 12.5 mg group and 11 of 238 patients (4.6%) in the placebo group. The absolute between-group difference of 5.4% in the naloxegol 25 mg group compared to the placebo group exceeded the minimally important threshold of 5% for clinical significance. Details of the specific AEs leading to discontinuation were not reported, but results from the full population indicate that discontinuations were due to gastrointestinal AEs.
- There were no treatment-related deaths reported in either study group in the LIR subpopulation. There were 2 deaths reported in the full population; both occurred in the KODIAC-04 trial in the 12.5 mg naloxegol group. One death was due to cancer diagnosed during the study and the other was due to complications of a heart valve replacement.
- In the full population, there were 2 patients with major cardiovascular events in the naloxegol groups (1 in the 12.5 mg group and 1 in the 25 mg group) and 2 events in the placebo group. It was not clear if the major cardiovascular events occurred in patients who had LIR.
- There were 8 patients who experienced drug withdrawal syndrome (5 in the naloxegol 25 mg group, 2 in the naloxegol 12.5 mg group, and 1 in the placebo group). It was unclear if these patients were part of the LIR population.

KODIAC-07

Results for harms in the long-term extension study (KODIAC-7) are available in Webster et al. (2016).⁹ Results presented here are for the full population of patients who entered the extension study up to 24 weeks:

- At 24 weeks, 40 of 97 patients (41.2%) in the naloxegol 25 mg group reported any AE compared to 32 of 94 (34.0%) in the naloxegol 12.5 mg group and 33 of 100 patients (33.0%) in the placebo group at 24 weeks. The most common AEs (> 3% of patients) in the naloxegol 12.5 mg group were diarrhea and sinusitis. The most common AEs in the naloxegol 25 mg group were arthralgia, abdominal pain, nausea, and gastroenteritis, back pain, and falls. Most AEs in all study groups were mild to moderate in severity.
- At 24 weeks, 6 SAEs occurred in 93 patients (6.4%) in the naloxegol 12.5 mg group and 6 SAEs in 97 patients (6.2%) in the naloxegol 25 mg group compared to 5 of 100 patients (5.0%) in the placebo group.
- Four of 94 patients (4.3%) in the naloxegol 12.5 mg group and 4 of 97 (4.1%) reported an AE that led to permanent discontinuation of the study drug compared to 5 of 100 patients (5.0%) in the placebo group.

- There was 1 report of a major cardiovascular event in the naloxegol 12.5 mg group. The patient was in a serious car accident and experienced a serious myocardial ischemia secondary to coronary artery disease.
- Two patients (1 in the naloxegol 12.5 mg group and 1 in the naloxegol 25 mg group) had AEs potentially related to opioid withdrawal syndrome.
- One patient in the naloxegol 25 mg group experienced orthostatic hypotension. Four patients (2 in the naloxegol 12.5 mg group, 1 in the naloxegol 25 mg group, and 1 in the placebo group) experienced hypertension. These events were mild to moderate.

Long-Term Extension Study

The long-term extension study⁹ was reported in the Systematic Review section.

Indirect Evidence

We did not identify any ITCs relevant to this report.

Studies Addressing Gaps in the Systematic Review Evidence

No randomized or nonrandomized studies were identified that compared naloxegol to relevant comparators in the population of patients with cancer. Three single-arm observational studies have been summarized to provide evidence of the potential efficacy and harms of naloxegol for OIC in adult patients with cancer pain and an LIR.

Table 6: Summary of Gaps in the Systematic Review Evidence

First author (year)	Study name	Evidence gap
Cobo Dols et al. (2023) ¹⁴	One-Year Efficacy and Safety of Naloxegol on Symptoms and Quality of Life Related to Opioid-Induced Constipation in Patients With Cancer: KYONAL Study ¹⁴	Evidence for treatment of naloxegol for OIC in adult patients with LIR and cancer pain
Lemaire et al. (2021) ¹⁵	Effectiveness of Naloxegol in Patients With Cancer Pain Suffering From Opioid-Induced Constipation ¹⁵	
Ostan et al. (2021) ¹⁶	Can Naloxegol Therapy Improve Quality of Life in Patients With Advanced Cancer? ¹⁶	

LIR = laxative inadequate response; OIC = opioid-induced constipation.

