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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memorandum

Date	March 23, 2017
From	Julie Beitz, MD
Subject	Office Director Decisional Memo
NDA #	208854
Applicant Name	Shionogi, Inc.
Date of Submission	March 23, 2016
PDUFA Goal Date	March 23, 2017
Proprietary Name / Established (USAN) Name	Symproic (naldemedine)
Dosage Forms / Strengths	Tablets 0.2 mg
Proposed Indication	Indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
Recommended Action:	Approval

Materials Reviewed/Consulted OND Action Package, including reviews from:	**Discipline Reviewers**
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DGIEP / Medical Team Leader	Anil Rajpal, MD
DGIEP / Pharmacology / Toxicology	Tracy Behrsing, PhD / Sushanta Chakder, PhD
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DGIEP = Division of Gastroenterology and Inborn Errors Products
DPMH = Division of Pediatrics and Maternal Health
OCP = Office of Clinical Pharmacology
OSE = Office of Surveillance and Epidemiology
DAAAP = Division of Anesthesia, Analgesia and Addiction Products
OB = Office of Biostatistics
OND = Office of New Drugs

1. Benefit-Risk Summary and Assessment

Symproic (naldemedine) is an antagonist of opioid binding at the mu-, delta- and kappa-opioid receptors, and functions as a peripherally acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids.

Constipation is the most common gastrointestinal symptom associated with chronic opioid use. The prevalence of opioid induced constipation (OIC) varies across studies, ranging from 15% to 81% of patients without cancer. Poorly controlled symptoms of OIC can lead to interruptions in opioid therapy and subsequently inadequate pain relief. Although many treatments for OIC are commercially available, additional treatment options are needed, particularly for patients who do not respond to, or tolerate, existing treatments.

Symproic (naldemedine) has been shown to be an efficacious, well-tolerated alternative for the treatment of OIC in adult patients with chronic non-cancer pain; its safety profile is consistent with that of other peripherally acting mu-opioid receptor antagonists. I concur with the recommendation of the Division of Gastroenterology and Inborn Errors Products to approve Symproic (naldemedine) for the treatment of OIC in adults with chronic non-cancer pain. The recommended dose is 0.2 mg taken orally once daily with or without food. The safety and effectiveness of Symproic (naldemedine) have not been established in pediatric patients. Symproic (naldemedine) will be the third orally administered peripherally acting mu-opioid receptor antagonist approved for this condition.

An FDA Advisory Committee Meeting was not held to discuss this application because the application did not raise significant safety or efficacy issues that were unexpected for a drug in this class.

Data submitted in the NDA supported the efficacy and safety of Symproic (naldemedine). The efficacy of Symproic (naldemedine) was established in two 12-week randomized, double-blind, placebo-controlled clinical trials involving adults with OIC and chronic non-cancer pain. The assumption that peripheral opioid receptor antagonism decreases the constipating effects of opioids has been borne out by the submitted clinical trials of Symproic (naldemedine). I concur that the observed improvements in stool frequency on naldemedine treatment were statistically superior to placebo and clinically meaningful to patients with OIC. Increases, albeit modest, in the frequency of stools associated with a sense of complete evacuation or without straining support the primary efficacy findings.

The safety profile of Symproic (naldemedine) is similar to that of other approved peripherally acting mu-opioid receptor antagonists. In adult patients with OIC, treatment with Symproic (naldemedine) was generally well tolerated. The adverse reactions most commonly reported were abdominal pain, diarrhea, nausea and gastroenteritis. The safety profile of Symproic (naldemedine) in a placebo-controlled, long-term safety

trial of 52 weeks duration was similar to that observed in the 12-week trials.

Although there are no data on naldemedine use in pregnancy to inform any drug-associated risks, as with other peripherally acting mu-opioid receptor antagonists, there is a potential for opioid withdrawal in a fetus when naldemedine is used in pregnant women. The potential risk of major adverse cardiovascular events or MACE remains a concern for this class of drugs. Although there was no direct evidence in the submitted data for a MACE risk for naldemedine in adults with OIC and chronic non-cancer pain, consistent with the Agency's requirements of other manufacturers of peripherally acting mu-opioid receptor antagonists, Shionogi will be required to conduct a postmarketing observational study comparing naldemedine to other treatments for OIC in patients with chronic non-cancer pain to assess the potential risk of MACE. This study will help further quantify the potential risk of MACE in real world settings and with larger numbers of patients.

The prescribers of Symproic (naldemedine) will likely be general practitioners and gastroenterologists familiar with the need to optimize control of OIC in patients with chronic non-cancer pain, and with the attendant risks of available treatments for OIC, including those associated with other peripherally acting mu-opioid receptor antagonists. The safety concerns identified in clinical trials of Symproic (naldemedine) can be adequately communicated in professional labeling that will include Warnings about the risks of gastrointestinal perforation and opioid withdrawal. A Medication Guide will be required as part of approved labeling to provide important safety information to patients.

A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Symproic (naldemedine) to ensure that the benefits of the drug outweigh the risks. Routine pharmacovigilance will be conducted in the postmarketing setting. The results of the required postmarketing study will inform product labeling regarding the potential risk of MACE with the use of Symproic (naldemedine).

