Help μnbind her

from the constipating effects of opioids

MOVANTIK is specifically designed to treat opioid-induced constipation (OIC) in adults with chronic non-cancer pain

movantik® (naloxegol) 25 mg tablets

INDICATION

MOVANTIK® (naloxegol) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation.

IMPORTANT SAFETY INFORMATION ABOUT MOVANTIK

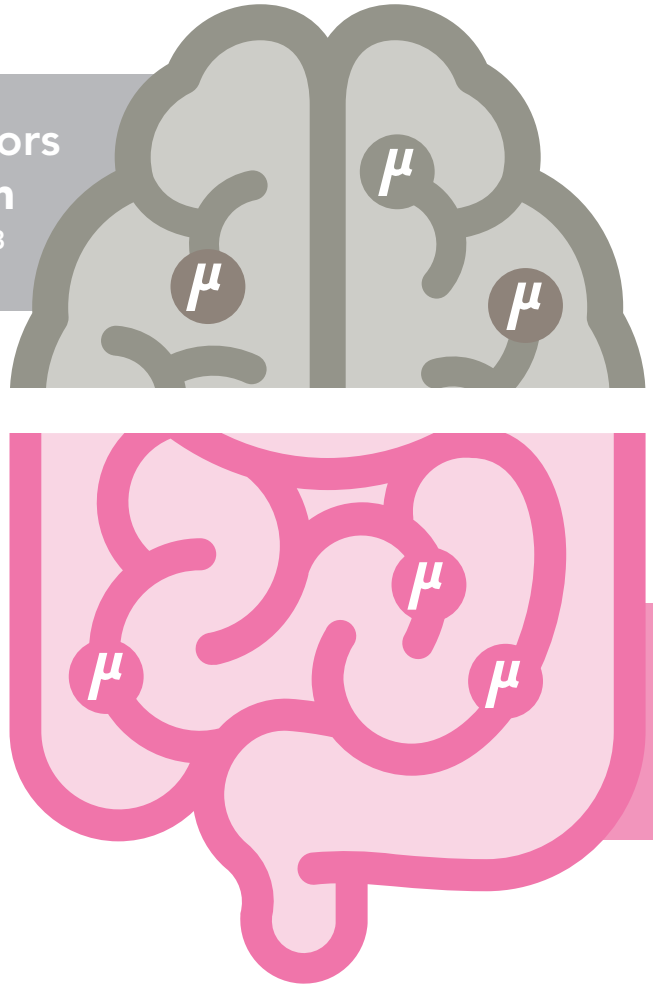
- MOVANTIK® (naloxegol) is contraindicated in[1]:
  - — Patients with known or suspected gastrointestinal (GI) obstruction and patients at risk of recurrent obstruction, due to the potential for GI perforation
  - — Patients receiving strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms
  - — Patients with a known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients

Please see complete Important Safety Information on page 9 and accompanying full Prescribing Information for MOVANTIK.

OIC is different from other types of constipation[3]

OIC is caused by the binding of opioids to mu (μ) receptors in the bowel[3]

Opioid binding to mu-receptors in the central nervous system primarily mediates analgesia[3]



Opioid binding to mu-receptors in the bowel may lead to OIC[3]

OIC remains a challenge for patients[4]

A longitudinal study of 493 patients with chronic non-cancer pain and OIC found that at baseline:

7 out of 10 patients reported **little to no benefit** from constipation treatments, including over-the-counter (OTC) laxatives*†[4]

*Constipation treatments included OTC laxatives (stool softeners, osmotics, stimulants, salines, and rectal options), prescription laxatives, and behavioral therapies (included fiber supplements, increased fluids and exercise, and dietary changes).

†29% of patients in the study reported "much benefit" from constipation treatments.

