FDA Approves Symproic® (naldemedine) Once-Daily Tablets C-II for the Treatment of Opioid-Induced Constipation in Adults with Chronic Non-Cancer Pain

OSAKA, Japan, FLORHAM PARK, N.J. and STAMFORD, Conn. (Mar. 23, 2017) – Shionogi Inc. and Purdue Pharma L.P. announced today that the U.S. Food and Drug Administration (FDA) approved Symproic® (naldemedine) 0.2 mg tablets C-II as a once-daily oral peripherally-acting mu-opioid receptor antagonist (PAMORA) medication for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Symproic is currently a Schedule II controlled substance because it is structurally related to naltrexone. Shionogi Inc. submitted a petition for the descheduling of Symproic, or removal of the controlled substance classification, to the U.S. Drug Enforcement Administration (DEA), which is currently under evaluation. Symproic will be jointly launched and commercialized in the U.S. with Purdue Pharma and is expected to be commercially available mid-summer.

"The FDA approval of Symproic provides a safe and effective therapy for adult patients suffering from chronic non-cancer pain and struggling with opioid-induced constipation," said John Keller, President and Chief Executive Officer, Shionogi Inc. "We believe Symproic will offer a new therapeutic option to help reduce the needless suffering for those who experience OIC. The launch of Symproic with Purdue Pharma this summer will mark yet another milestone in our commitment to protect the health and well-being of patients we serve."

The FDA approval of Symproic was based on data from the COMPOSE program, a global comprehensive development program comprised of clinical studies conducted in adult patients with OIC and chronic non-cancer pain. It was comprised of three studies: COMPOSE I, COMPOSE II and COMPOSE III. COMPOSE I and II were 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies, while COMPOSE III was a 52-week, randomized, double-blind, placebo-controlled, long-term safety study.

"By entering this exciting new therapeutic area with Shionogi Inc., we have the opportunity to further help patients with chronic non-cancer pain by offering more comprehensive care to both patients and doctors," said Mark Timney, President and Chief Executive Officer, Purdue Pharma L.P. "The approval of Symproic marks a significant advancement in our partnership with Shionogi as well as the diversification of our product portfolio."

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.[1] 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 in 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.[2] In patients with chronic non-cancer pain, the prevalence of OIC ranges from approximately 40-50 percent.[3,4,5,6] In a survey of 322 patients taking daily opioids for chronic pain, 33 percent of patients missed, decreased or stopped opioid use to ease bowel movements.[7]

Indication
Symproic® (naldemedine) CII is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Important Safety Information about Symproic
Symproic is contraindicated in:

- 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, carbamazepine, phenytoin, St. John's Wort) because it may reduce the efficacy of Symproic.

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 nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Controlled Substance
Symproic contains naldemedine, a Schedule II controlled substance.

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%).

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see complete U.S. Prescribing Information and Medication Guide at www.shionogi.com by clicking here.

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 is a privately-held pharmaceutical company and is part of a global network of independent associated companies that is known for pioneering research in chronic pain and opioids with abuse-deterrent properties. The company's leadership and employees are committed to providing healthcare professionals, patients and caregivers quality products and educational resources to support their proper use. Purdue Pharma is engaged in the development, production and distribution of both prescription and over-the-counter medicines and hospital products. With Purdue Pharma's expertise in drug development, commercialization and life-cycle management, the company is diversifying in high-need areas to expand through strategic acquisitions and creative partnerships. For more information, please visit www.purduepharma.com.

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REFERENCES

[1] Sehgal N, Colson J, Smith HS. Chronic pain treatment with opioid analgesics: benefits versus harms of long-term therapy. *Expert Rev Neurother*. 2013;13:1201-1220.
[2] 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: 1386-1395.
[3] Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic noncancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372–80.
[4] 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.
[5] 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.
[6] 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.
[7] Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid induced bowel dysfunction: Results of a US and European Patient Survey (PROBE 1). *Pain Med.* 2009; 10:35-42.