Dimension	Evidence, Uncertainties and Conclusions
Analysis of Condition	Opioid analgesics are effective in the treatment of moderate to severe pain due to cancer and non-malignant conditions including musculoskeletal and neurological disorders and following surgery, and are widely prescribed in the U.S. In any given week, over 4 million individuals in the U.S. are estimated to be taking opioids as part of their regular regimen for pain relief. Regular opioid use increases with age, decreases with education level, and is more common in females and in non-Hispanic whites. Nearly one-fifth of regular users have been taking opioids for 5 years or more.[1]

[1] Parsells Kelly J, Cook SF, Kaufman DW, Anderson T, Rosenberg L, Mitchell AA. Prevalence and characteristics of opioid use in the US adult population. *Pain* (2008) 138:507-513.

Dimension	Evidence, Uncertainties and Conclusions
	Opioid use is associated with a host of bothersome gastrointestinal symptoms, with constipation reported most commonly. These symptoms are the result of binding of exogenous opioids to opioid receptors in the gastrointestinal tract and disturbance of three important gastrointestinal functions: motility, coordination of sphincter function and secretion. The prevalence of opioid induced constipation (OIC) varies across studies, ranging from 15% to 81% in patients without cancer. Recently, an international multidisciplinary working group defined OIC as "a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency". Such bothersome symptoms can lead to interruptions in opioid therapy and subsequently inadequate pain relief.[2] ***Comment.*** The availability of Symproic (naldemedine) would offer an FDA-approved, safe and effective alternative oral treatment for adults with symptoms of OIC. Although not life-threatening, symptoms of OIC can be bothersome to many millions of individuals in the U.S., resulting in interruption of opioid therapy and inadequate pain relief.
Current Treatment Options	Treatment for adults with OIC is highly individualized and usually involves combining laxatives with dietary and lifestyle changes. However, patients often obtain only partial relief, as these interventions do not address the underlying cause of OIC and most patients receiving chronic pain treatment suffer from comorbidities resulting in, for example, less mobility. Laxatives available over-the-counter are not intended for chronic use. Chronic use of non-bulking laxatives may lead to dependency and progressive tolerance, electrolyte imbalance, and, for the anthraquinones, melanosis coli. Chronic use of stimulant laxatives may result in bloating, feelings of fullness, abdominal pain, and incomplete fecal evacuation. Amitiza (lubiprostone) induces chloride-rich intestinal fluid secretion and thereby softens stool consistency. In 2013, lubiprostone was approved for the treatment of OIC in adult patients with non-cancer pain.[3] In contrast to other treatment strategies for OIC, opioid antagonists target the mu-opioid receptors in the gastrointestinal tract. In the U.S., two orally administered peripherally acting mu-opioid receptor antagonists have been approved for the treatment of OIC in adults with chronic non-cancer pain: Movantik (naloxegol) in 2014 and Relistor (methylnaltrexone bromide) in 2016. CNS penetration of these drugs is expected to be negligible at recommended doses, limiting their potential for interference

[2] Poulsen JL, Brock C, Olesen AE, Nilsson M, Drewes AM. Evolving paradigms in the treatment of opioid-induced bowel dysfunction. *Therap Adv Gastroenterol* (2015) 8:360-372.
[3] *Ibid.*

Dimension	Evidence, Uncertainties and Conclusions
	with centrally mediated opioid analgesia. Like naloxegol and methylnaltrexone bromide, naldemedine functions as a peripherally acting mu-opioid receptor antagonist in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects in the CNS. If approved, Symproic (naldemedine) would be the third orally administered peripherally acting mu-opioid receptor antagonist for the treatment of OIC in adults with chronic non-cancer pain. ***Comment.*** Although several treatments for OIC are commercially available in the U.S., additional therapeutic options are needed, particularly for patients who do not respond to, or tolerate, existing treatments. Symproic (naldemedine) would offer an FDA-approved, safe and effective alternative oral treatment for OIC in adults with chronic non-cancer pain.
Benefit	The efficacy of Symproic (naldemedine) was established in two identical randomized, double-blind, placebo-controlled clinical trials involving adults with OIC and chronic non-cancer pain, Trials V9231 and V9232. Patients were randomized 1:1 to receive either placebo or naldemedine 0.2 mg, once daily for 12 weeks, without respect to food intake. The mean age of participants was 54 years; 59% were women; and 80% were white. Back pain was the most common type of pain for which opioids were taken. The mean baseline opioid morphine equivalent daily dosage was 132 mg and 121 mg per day for patients in the two trials, respectively. Opioid induced constipation was confirmed during a two-week run-in period and was defined as no more than 4 spontaneous bowel movements (SBMs) over 14 consecutive days and less than 3 SBMs in a given week with at least 25% of the SBMs associated with one or more of the following: 1) straining; 2) hard or lumpy stools; 3) having a sensation of incomplete evacuation; or 4) having a sensation of anorectal obstruction/blockage. An SBM was defined as a bowel movement without rescue laxative taken within the past 24 hours. Patients had to either not be using laxatives or willing to discontinue laxative use at the time of screening and use only the provided rescue laxatives during the screening and treatment periods (bisacodyl if the patient had not had a BM for 72 hours and a one-time use of an enema, if after 24 hours of taking bisacodyl they still had not had a BM.) Patients with evidence of significant structural abnormalities of the GI tract were not enrolled in these trials. The primary efficacy endpoint was the proportion of patients meeting response criteria defined as having at least 3 SBMs per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4