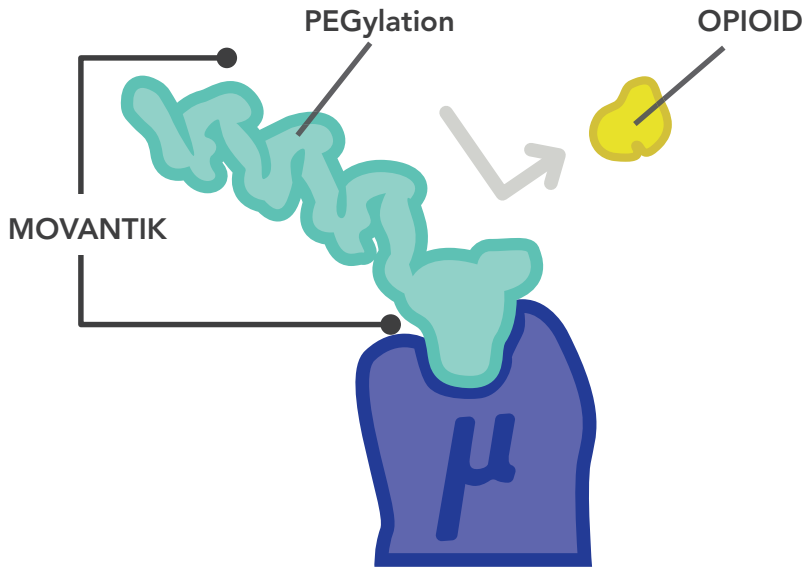
"Because OIC results from the specific effects of opioids, it differs mechanistically from other forms of constipation, and therefore, medical management of this disorder deserves dedicated attention."[5]

–American Gastroenterological Association

When an adequate trial of traditional laxatives results in suboptimal symptom control,*

The AGA recommends the use of MOVANTIK as one of the prescription treatment options for the management of OIC[5]

MOVANTIK targets the source of OIC by blocking the binding of opioids to mu-receptors in the bowel[3,1]



- When administered at the recommended dose levels, once-daily MOVANTIK functions as a PAMORA in tissues such as the bowel, thereby decreasing the constipating effects of opioids[1]
- Due to its PEGylated structure, the CNS penetration of MOVANTIK is expected to be negligible at recommended dose levels, limiting the potential for interference with centrally mediated opioid pain relief[1]

*The AGA favors the use of a combination of at least 2 types of laxatives and scheduled dosing before escalating therapy

AGA=American Gastroenterological Association; CNS=central nervous system; PAMORA=peripherally acting mu-opioid receptor antagonist.

IMPORTANT SAFETY INFORMATION (Cont'd)

- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning, occurred in patients treated with MOVANTIK.[1] Patients receiving methadone as therapy for their pain condition were observed in the clinical trials to have a higher frequency of GI adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids. Patients with disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. These patients (eg, multiple sclerosis, recent brain injury, Alzheimer's disease, and uncontrolled epilepsy) were not enrolled in the clinical studies.[1,2] Take into account the overall risk-benefit profile when using MOVANTIK in such patients.[1] Monitor for symptoms of opioid withdrawal when using MOVANTIK in such patients

Please see complete Important Safety Information on page 9 and accompanying full Prescribing Information for MOVANTIK.

Help μnbind your patients from the constipating effects of opioids[1]

MOVANTIK 25 mg achieved significantly higher response rates compared with placebo[1,6]

Studied in 1352 patients, aged 18-84, who had chronic non-cancer pain and struggled with OIC[1]

OIC was defined as[1]

- <3 SBMs per week on average
- with at least 25% of the SBMs associated with one or more of the following:

Straining	Hard or lumpy stools	Sense of incomplete evacuation

Primary Endpoint

Response rate in the overall population was 44% (95/214) for MOVANTIK 25 mg vs 29% (63/214) for placebo in KODIAC-04, and 40% (92/232) for MOVANTIK 25 mg vs 29% (68/232) for placebo in KODIAC-05 (*P*<0.05 vs placebo in both studies)[1,6]

- Response was defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks

SBM=spontaneous bowel movement, defined as a bowel movement without a rescue laxative taken within the past 24 hours.