Description of Studies

Characteristics of the 3 included studies are summarized in [Table 7](#).

Table 7: Characteristics of Studies Addressing Gaps in Systematic Review Evidence

First author (year), design, country, sample size	Patient population	Intervention	Relevant end points, follow-up
Cobo Dols et al. (2023) ¹⁴ Multicentre,	• Patients aged > 18 years (mean = 61.5 years) • Diagnosis of active oncological disease	Naloxegol • 25 mg/day (n = 111) or 12.5 mg/day (n = 14) or	Efficacy • Response rate

First author (year), design, country, sample size	Patient population	Intervention	Relevant end points, follow-up
prospective, noncomparative, observational study Spain N = 126	requiring treatment with opioids for pain control (mean time from cancer diagnosis = 34.7 months; presence of metastases = 67.5%) • Symptoms of OIC (average < 3 SBM per week with associated symptoms of constipation in at least 25% of SBM mean duration = 3.1 months) • LIR to the treatment of OIC • Indication for the treatment with naloxegol • Concomitant laxative use during the study = 48.4%	6.25 mg/day (n = 1) Rescue treatment was allowed.	• PAC-SYM • PAC-QOL Harms • AEs • SAEs • WDAEs Follow-up: 12 months
Lemaire et al. (2021) ¹⁵ Multicentre, prospective, noncomparative, observational study France N = 124	• Patients aged > 18 years (mean = 62.1 years) • Cancer pain treated with step II or III opioids for their cancer pain (median duration of opioid use = 9.0 weeks) • OIC (in accordance with the ROME IV criteria; mean duration = 4.9 weeks) • LIR to the treatment of OIC (symptoms despite the use of laxatives for at least 4 days) • Starting naloxegol treatment for OIC with LIR • Concomitant laxative use = 76.2%	Naloxegol • 25 mg/day (78.2%) or 12.5 mg/day (21.8%)	Efficacy • Response rate • PAC-SYM • PAC-QOL Harms • AEs • SAEs • WDAEs Follow-up: 4 weeks (efficacy), up to 14.9 months (harms)
Ostan et al. (2021) ¹⁶ Multicentre, prospective, noncomparative, observational study Italy N = 150	• Patients aged > 18 years (mean = 72.7 years) • Patients with advanced care (unlikely to be cured or controlled with treatment) • OIC (in accordance with the ROME IV criteria; mean duration = 4.9 weeks) • LIR for at least 3 days (not relieved by first-line laxatives) • Clinical indication for starting a therapy with 25 mg/day naloxegol • Concomitant laxative use = 100%	Naloxegol • 25 mg/day Rescue treatment was allowed.	Efficacy • Time to first postdose SBM • PAC-QOL Harms • AEs • SAEs • WDAEs Follow-up: 4 weeks

AE = adverse event; LIR = laxative inadequate response; OIC = opioid-induced constipation; PAC-QOL = Patient Assessment of Constipation – Quality of Life; PAC-SYM = Patient Assessment of Constipation – Symptoms; SAE = serious adverse event; SBM = spontaneous bowel movement; WDAE = withdrawal due to adverse event.

Source: Cobo Dols et al. (2023),¹⁴ Lemaire et al. (2021),¹⁵ Ostan et al. (2021).¹⁶

Critical Appraisal

Cobo Dols et al. (2023)

The single-group design of the study by Cobo Dols et al. (2023)¹⁴ does not support causal interpretations about the effect of naloxegol. It is not clear how patients were selected so there may be a possibility of selection bias. The open-label design results in risk of bias in measurement of subjective HRQoL outcomes and reporting of harms. Rescue treatment was allowed, and this was not considered in the definition of the response end point. There was no mention of a stable opioid dose and patients could use concomitant treatments, including 48% of patients who used laxatives; therefore, the effect of naloxegol cannot be isolated. Loss to follow-up was substantial (75% at 12 months). The methods used to deal with missing data were either not reported (response rate) or not appropriate (last observation carried forward for PAC-SYM and PAC-QOL), resulting in bias due to missing outcome data. Most patients (78%) received the 25 mg per day dose; therefore, generalizability to other doses may be reduced. Although the study took place in Spain, according to the clinical experts on the review team, it is likely generalizable to Canada.

