Symproic®
(naldemedine) tablets
0.2 mg

GO WITH IT

Induce spontaneity

Get back to treating chronic pain

INDICATION

SYMPROIC® (naldemedine) 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 (e.g., weekly) opioid dosage escalation.

Is OIC getting in the way?

Opioids bind to the mu-opioid receptors in the gut, which may lead to OIC[1]

About 40% to 50% of patients receiving opioid therapy for chronic non-cancer pain report developing OIC[2-5]

In a longitudinal study of 493 adults with chronic non-cancer pain and OIC, 83% reported straining to pass bowel movements[6]

OTC laxatives do not address the underlying mechanism of OIC[7]

OIC is defined as a change from baseline bowel habits after initiation of opioid therapy, including any of the following[8]:

- Decreased frequency
- Straining
- Incomplete evacuation
- Harder stool consistency

OIC=opioid-induced constipation; OTC=over the counter.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue if this symptom develops.

Please see additional Important Safety Information on pages 14-15 and see full Prescribing Information at SYMPROIC.com.

SYMPROIC® (naldemedine)

- A PAMORA[9]
- An opioid antagonist with binding affinities for mu-, delta-, and kappa-opioid receptors[9]
- Designed to have reduced ability to cross the blood–brain barrier, thereby limiting its potential to interfere with centrally mediated opioid analgesia[9]

Only OIC therapy with a strong recommendation and a high quality of evidence from the American Gastroenterological Association[10]

PAMORA=peripherally acting mu-opioid receptor antagonist.

SYMPROIC® clinical trials included >1000 patients with OIC

Two replicate, 12-week, randomized, double-blind, placebo-controlled trials[9,11]

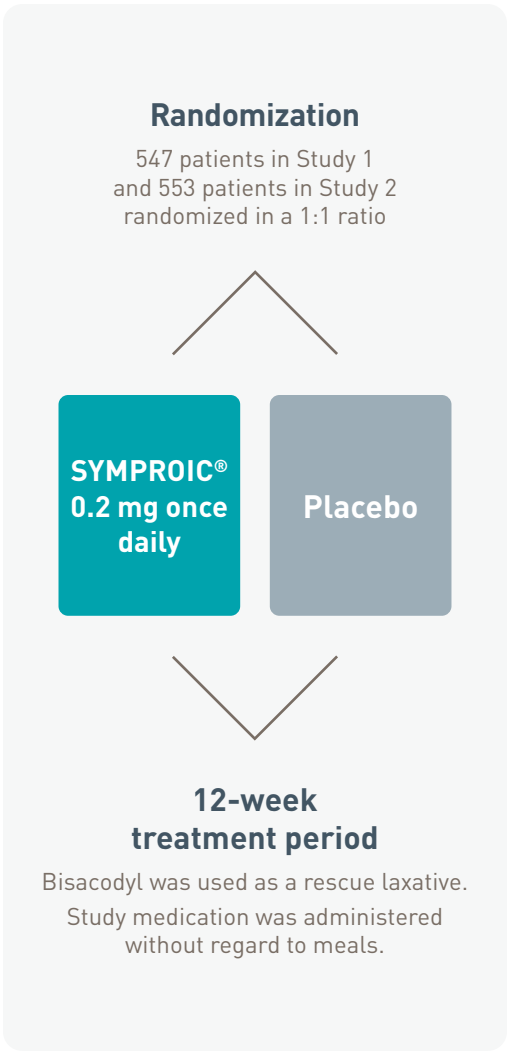
Study population[9,11]

- Eligible patients were receiving a stable opioid morphine equivalent daily dose of at least 30 mg for 4 weeks or more before enrollment and self-reported OIC
- OIC was confirmed through a 2-week run-in period and was defined as no more than 4 SBMs over 14 consecutive days and fewer than 3 SBMs in a given week, with at least 25% of the SBMs associated with one or more of the following conditions: (1) straining, (2) hard or lumpy stools, (3) having a sensation of incomplete evacuation, or (4) having a sensation of anorectal obstruction/blockage. SBM was defined as a BM without rescue laxative taken within the past 24 hours
- Patients were not using laxatives or were willing to discontinue laxatives
- Patients were excluded if they had no BMs over the 7 consecutive days before and during the 2-week screening period; patients who had never taken laxatives were excluded, as were those with evidence of significant structural abnormalities of the gastrointestinal tract

Patient demographics[9,11]

The mean age of patients was 54 years; 59% were women; the mean body mass index was 31 kg/m^2. The mean baseline number of SBMs was 1.3 and 1.2 per week for Studies 1 and 2, respectively.

