



Shionogi Inc. and Purdue Pharma L.P. Announce U.S. Availability of Symproic® (naldemedine) for the Treatment of Opioid-Induced Constipation in Adults with Chronic Non-Cancer Pain

OSAKA, Japan, FLORHAM PARK, N.J. and STAMFORD, Conn., October 12, 2017 -- [Shionogi Inc.](#) and [Purdue Pharma L.P.](#) announced today that Symproic® (naldemedine) 0.2 mg tablets are now available throughout the United States. The U.S. Food and Drug Administration (FDA) approved Symproic as a once-daily oral tablet 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.

Symproic was descheduled, or removed from the controlled substance classification list, by the U.S. Drug Enforcement Administration (DEA) on September 29, 2017.

“We are very pleased to launch Symproic with our partner, Purdue Pharma, in the U.S. Together we are providing a new treatment option for many adult patients with chronic non-cancer pain who suffer from opioid-induced constipation. We are committed to addressing this important need for the management of chronic non-cancer pain patients,” said John Keller, president and chief executive officer, Shionogi Inc.

Symproic is a peripherally-acting mu-opioid receptor antagonist (PAMORA). Symproic comes as a 0.2 mg once-daily oral tablet and may be taken at any time of day, with or without food, and with or without laxatives. Alteration of analgesic dosing regimen prior to initiating Symproic is not required. Patients receiving opioids for less than 4 weeks may be less responsive to Symproic. Treatment with Symproic should be discontinued if treatment with the opioid medicine is also discontinued.

“At Purdue Pharma, we are committed to delivering innovative products that improve the health of patients. The launch of Symproic marks an important milestone, as we continue to diversify our portfolio to provide more comprehensive care for patients,” said Craig Landau, MD, chief executive officer, Purdue Pharma L.P. “We are delighted to partner with Shionogi to bring Symproic to patients across the U.S. who are suffering from OIC, a potentially severe condition that affects many individuals who are on opioid medication to manage chronic non-cancer pain. Symproic is a new oral treatment option that helps to address the underlying mechanism of OIC, by blocking opioids from binding to mu-opioid receptors in tissues such as those in the gastrointestinal tract, thereby decreasing the constipating effects of opioids.”

The FDA approval of Symproic was based on data from the global Phase 3 COMPOSE clinical trial program, which enrolled 2346 patients with OIC and chronic non-cancer pain. It was comprised of three studies: COMPOSE 1, COMPOSE 2 and COMPOSE 3. COMPOSE 1 and 2 were two replicate, 12-week, randomized, double-blind, placebo-controlled trials, while COMPOSE 3 was a 52-week, randomized, double-blind, placebo-controlled, long-term safety study.

For the primary endpoint, the proportion of responders was significantly higher with Symproic versus placebo in COMPOSE 1 (48%; n = 273 versus 35%; n = 272, p=0.0020) and COMPOSE 2 (53%; n = 276 versus 34%; n = 274, p<0.0001). A responder was defined as a patient who had at least 3 spontaneous

bowel movements (SBMs) per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 weeks including 3 out of the last 4 weeks.¹

Treatment with Symproic resulted in a statistically significant increase versus placebo in frequency from baseline in all secondary endpoints including frequency of SBMs per week to week 1 and to the last 2 weeks of the treatment period and in the frequency of complete SBMs and SBMs without straining per week to the last 2 weeks of the treatment period.¹ The most common adverse reactions with Symproic as compared to placebo in clinical trials were: abdominal pain (8% vs 2%), diarrhea (7% vs 2%), nausea (4% vs 2%), and gastroenteritis (2% vs 1%).

Please see Important Safety Information, including Warnings & Precautions, and Adverse Reactions below.

About Opioid-Induced Constipation

Constipation is one of the most commonly reported side effects associated with opioid treatment, including among patients with chronic non-cancer pain.² When opioids bind to specific proteins called mu-opioid receptors in the gastrointestinal (GI) tract, constipation may occur. Opioid-induced constipation (OIC) is a result of increased fluid absorption and reduced GI motility due to opioid receptor binding in the GI tract. OIC is defined as a change from baseline bowel habits that is characterized by any of the following after initiating opioid therapy: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency.³ In patients with chronic non-cancer pain taking opioids, the prevalence of OIC ranges from approximately 40-50 percent.⁴⁻⁷

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 Symproic. 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.

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.

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 potential for additive effect and increased risk of opioid withdrawal.

USE IN SPECIFIC POPULATIONS

Symproic 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.

ADVERSE REACTIONS

The most common adverse reactions with Symproic as compared to placebo in clinical trials were: abdominal pain (8% vs 2%), diarrhea (7% vs 2%), nausea (4% vs 2%), and gastroenteritis (2% vs 1%).

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.

To report suspected Adverse Reactions, contact Shionogi at 1-800-849-9707 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying Full Prescribing Information including Medication Guide for Symproic or visit www.symproic.com/pi.

About Shionogi

Shionogi & Co., Ltd., is a Japanese pharmaceutical company with a 139-year history discovering and developing innovative therapies. Shionogi Inc., the U.S. based subsidiary of Shionogi & Co., Ltd., continues this focus on the development and commercialization of high quality medicines that protect the health and well-being of the patients we serve. The company currently markets products in several therapeutic areas including anti-infectives, pain and cardiovascular diseases. Our pipeline is focused on infectious disease, pain, CNS and oncology. For more details on Shionogi Inc., visit www.shionogi.com. For more information on Shionogi & Co., Ltd., visit www.shionogi.co.jp/en.

About Purdue Pharma L.P.

Purdue Pharma L.P. is a privately held pharmaceutical company headquartered in Stamford, Conn. Purdue Pharma is part of a network of independent associated companies dedicated to providing patients and providers with innovative medicines. The company's leadership and employees are committed to serving healthcare professionals, patients and caregivers quality products and educational resources that make a positive impact on healthcare — and on lives. For more information, please visit www.purduepharma.com.

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