Lemaire et al. (2021)

The single-group design of the study by Lemaire et al. (2021)¹⁵ does not support causal interpretations about the effect of naloxegol. There may be a risk of selection bias; 51 of 84 specialists who were invited agreed to participate and it was unclear how participating physicians selected patients to include in the study. The open-label design results in risk of bias in measurement of subjective HRQoL outcomes and reporting of harms. There was no mention of a stable opioid dose; patients could also use concomitant treatments, including 76% of patients who used laxatives. The magnitude of the response rate appeared to be lower (not tested) in patients without laxative use; however, the reliability of this result was limited due to a rather small sample size ($n = 19$) and there was no formal testing. Loss to follow-up was high (31% at 4 weeks). Missing data were not replaced, resulting in bias due to missing outcome data. Efficacy was assessed at 4 weeks, so longer-term benefit is unknown, whereas the median follow-up for harms was 4.3 months (range, 0.3 to 14.9 months). The study occurred in France; however, according to the clinical experts on the review team, this is likely generalizable to Canada.

Ostan et al. (2021)

The single-group design of the study by Ostan et al. (2021)¹⁶ does not support causal interpretations about the effect of naloxegol. The enrolment method was unclear, and there may be a possibility of selection bias. The open-label design results in risk of bias in measurement of subjective HRQoL outcomes and reporting of harms. There was no mention of a stable opioid dose, and patients could use concomitant treatments. All patients were using laxatives; therefore, the effect of naloxegol cannot be isolated. Loss to follow-up was substantial (76% stopped taking naloxegol before 4 weeks). The methods used to deal with missing data were not reported, which likely resulted in bias due to missing outcome data. Follow-up time was 4 weeks so longer-term benefits and harms are unknown. Reporting of AEs was not comprehensive and included only patients who completed follow-up (rather than the safety population). The study occurred in Italy; however, according to the clinical experts on the review team, this is likely generalizable to Canada.

Results

Results from the observational studies for efficacy, HRQoL, and harms outcomes important to this review are presented in [Table 8](#).

Table 8: Summary of Outcomes in Studies Addressing Gaps in Systematic Review Evidence

First author (year), sample size, follow-up	Efficacy outcomes	Harms outcomes
Cobo Dols et al. (2023) ¹⁴ N = 126 Follow-up: 12 months	Response rates - Month 3 (n = 96) = 76.2% (95% CI, 67.8% to 83.3%) - Month 12 (n = 98) = 77.8% (95% CI, 69.5% to 84.7%) PAC-SYM: - Authors noted an improvement in total scores from baseline to 12 months ($P < 0.0001$), but no data were provided. - Clinically relevant improvement (≥ 0.5 points): 64.3% at 3 months and 65.9% at 12 months. CIs were not reported. PAC-QOL: - Authors noted an improvement in total scores from baseline to 12 months ($P < 0.0001$), but no data were provided. - Clinically relevant improvement (≥ 0.5 points): 61.9% at 3 months and 58.7% at 12 months. CIs not reported.	28 AEs in 19 (15.1%) patients 2 of the 28 AEs were SAEs 67% of AEs occurred in first 15 days of treatment: abdominal pain (n = 13), diarrhea (n = 6), abdominal bloating (n = 5), nausea (n = 3), dysesthesia (n = 1) - WDAEs by 6 (4.8%) patients (abdominal pain, nausea, or diarrhea) - Deaths due to AE: NR
Lemaire et al. (2021) ¹⁵ N = 124 Follow-up: 4 weeks (efficacy); up 14.9 months (harms)	Response rates, - All patients with evaluable data at follow-up (n = 79) = 73.4% (95% CI, 63.7% to 83.2%) - Patients with laxative use (n = 60) = 76.7% (95% CI, 66.0% to 87.4%) - Patients without laxative use (n = 19) = 63.2% (95% CI, 41.5% to 84.8%) PAC-SYM (n = 62) - Baseline: mean = 2.1 (SD = 0.7) - Week 4: mean = 1.3 (SD = 0.8) - Clinically relevant improvement (≥ 0.5 points): 70.7% (95% CI, 60.4% to 81.0%) PAC-QOL (n = 62) - Baseline: mean = 2.2 (SD = 0.6) - Week 4: mean = 1.5 (SD = 0.7) - Clinically relevant improvement (≥ 0.5 points): 62.9% (95% CI, 51.5% to 74.2%)	43 (32.8%) patients with ≥ 1 AE 15 AEs in 11 (8.9%) patients related to naloxegol, including 12 GI events in 9 (7.2%) patients 21 patients (16.0%) with ≥ 1 SAE - WDAEs by 22 (16.9%) patients (mainly cancer progression or diarrhea) - Deaths due to AE: NR