Study Design: The KODIAC-04 and KODIAC-05 studies were identical 12-week, phase 3, replicate, randomized, double-blind, parallel-group, placebo-controlled studies in 1352 adult patients with chronic non-cancer pain and OIC who received an opioid morphine-equivalent daily dose of between 30 mg and 1000 mg for at least 4 weeks before enrollment. OIC was confirmed during a 2-week run-in period. A total of 652 patients in KODIAC-04 and 700 patients in KODIAC-05, aged 18 to 84 years (mean age 52 years), were randomized to receive MOVANTIK 12.5 mg, MOVANTIK 25 mg, or placebo once daily for 12 weeks. Throughout the studies, patients were prohibited from using laxatives other than bisacodyl rescue laxative and one-time use of an enema. Prior to enrollment, patients had been using their current opioid for an average of 3.6 and 3.7 years. The patients who participated in KODIAC-04 and KODIAC-05 were taking a wide range of opioids. The mean baseline opioid morphine equivalent daily dosage was 140 mg and 136 mg per day.[1]

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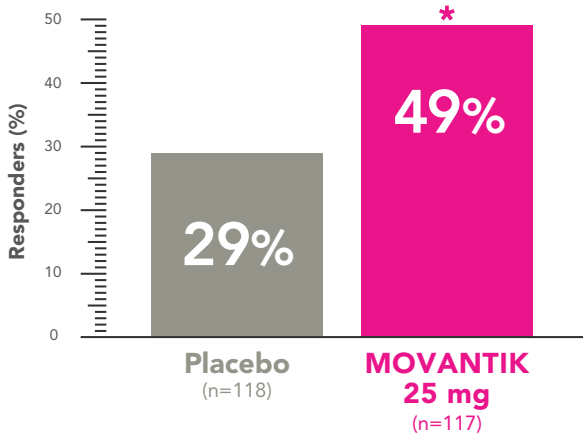
(naloxegol) 25 mg tablets

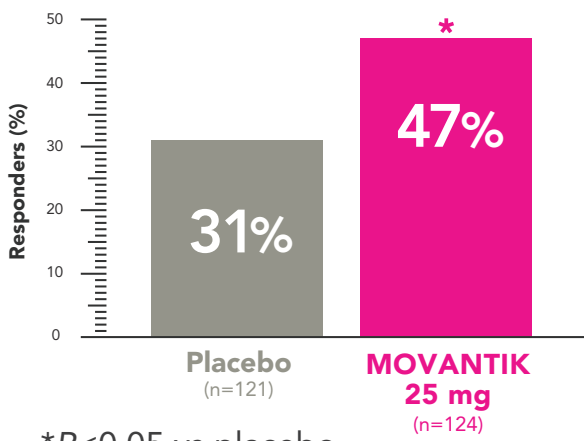
MOVANTIK may help patients who try laxatives but still have OIC symptoms[1,6]

Secondary Endpoint: In patients previously taking laxatives and still experiencing OIC symptoms, MOVANTIK 25 mg achieved significantly higher response rates compared with placebo[1,6]

KODIAC-04



KODIAC-05



*$P<0.05$ vs placebo.

MOVANTIK is the only PAMORA with FDA-approved data showing efficacy in this specific subgroup of patients[1,7,8]

Prior to enrollment, patients in this subgroup reported taking laxatives ≥4 of the past 14 days and reported ≥1 of the following OIC symptoms of moderate, severe, or very severe intensity[1,6]:

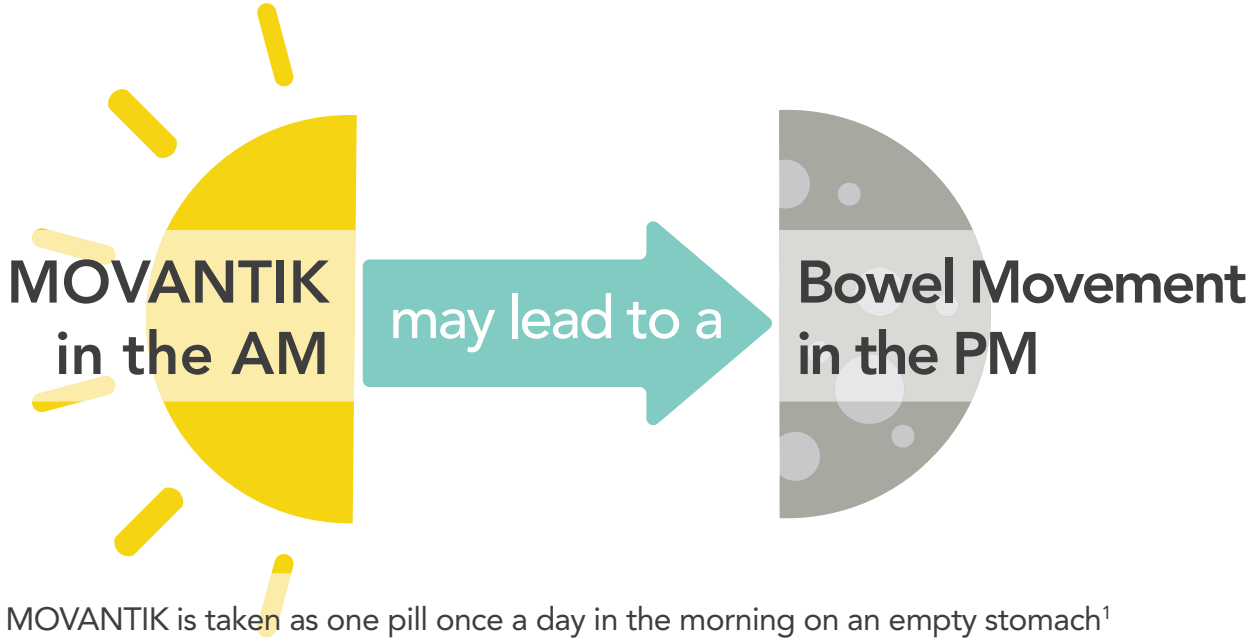
- Incomplete bowel movements (BMs)
- Hard stool
- Straining
- Sensation of needing to pass a BM but being unable to do so

In this subgroup, 42% (KODIAC-04) and 50% (KODIAC-05) reported using laxatives daily, with the following used most frequently on a daily basis[1,6]:

- **Stool softeners** (18% and 24%)
- **Stimulants** (16% and 18%)
- **Polyethylene glycol** (6% and 5%)

MOVANTIK can work the same day patients start treatment[1]

Secondary Endpoint: In KODIAC-04 and KODIAC-05, the median time to first post-dose SBM was 6 and 12 hours for MOVANTIK 25 mg, and 36 and 37 hours for placebo, respectively[1]



MOVANTIK is taken as one pill once a day in the morning on an empty stomach[1]

MOVANTIK is the only oral PAMORA with FDA-approved data showing time to first post-dose SBM[1,7,8]

IMPORTANT SAFETY INFORMATION (Cont'd)

- Severe abdominal pain and/or diarrhea have been reported, generally within a few days of initiation of MOVANTIK.[1] Monitor and discontinue if severe symptoms occur. Consider restarting MOVANTIK at 12.5 mg once daily

Please see complete Important Safety Information on page 9 and accompanying full Prescribing Information for MOVANTIK.

movantik®
(naloxegol) 25 mg tablets

The safety of MOVANTIK was investigated in 1497 patients across four clinical studies[1]

Adverse reactions in KODIAC-04 and KODIAC-05, which occurred in ≥3% of patients receiving MOVANTIK, and at an incidence greater than placebo[1]

	MOVANTIK 25 mg (n=446)	MOVANTIK 12.5 mg† (n=441)	Placebo (n=444)
Abdominal pain*	21%	12%	7%
Diarrhea	9%	6%	5%
Nausea	8%	7%	5%
Flatulence	6%	3%	3%
Vomiting	5%	3%	4%
Headache	4%	4%	3%
Hyperhidrosis	3%	<1%	<1%

*Includes abdominal pain, abdominal pain upper, abdominal pain lower, and gastrointestinal pain.[9]

