SYMPROIC® (Naldemedine tablets for oral use)

INDICATIONS AND USAGE

SYMPROIC 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.

CONTRAINDICATIONS

SYMPROIC is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforation

Cases of gastrointestinal 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 gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies, or peritoneal metastases). Take into account the overall risk-benefit profile when using SYMPROIC in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue SYMPROIC in patients who develop this symptom.

Opioid Withdrawal

Clusters of 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.

ADVERSE REACTIONS

Serious and important adverse reactions described elsewhere in labeling include:

- Gastrointestinal perforation
- Opioid withdrawal

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to SYMPROIC in 1163 patients in clinical trials, including 487 patients with exposures greater than six months and 203 patients with exposures of 12 months.

The following safety data are derived from three double-blind, placebo-controlled trials in patients with OIC and chronic non-cancer pain: two 12-week studies (Studies 1 and 2) and one 52-week study (Study 3).

In Studies 1 and 2, patients on laxatives were required to discontinue their use prior to study enrollment. All patients were restricted to bisacodyl rescue treatment during the study. In Study 3, approximately 60% of patients in both treatment groups were on a laxative regimen at baseline; patients were allowed to continue using their laxative regimen throughout the study duration. The safety profile of SYMPROIC relative to placebo was similar regardless of laxative use.

Tables 1 and 2 list common adverse reactions occurring in at least 2% of patients receiving SYMPROIC and at an incidence greater than placebo. Table 1 shows pooled 12-week data from Studies 1 and 2. Table 2 shows 12-week data from Study 3.

Table 1: Common Adverse Reactions* in Patients with OIC and Chronic Non-Cancer Pain (12-week data from Studies 1 and 2)

Adverse Reaction	**SYMPROIC 0.2 mg once daily N=542**	**Placebo N=546**
Abdominal pain**	8%	2%
Diarrhea	7%	2%
Nausea	4%	2%
Gastroenteritis	2%	1%

*Adverse reactions occurring in at least 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.

Table 2: Common Adverse Reactions* in Patients with OIC and Chronic Non-Cancer Pain (12-week data from Study 3)

Adverse Reaction	**SYMPROIC 0.2 mg once daily N=621**	**Placebo N=619**
Abdominal pain**	11%	5%
Diarrhea	7%	3%
Nausea	6%	5%
Vomiting	3%	2%
Gastroenteritis	3%	1%

*Adverse reactions occurring in at least 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.

Adverse reactions up to 12 months in Study 3 are similar to those listed in Tables 1 and 2 (diarrhea: 11% vs. 5%, abdominal pain: 8% vs. 3%, and nausea: 8% vs. 6% for SYMPROIC and placebo, respectively).

Opioid Withdrawal

In Studies 1, 2 and 3, adverse reactions consistent with opioid withdrawal were based on investigator assessment and adjudicated based upon the occurrence of at least 3 adverse reactions potentially related to opioid withdrawal with onset of a constellation of those symptoms occurring on the same day or within one day of each other.

Adverse reactions of possible opioid withdrawal could include non-gastrointestinal (GI) symptoms (e.g., hyperhidrosis, hot flush or flushing, chills, tremor, tachycardia, anxiety, agitation, yawning, rhinorrhea, increased lacrimation, sneezing, feeling cold, and pyrexia), GI symptoms (e.g., vomiting, diarrhea, or abdominal pain), or both GI and non-GI symptoms.

In pooled Studies 1 and 2, the incidence of adverse reactions of opioid withdrawal was 1% (8/542) for SYMPROIC and 1% (3/546) for placebo. In Study 3 (52-week data), the incidence was 3% (20/621) for SYMPROIC and 1% (9/619) for placebo. Most SYMPROIC treated subjects experienced nearly equal incidence of GI only or both GI and non-GI symptoms.

Less Common Adverse Reactions:

Two patients developed symptoms of hypersensitivity following a single dose of SYMPROIC. One patient reported bronchospasm and another rash.