First author (year), sample size, follow-up	Efficacy outcomes	Harms outcomes
Ostan et al. (2021) ¹⁶ N = 150 Follow-up: 4 weeks	Time to first SBM (n = NR): mean = 10 hours (SD = 16 hours) • PAC-QOL (n = 78): Authors noted improvement in all 4 dimensions ($P < 0.010$), but no data were provided.	Reporting of AEs was not comprehensive and included only patients who completed follow-up; the following were mentioned: • moderate abdominal pain in 15 patients • severe abdominal pain in 6 patients • nausea in 6 patients • other AEs (meteorism, lower back pain, headache) in 10 patients • WDAEs in 13 patients • deaths in 21 patients

AE = adverse event; CI = confidence interval; NR = not reported; PAC-QOL = Patient Assessment of Constipation – Quality of Life; PAC-SYM = Patient Assessment of Constipation – Symptoms; SAE = serious adverse event; SBM = spontaneous bowel movement; SD = standard deviation; WDAE = withdrawal due to adverse event.

Sources: Cobo Dols et al. (2023),¹⁴ Lemaire et al. (2021),¹⁵ and Ostan et al. (2021).¹⁶

Discussion

Efficacy

Based on input from the clinical experts, not all patients respond, and others may become refractory to existing treatment options for OIC. Additionally, available treatment options may be undesirable to patients due to taste, need for high fluid intake, or harms. There is an unmet need for treatments that are better tolerated and easily administered. Therefore, a review was undertaken to understand the efficacy of naloxegol compared to osmotic laxatives, stimulant laxatives, and methylnaltrexone for OIC in patients with LIR and noncancer or cancer pain. No evidence was identified regarding the efficacy of naloxegol versus an active comparator, but we did find evidence for naloxegol compared to placebo for the treatment of OIC in adult patients with LIR and noncancer pain.

We identified 2 trials (KODIAC-04 and KODIAC-05) that included patients with OIC and noncancer pain. The studies tested the efficacy and safety of naloxegol versus placebo in patients with and without response to laxatives. The primary end point, treatment response at 12 weeks, was met in the full population for the 25 mg dose. The magnitude of effect seemed slightly smaller for the 12.5 mg dose and did not reach statistical significance in the KODIAC-05 trial. In the LIR subgroup, the results of the 2 trials (KODIAC-04 and KODIAC-05) demonstrated that naloxegol at a dosage of 25 mg or 50 mg daily likely improves treatment response for OIC compared to placebo at 12 weeks in adult patients with LIR and noncancer pain. The mean improvements in both studies represented a clinically meaningful group-level improvement. In the LIR population, the clinical experts consulted by the review agreed that the effects in both dose groups were clinically important. Sources of uncertainty included that the lower bound of the CIs included small effects that might not be considered clinically important and a potential for risk of bias due to missing outcome data. The clinical experts on the review team agreed that the lower bound of the 95% CI for the difference in response rates in both studies did not meet the expectation for clinical significance.

The beneficial effect on response rates was supported by a shorter median time to first postdose SBM that was considered clinically important by the experts consulted for this review. Full interpretation was

limited due to lack of reporting of the between-group differences and CIs. The mean number of days per week with at least 1 complete SBM was increased with both doses of naloxegol compared to placebo; the clinical experts consulted felt that the result (< 1 day difference between groups) was supportive of the primary end point. There was an improvement in PAC-SYM scores between both the naloxegol groups and placebo groups at 12 weeks. However, this improvement was not clinically significant based on an MID of 1.0. A limitation of the findings was the potential for risk of bias due to missing outcome data. It is difficult to interpret the findings of the long-term extension study on the PAC-SYM and PAC-QOL scores due to limitations (e.g., no inferential testing and selection bias).