† For the primary endpoint in KODIAC-04 and KODIAC-05, there was a statistically significant difference for the 25 mg treatment group vs placebo. Statistical significance for the 12.5 mg treatment group vs placebo was observed in KODIAC-04 but not KODIAC-05.[1]

Safety data from two safety and tolerability trials (12-week extension study: KODIAC-07 [n=302]; 52-week, open-label study of MOVANTIK vs usual care: KODIAC-08 [n=844]) were similar to the KODIAC-04 and KODIAC-05 trials.[1]

IMPORTANT SAFETY INFORMATION (Cont'd)

- Cases of GI perforation have been reported with the use of peripherally acting opioid antagonists, including MOVANTIK. Postmarketing cases of GI perforation, including fatal cases, were reported when MOVANTIK was used in patients at risk of GI perforation (eg, infiltrative gastrointestinal tract malignancy, recent gastrointestinal tract surgery, diverticular disease including diverticulitis, ischemic colitis, or concomitantly treated with bevacizumab).[1] Monitor for severe, persistent, or worsening abdominal pain; discontinue if this symptom develops

Please see complete Important Safety Information on page 9 and accompanying full Prescribing Information for MOVANTIK.

Important Safety Information About MOVANTIK

- MOVANTIK® (naloxegol) is contraindicated in[1]:
  - Patients with known or suspected gastrointestinal (GI) obstruction and patients at risk of recurrent obstruction, due to the potential for GI perforation
  - Patients receiving strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms
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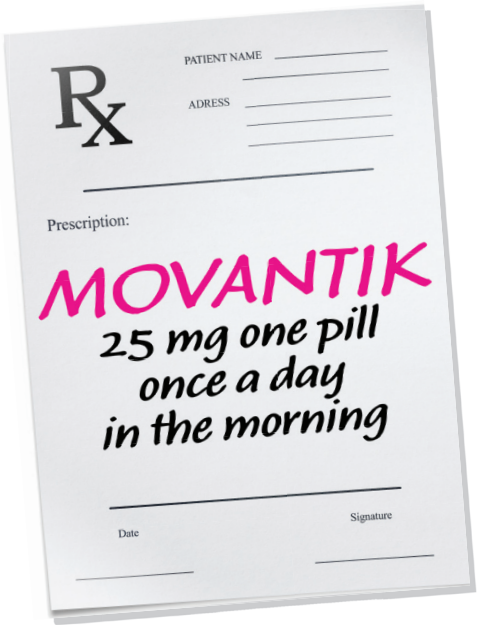
- Avoid concomitant use of moderate CYP3A4 inhibitors (eg, diltiazem, erythromycin, verapamil) because they may increase the risk of adverse reactions.[1] Use of strong CYP3A4 inducers (eg, rifampin, carbamazepine, St. John's Wort) is not recommended because they may decrease the efficacy of MOVANTIK. Avoid concomitant use of MOVANTIK with another opioid antagonist due to the increased risk of opioid withdrawal
- The use of MOVANTIK during pregnancy may precipitate opioid withdrawal in the pregnant woman and the fetus. Because of the potential for adverse reactions, including opioid withdrawal in breastfed infants, advise women that breastfeeding is not recommended during treatment with MOVANTIK
- The most common adverse reactions with MOVANTIK in clinical trials were: abdominal pain (21%), diarrhea (9%), nausea (8%), flatulence (6%), vomiting (5%), headache (4%), and hyperhidrosis (3%)[1]

movantik®
(naloxegol) 25 mg tablets

Prescribe once-daily MOVANTIK for as long as your patients with OIC continue opioid therapy[1]



MOVANTIK has 2 approved strengths, allowing for clinical flexibility when treating OIC in adults with chronic non-cancer pain

- The recommended starting dose of MOVANTIK is **one 25 mg tablet once daily in the morning** on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal
  - MOVANTIK 12.5 mg tablet may be used as a step-down dose for patients unable to tolerate the 25 mg strength
- MOVANTIK 12.5 mg is the recommended starting dose for patients with moderate, severe, or end-stage renal impairment
- If concurrent use of MOVANTIK with moderate CYP3A4 inhibitor drugs is unavoidable, reduce the dose to 12.5 mg once daily and monitor for adverse reactions

Please see full Prescribing Information for additional dosing information.