BM=bowel movement; SBM=spontaneous bowel movement.



IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont)

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with SYMPROIC®.

Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using SYMPROIC® in such patients. Monitor for symptoms of opioid withdrawal in such patients.

Proven efficacy
in two 12-week clinical trials

Endpoints are consistent with the symptoms of OIC[9,11]

Primary endpoint: Responder rate[9,11]

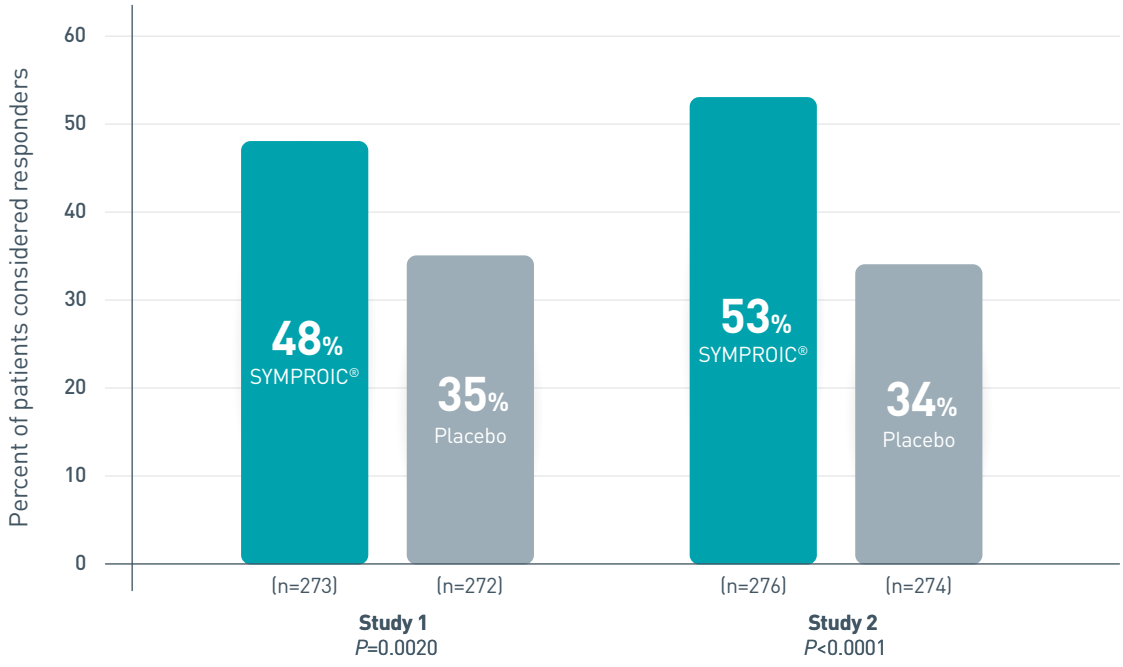
To be considered a responder, patients had to achieve:

≥3 SBMs per week + Change from baseline of **≥1 SBM** per week

At least **9** out of **12** weeks, **INCLUDING** 3 out of the last 4 weeks

SBM=spontaneous bowel movement.

Responder rates were significantly higher with SYMPROIC® than with placebo[9,11]



IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

Avoid use with strong CYP3A inducers (e.g., rifampin) because they may reduce the efficacy of SYMPROIC®.

Use with moderate (e.g., fluconazole) and strong (e.g., itraconazole) CYP3A inhibitors and P-glycoprotein inhibitors (e.g., cyclosporine) may increase SYMPROIC® concentrations. Monitor for potential adverse reactions.

Avoid use of SYMPROIC® with another opioid antagonist due to the potential for additive effect and increased risk of opioid withdrawal.

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More frequent
SBMs with SYMPROIC®

Statistically significant increase vs placebo in frequency of SBMs per week from baseline to week 1[9,11]

Frequency of SBMs per week from baseline to the first week

CI=confidence interval; SBM=spontaneous bowel movement.