The dropout rates were higher than typically seen in clinical practice. The clinical experts on the review team explained that patients with advanced cancer may have problems with naloxegol, including an inability to take oral medication or incapacity to ingest enough liquid for naloxegol to be effective, but this was not expected in patients with OIC and noncancer pain. Rather, patients with noncancer pain were highly motivated to be on treatment for OIC. Despite a few limitations, the results of the pivotal trials appeared to be generalizable to Canadian clinical practice for treating patients with OIC and noncancer pain.

We identified no comparative evidence on the effect of naloxegol in patients with cancer pain. Two RCTs^{12,13} were initiated, but both were stopped early due to enrolment challenges. The open-label single-arm studies reported high response rates and improvement in constipation symptoms and HRQoL; however, it is not possible to draw causal interpretations from these studies. Although we did not identify any completed RCTs on the efficacy of naloxegol for OIC in patients with LIR and cancer pain, in the opinion of the clinical experts consulted for this review, the findings in the noncancer population are likely to be generalizable to patients with cancer. The clinical experts also confirmed that there are additional considerations in patients with cancer (e.g., patients may not be willing to take yet another medication and a small proportion cannot swallow oral tablets).

Harms

In the KODIAC-04 and KODIAC-05 trials, 25 mg naloxegol was associated with a higher rate of AEs ($> 12.5\%$ higher) compared to placebo; the rate of AEs in the 12.5 mg group was similar to placebo. The harms were primarily gastrointestinal in nature and, according to the clinical experts consulted for the review, were similar to harms experienced with other constipation treatments (e.g., laxatives). However, the rate of SAEs was low and not higher compared to placebo. In the 25 mg naloxegol group, gastrointestinal AEs led to discontinuation more commonly than with placebo or the 12.5 mg dose. Few deaths and AEs of special interest were observed during the 12-week trials.

When looking at the harms results, the most commonly reported AEs (abdominal pain, diarrhea, nausea, and flatulence) were also commonly seen in clinical practice, and are in line with other laxative or constipation treatments on the market. The clinical expert suggested that headache and back pain may be potentially associated with the effect (or noneffect) of the opioid therapy.

No new harms were identified during the KODIAC-07 extension trial, and commonly reported AEs associated with naloxegol treatment were consistent with those observed in the KODIAC-04 and KODIAC-05 trials. Most AEs were considered mild or moderate in severity.

Based on harms outcomes from 3 open-label single-arm studies, there were few SAEs and no notable safety concerns in patients with OIC and cancer pain. However, there was a lack of evidence on the harms of naloxegol versus any relevant comparator. The clinical experts consulted by the review team indicated that they would not expect any additional safety issues in using this drug in patients with cancer. The lower dose might be used to mitigate the occurrence of AEs.

The clinical experts consulted by the review team determined that, overall, the safety profile of naloxegol was acceptable.

Conclusion

The clinical experts identified a need for additional treatments in patients with noncancer or cancer pain and OIC with LIR to improve bowel function, reduce OIC-associated symptoms, improve HRQoL, and minimize AEs. The evidence from 2 randomized phase III trials comparing naloxegol with placebo suggests that naloxegol results in a clinically important increased rate of response compared to placebo over 12 weeks of follow-up in adult patients with chronic noncancer pain and OIC with LIR. The evidence for response rate was supported by a shorter time to first postdose SBM, increased number of days per week with a complete SBM, and reduced symptoms. There is some uncertainty in the evidence due to potential risk of bias related to missing outcome data, and because the CIs included effects that might not be considered clinically important. AEs were higher in the naloxegol 25 mg group compared to placebo and these were attributed to gastrointestinal effects. The number of SAEs in the 2 trials and the long-term extension study was very small. No evidence was available from RCTs for the cancer population. However, the clinical experts advised that it may be reasonable to extrapolate the findings of the trials in patients with noncancer pain to the cancer population. Based on the results of 3 open-label single-arm studies, naloxegol was associated with high response rates, improvements in constipation symptoms and HRQoL, and no notable harms; however, it is not possible to draw causal interpretations from these studies. Finally, there is a lack of comparative evidence regarding the efficacy and safety of naloxegol versus osmotic laxatives, stimulant laxatives, and methylnaltrexone for OIC in patients with noncancer or cancer pain and LIR.