IMPORTANT SAFETY INFORMATION (Cont'd)

- Avoid concomitant use of moderate CYP3A4 inhibitors (eg, diltiazem, erythromycin, verapamil) because they may increase the risk of adverse reactions.[1] Use of strong CYP3A4 inducers (eg, rifampin, carbamazepine, St. John's Wort) is not recommended because they may decrease the efficacy of MOVANTIK. Avoid concomitant use of MOVANTIK with another opioid antagonist due to the increased risk of opioid withdrawal
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Please see complete Important Safety Information on page 9 and accompanying full Prescribing Information for MOVANTIK.

When you prescribe MOVANTIK, feel confident that your patients can get it

MOVANTIK is preferred* without prior authorization† for the majority of Commercial and Medicare Part D patients‡ nationwide[10]

Eligible commercially insured patients can pay as little as

$0/month with the MOVANTIK Savings Card

with savings valued up to $100 per 30-day supply§

3 out of 4

Medicare Part D patients pay $20 or less for MOVANTIK[11]

AstraZeneca does not endorse any individual, commercial, Medicare Part D, or Medicaid plan or plans.

*"Preferred" means Tier 1, Tier 2, or Tier 3 when Tier 3 is the lowest branded tier.

† "Without Prior Authorization" means that additional information is not required to be provided to the health plan in order for MOVANTIK to be covered. Step edits and quantity limits may apply.

‡ "Patients" means covered lives (Commercial, Employer, Fed Prog, FEHBP, Municipal Plan, PBM, Union, EGWP, Medicare MA, Medicare PDP, Medicare SN, Medi-Medi, PACE) at Tiers 1-2 and 3 Preferred in the Nation, as calculated by Fingertip Formulary® as of February 27, 2019.

§ Subject to complete eligibility rules; restrictions apply.

movantik®
(naloxegol) 25 mg tablets

As part of your treatment plan for adult patients with chronic non-cancer pain struggling with OIC

Make MOVANTIK your first prescription choice

When an adequate trial of traditional laxatives results in suboptimal symptom control,* the AGA recommends the use of MOVANTIK as one of the prescription treatment options for the management of OIC[5]

Since 2015

The #1 prescribed oral PAMORA[12]

Over 1,750,000 prescriptions written[13]

Preferred† without prior authorization‡ for the majority of Commercial and Medicare Part D patients§ nationwide[10]

*The AGA favors the use of a combination of at least 2 types of laxatives and scheduled dosing before escalating therapy.[5]
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References: 1. MOVANTIK® (naloxegol) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **2.** Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med.* 2014;370:2387-2396 [protocol]. **3.** Brock C, Olesen SS, Olesen AE, Frøkjaer JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs.* 2012;72:1847-1865. **4.** Coyne KS, LoCasale RJ, Datto CJ, Sexton CC, Yeomans K, Tack J. Opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK: descriptive analysis of baseline patient-reported outcomes and retrospective chart review. *Clinicoecon Outcomes Res.* 2014;6:269-281. **5.** Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. *Gastroenterology.* 2019;156:218-226. **6.** Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med.* 2014;370:2387-2396. **7.** Symproic [Prescribing Information]. Florham Park, NJ. Shionogi Inc; 2018. **8.** Relistor [Prescribing Information]. Bridgewater, NJ. Salix Pharmaceuticals; 2017. **9.** Data on file, REF-4912. AstraZeneca Pharmaceuticals LP. **10.** Fingertip Formulary®. February 27, 2019. **11.** Data on file, US-23564. AstraZeneca Pharmaceuticals LP. **12.** Data on file, US-26407. AstraZeneca Pharmaceuticals LP. **13.** IQVIA NPA Monthly (retail, mail order, LTC), March 22, 2019.

Daiichi-Sankyo

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