Week 1

Secondary endpoint: **Frequency**

IMPORTANT SAFETY INFORMATION

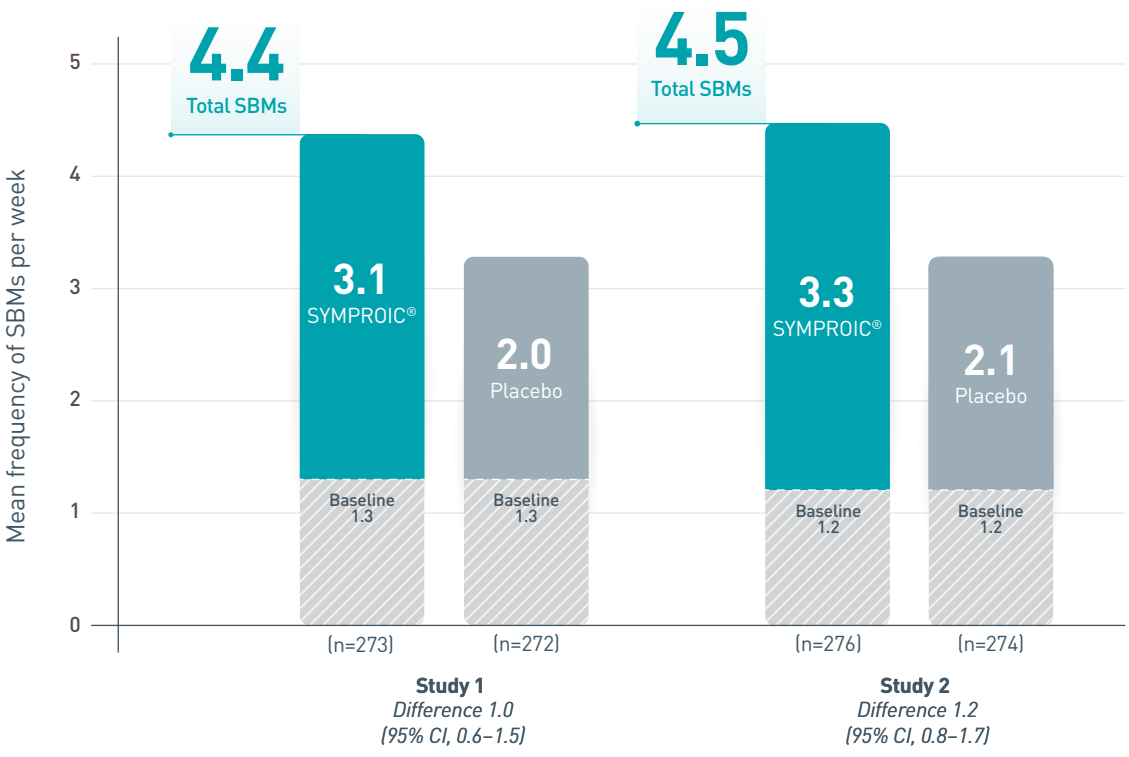
USE IN SPECIFIC POPULATIONS

Naldemedine crosses the placenta and may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. SYMPROIC® should be used during pregnancy only if the potential benefit justifies the potential risk. Because of the potential for serious adverse reactions, including opioid withdrawal in breastfed infants, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Avoid use in patients with severe hepatic impairment. No dose adjustment of SYMPROIC® is required in patients with mild or moderate hepatic impairment.

Statistically significant increase vs placebo in frequency of SBMs per week from baseline to the last 2 weeks[9,11]

Frequency of SBMs per week from baseline to the last 2 weeks



CI=confidence interval; SBM=spontaneous bowel movement.

Last 2 Weeks

Secondary endpoint: **Frequency**

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

The most common adverse reactions with SYMPROIC® compared to placebo in two pooled 12-week studies were: abdominal pain (8% vs 2%), diarrhea (7% vs 2%), nausea (4% vs 2%), and gastroenteritis (2% vs 1%).

The incidence of adverse reactions of opioid withdrawal in two pooled 12-week studies was 1% (8/542) for SYMPROIC® and 1% (3/546) for placebo. In a 52-week study, the incidence was 3% (20/621) for SYMPROIC® and 1% (9/619) for placebo.