Economic Review

The economic review consisted of a cost comparison for naloxegol compared with relevant comparators for patients with OIC and cancer or noncancer pain who have had an inadequate response to laxatives.

Based on public list prices, naloxegol is expected to have a per patient cost of \$44 per 7 days (Supplementary Materials, Appendix 5, Table 14). Prices of comparators ranged within and between laxative classes (osmotic laxatives: \$2 per patient to \$107 per patient over 7 days; stimulant laxatives: \$0.32 per patient to \$4 per patient over 7 days; and opioid agonists: \$72 per patient to \$215 per patient over 7 days, depending on patient weight). Therefore, treatment with naloxegol is more costly than osmotic (\$38 to \$42) and stimulant (\$40 to \$44) laxatives but less costly than opioid agonists (\$28 less to \$171 less). Because the eligible patient population for naloxegol is those who have had an inadequate response to laxatives, clinical expert feedback received for this review indicated that naloxegol may not displace traditional laxative

comparators. Therefore, rather than switch from 1 laxative to another, patients who receive naloxegol may be receiving no laxative treatment instead because they would have had an inadequate response to it. As such, it is unclear if there will be any cost-offsets in terms of drug acquisition costs for laxative use should naloxegol be reimbursed. If there is no displacement of traditional laxatives, the reimbursement of naloxegol is expected to increase overall drug acquisition costs. If naloxegol displaces stimulant or osmotic laxatives, it is also expected to increase overall drug acquisition costs. If naloxegol displaces opioid agonists, it may reduce overall drug acquisition costs.

Additional items for consideration are provided in the following bullets:

- According to the CDA-AMC Clinical Review, compared with placebo, treatment with naloxegol results in a clinically important increased rate of response over 12 weeks of follow-up in adult patients with chronic noncancer pain and OIC with LIR. Based on the Clinical Review conclusions, no comparative evidence was identified versus any active comparators. No evidence was available from RCTs for the cancer population. However, the clinical experts advised that it may be reasonable to extrapolate the findings of the trials in patients with noncancer pain to the cancer population.
- As of March 2025, naloxegol is only available as a brand name product in Canada. There is 1 generic product under review at Health Canada ([Table 1](#)). Should generic naloxegol become available in Canada, drug acquisition costs will likely be lower than estimated in this review; however, it is likely that its reimbursement will still lead to incremental drug acquisition costs.
- Clinical expert feedback received for this review indicated that, depending on clinician preference, some physicians will begin at a dose of naloxegol 12.5 mg and dose escalate to 25 mg daily whereas other physicians will start at 25 mg daily and taper to 12.5 mg daily. Because the price per 12.5 mg and 25 mg tablet is the same based on public list prices, alternative dosing regimens are not expected to alter overall drug acquisition costs associated with naloxegol.
- No health care resource use outcomes were reported in the clinical trials included in the CDA-AMC Clinical Review.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on March 24, 2025.

Conclusion

The reimbursement of naloxegol for the treatment of patients with OIC who have had an inadequate response to laxatives is generally expected to increase overall drug acquisition costs. Based on the Clinical Review conclusions, no comparative evidence was identified versus any active comparators. According to the Clinical Review, compared with placebo, naloxegol results in a clinically important increased rate of response compared to placebo over 12 weeks of follow-up in adult patients with chronic noncancer pain and OIC with LIR.

Naloxegol is associated with increased drug acquisition costs and incremental benefit in terms of response rate, time to first postdose SBM, and increased number of days per week with a complete SBM; therefore, a cost-effectiveness analysis would be required to determine the cost-effectiveness of naloxegol relative to

placebo or no active treatment. Because this was not available, the cost-effectiveness of naloxegol relative to placebo or no active treatment in patients with OIC who have had an inadequate response to laxatives could not be determined.

Compared with currently used laxatives, naloxegol is associated with increased drug acquisition costs and uncertain clinical benefit; therefore, reimbursement of naloxegol will add costs to the public health care system with uncertain benefit.

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