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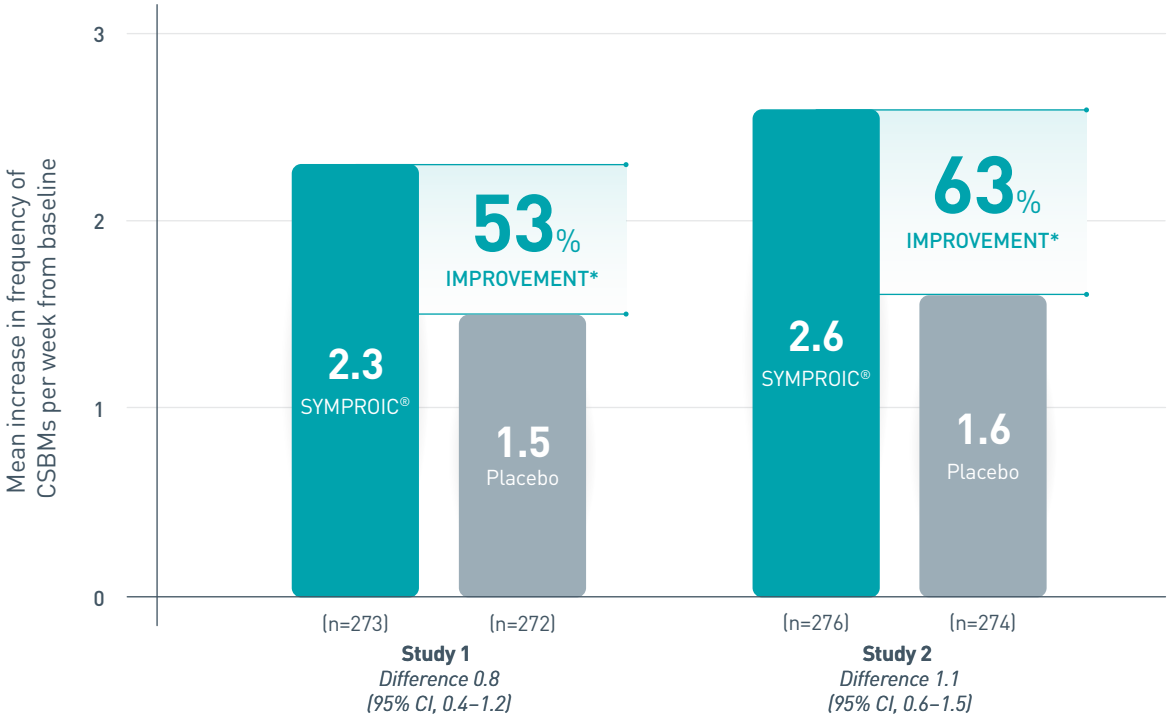
More complete SBMs
with SYMPROIC®

Statistically significant increase vs placebo in frequency of complete SBMs per week from baseline to the last 2 weeks[9,11]

Frequency of CSBMs

Change in frequency of CSBMs per week from baseline to the last 2 weeks



CI=confidence interval; CSBM=complete spontaneous bowel movement.
*Compared with placebo.
The mean baseline number of SBMs was 0.4 per week for Studies 1 and 2.[12]

Last 2 Weeks

Secondary endpoint: **Completeness**

IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS

Naldemedine crosses the placenta and may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. SYMPROIC® should be used during pregnancy only if the potential benefit justifies the potential risk. Because of the potential for serious adverse reactions, including opioid withdrawal in breastfed infants, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

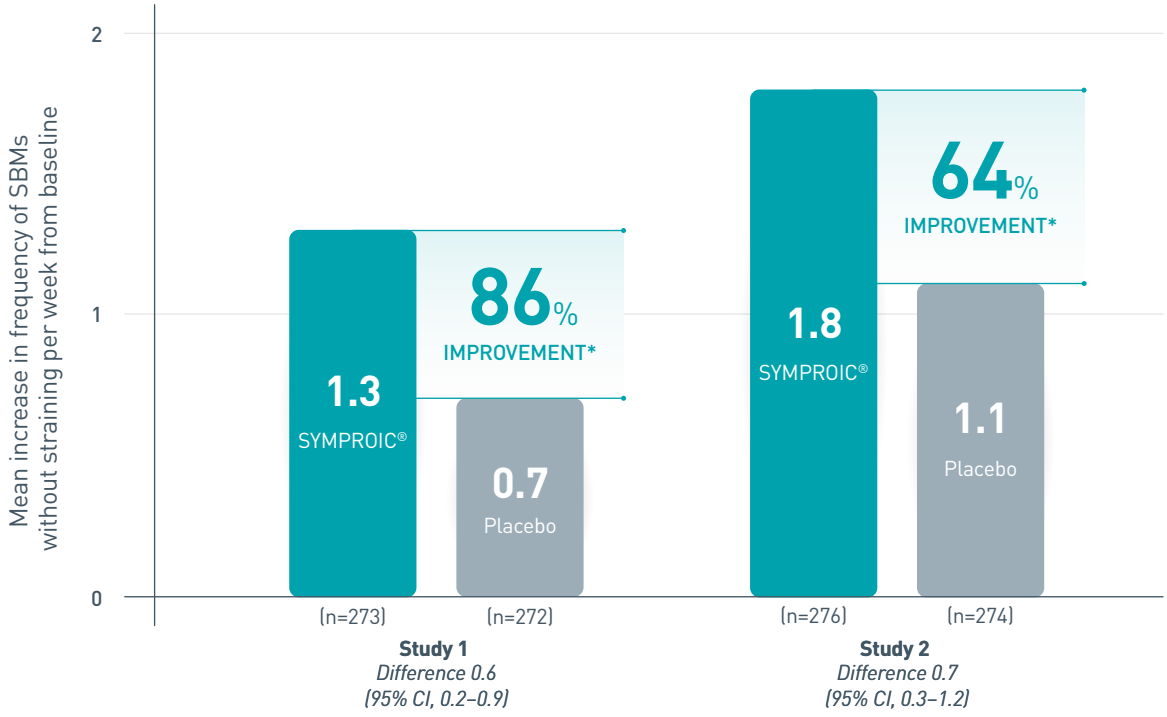
Avoid use in patients with severe hepatic impairment. No dose adjustment of SYMPROIC® is required in patients with mild or moderate hepatic impairment.

More SBMs without straining
with SYMPROIC®

Statistically significant increase vs placebo in frequency of SBMs without straining per week from baseline to the last 2 weeks[9,11]

Frequency of SBMs without straining

Change in frequency of SBMs without straining per week from baseline to the last 2 weeks



CI=confidence interval; SBM=spontaneous bowel movement.
*Compared with placebo.
The mean baseline number of SBMs was 0.1 per week for Studies 1 and 2.[12]

Last 2 Weeks

Secondary endpoint: **Straining**

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

The most common adverse reactions with SYMPROIC® compared to placebo in two pooled 12-week studies were: abdominal pain (8% vs 2%), diarrhea (7% vs 2%), nausea (4% vs 2%), and gastroenteritis (2% vs 1%).

The incidence of adverse reactions of opioid withdrawal in two pooled 12-week studies was 1% (8/542) for SYMPROIC® and 1% (3/546) for placebo. In a 52-week study, the incidence was 3% (20/621) for SYMPROIC® and 1% (9/619) for placebo.

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Tolerability comparable
to placebo in clinical trials

Low rate of adverse reactions, including abdominal pain[9,11]

12-week data from Studies 1 and 2

Adverse reactions*	SYMPROIC® n=542	Placebo n=546
Abdominal pain†	8%	2%
Diarrhea	7%	2%
Nausea	4%	2%
Gastroenteritis	2%	1%

*Adverse reactions occurring in ≥2% of patients receiving SYMPROIC® and at an incidence greater than placebo.
†Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain.

Opioid withdrawal[9,11]

In pooled Studies 1 and 2, the incidence of adverse reactions associated with opioid withdrawal was 1% (8/542) for SYMPROIC® and 1% (3/546) for placebo.

IMPORTANT SAFETY INFORMATION

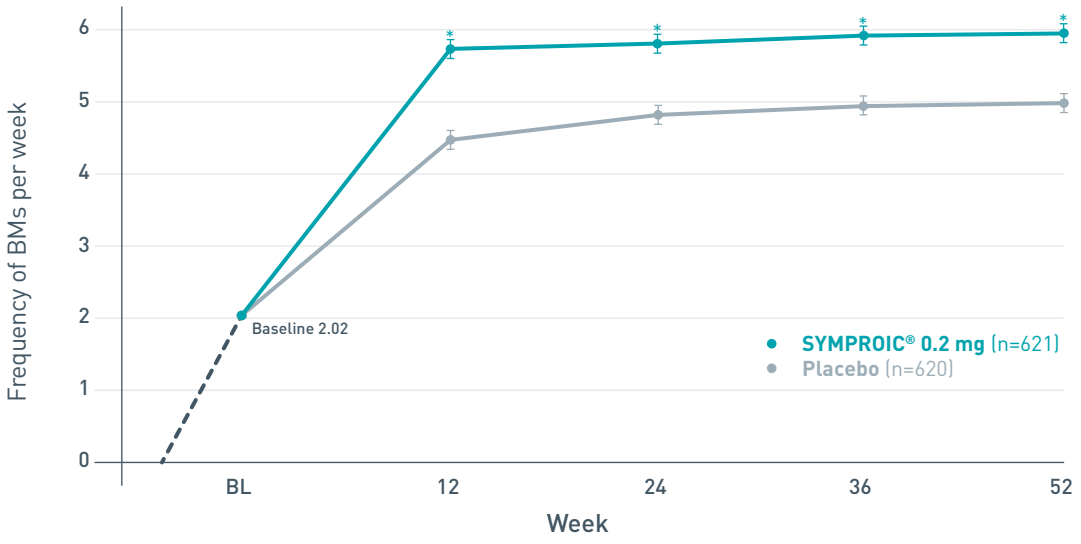
WARNINGS AND PRECAUTIONS

Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue if this symptom develops.

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with SYMPROIC®.

Proven long-term
efficacy and tolerability

Significant and sustained increase in bowel movements from baseline vs placebo over 52 weeks[11,13]



BL=baseline; BM=bowel movement.
*$P \leq 0.0001$ vs placebo.
Intent-to-treat population; least squares mean ± SE.

Safety[11,13]

- In Study 3 (52-week data), the incidence of adverse reactions associated with opioid withdrawal was 3% (20/621) for SYMPROIC® and 1% (9/619) for placebo
- Adverse reactions† up to 12 months were similar to those in the two 12-week studies (abdominal pain‡ 11% vs 5%, diarrhea 7% vs 3%, nausea 6% vs 5%, vomiting 3% vs 2%, and gastroenteritis 3% vs 1% for SYMPROIC® and placebo, respectively)

Study design[11,13]

Randomized, double-blind, placebo-controlled safety study. Patients were allowed to maintain their current laxative therapy throughout study duration.

†Adverse reactions occurring in ≥2% of patients receiving SYMPROIC® and at an incidence greater than placebo.
‡Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont)

Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using SYMPROIC® in such patients. Monitor for symptoms of opioid withdrawal in such patients.

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Guidelines for dosing
and administration

The PAMORA with more flexibility[11]

With or without food

With or without laxatives

Once daily

Any time of day

SYMPROIC® is the ONLY PAMORA that can be taken with or without laxatives or food.

IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

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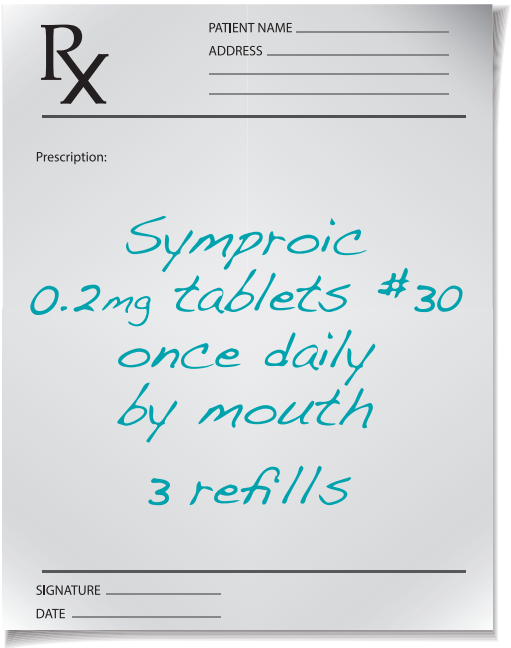
Prescribing
SYMPROIC® (naldemedine)



- Alteration of analgesic dosing regimen before initiating SYMPROIC® is not required[11]
- Patients receiving opioids for less than 4 weeks may be less responsive to SYMPROIC®[11]
- Discontinue SYMPROIC® if treatment with the opioid pain medication is discontinued[11]
- Patients with mild, moderate, or severe renal disease, or end-stage renal disease requiring hemodialysis had similar pharmacokinetics to patients with normal renal function[11]
  - No dose adjustments of SYMPROIC® are required in patients with renal impairment[11]
- No dose adjustments of SYMPROIC® are required in patients with mild or moderate hepatic impairment. Avoid use in patients with severe hepatic impairment[11]

IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS

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INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

SYMPROIC® (naldemedine) 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 (e.g., weekly) opioid dosage escalation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Patients with known or suspected gastrointestinal (GI) obstruction and patients at increased risk of recurrent obstruction, due to the potential for GI perforation.
- Patients with a history of a hypersensitivity reaction to naldemedine. Reactions have included bronchospasm and rash.

WARNINGS AND PRECAUTIONS

Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue if this symptom develops.

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ADVERSE REACTIONS

The most common adverse reactions with SYMPROIC® compared to placebo in two pooled 12-week studies were: abdominal pain (8% vs 2%), diarrhea (7% vs 2%), nausea (4% vs 2%), and gastroenteritis (2% vs 1%).

The incidence of adverse reactions of opioid withdrawal in two pooled 12-week studies was 1% (8/542) for SYMPROIC® and 1% (3/546) for placebo. In a 52-week study, the incidence was 3% (20/621) for SYMPROIC® and 1% (9/619) for placebo.

Please see full Prescribing Information and Medication Guide at SYMPROIC.com.

To report SUSPECTED ADVERSE REACTIONS, contact BioDelivery Sciences International, Inc. at 1-800-469-0261 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. Argoff CE, Brennan MJ, Camilleri M, et al. Consensus recommendations on initiating prescription therapies for opioid-induced constipation. *Pain Med*. 2015;16(12):2324-2337. **2.** Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380. **3.** Cook SF, Lanza L, Zhou X, et al. Gastrointestinal side effects in chronic opioid users: results from a population-based survey. *Aliment Pharmacol Ther*. 2008;27(12):1224-1232. **4.** Brown RT, Zuelsdorff M, Fleming M. Adverse effects and cognitive function among primary care patients taking opioids for chronic nonmalignant pain. *J Opioid Manag*. 2006;2(3):137-146. **5.** Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil*. 2010;22(4):424-430, e96. **6.** 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. **7.** Emmanuel A, Johnson M, McSkimming P, Dickerson S. Laxatives do not improve symptoms of opioid-induced constipation: results of a patient survey. *Pain Med*. 2017;18(10):1932-1940. **8.** Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. *Neurogastroenterol Motil*. 2014;26(10):1386-1395. **9.** Hale M, Wild J, Reddy J, Yamada T, Arjona Ferreira JC. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase 3, double-blind, randomised, parallel-group trials. *Lancet Gastroenterol Hepatol*. 2017;2(8):555-564. **10.** Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter, 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(1): 218-226. **11.** SYMPROIC [package insert]. Raleigh, NC: BioDelivery Sciences International, Inc.; 2019. **12.** Data on file, BioDelivery Sciences International, Inc. **13.** Webster LR, Nalamachu S, Morlion B, et al. Long-term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: a randomized, double-blind, placebo-controlled phase 3 study. *Pain*. 2018;159(5):987-994.

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GO WITH IT

Go with SYMPROIC® (naldemedine)

- **Proven efficacy for OIC[9,11]**
- **Demonstrated long-term efficacy and tolerability in clinical trials[11,13]**
- **Low rates of abdominal pain across 3 studies[9,11,13]**
- **Convenient dosing[11]**
- **AGA recommendation[10]**
- **Visit SYMPROIC.com for savings**

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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