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	weeks. In Trial V9231, 48% of naldemedine-treated patients vs. 35% of placebo-treated patients met response criteria, for a treatment difference of 13% (95% CI: 5, 21). In Trial V9232, 53% of naldemedine-treated patients vs. 34% of placebo-treated patients met response criteria, for a treatment difference of 19% (95% CI: 11, 27). In both trials, the response rate for naldemedine was statistically superior to the placebo response rate. In addition, patients who received naldemedine 0.2 mg in these trials had statistically significant improvements in the secondary efficacy endpoints of mean increase in frequency from baseline to the last two weeks of the 12-week treatment period in: SBMs per week, in complete SBMs per week (i.e., spontaneous bowel movements associated with a sense of complete evaluation), and in SBMs without straining per week. ***Comment.*** The efficacy of Symproic (naldemedine) has been established in two 12-week randomized, double-blind, placebo-controlled clinical trials involving adults with OIC and chronic non-cancer pain. The assumption that mu-opioid receptor antagonism in the gastrointestinal tract decreases the constipating effects of opioids has been borne out by the submitted clinical trials of Symproic (naldemedine). I concur that the observed improvements in stool frequency on naldemedine treatment were statistically superior to placebo and clinically meaningful to patients with OIC. Increases, albeit modest, in the frequency of stools associated with a sense of complete evacuation or without straining support the primary efficacy findings. The efficacy of naldemedine in pediatric patients has not been established.
Risk	**General Considerations.** A total of 1163 patients received naldemedine in clinical trials, including 487 patients with exposures greater than six months and 203 with exposures of 12 months. Following oral administration, naldemedine is absorbed with a T_{max} of approximately 0.75 hours in a fasted state. A high-fat meal decreased the rate, but not the extent of naldemedine absorption. Naldemedine is primarily metabolized by CYP3A. A population pharmacokinetic analysis did not identify a clinically meaningful effect of age, sex, or race on the pharmacokinetics of naldemedine. Although there are no data on naldemedine use in pregnancy to inform any drug-associated risks, as with other peripherally

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	acting mu-opioid receptor antagonists, there is a potential for opioid withdrawal in a fetus when naldemedine is used in pregnant women. Effects on the breast-fed infant are unknown, however, because of the potential for serious adverse reactions, including opioid withdrawal in breast-fed infants, either discontinuation of breastfeeding or use of the drug is recommended. Breastfeeding may be resumed 3 days after the last dose of naldemedine. The safety of naldemedine in pediatric patients has not been established. In clinical trials, 16% and 3% of naldemedine-exposed patients were 65 years and over or 75 years and over, respectively. No differences in safety between these and younger patients were observed. Naldemedine was not tumorigenic in 2-year carcinogenicity studies in mice and rats. Naldemedine was not genotoxic in *in vitro* assays or the *in vivo* rat bone marrow micronucleus assay, and had no effect on fertility or reproductive function in male or female rats. **Common Adverse Reactions.** In adults with OIC, treatment with naldemedine was generally well tolerated. During the 12-week double-blind, placebo-controlled period of Trials V9231 and V9232, the most frequent adverse reactions were gastrointestinal in nature, namely abdominal pain, diarrhea, nausea and gastroenteritis. The frequency of these reactions in patients treated with naldemedine 0.2 mg vs. placebo was: abdominal pain, 8% vs. 2%; diarrhea, 7% vs. 2%; nausea, 4% vs. 2%; and gastroenteritis, 2% vs. 1%. The safety profile of naldemedine in a placebo-controlled, long-term safety trial of 52 weeks duration (Trial V9235) was similar to that observed in the 12-week trials. **Gastrointestinal Perforation.** Cases of gastrointestinal perforation have been reported with use of another peripherally acting mu-opioid receptor 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). ***Comment.*** Given the cases of gastrointestinal perforation that have been reported with use of another peripherally acting mu-opioid receptor antagonist, I concur with the recommendation to contraindicate use of Symproic (naldemedine) in patients with known or suspected gastrointestinal obstruction and in patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation in these patients.

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	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 more frequently in patients treated with naldemedine than in patients receiving placebo. In the pooled 12-week trials (V9231 and V9232), adverse reactions of opioid withdrawal[4] were reported in 1% of naldemedine-treated and placebo-treated patients. In the 52-week V9235 trial, adverse reactions of opioid withdrawal were reported in 3% of naldemedine-treated patients vs. 1% of placebo-treated patients. ***Comment.*** Given the mechanism of action of peripherally acting mu-opioid receptor antagonists such as naldemedine, opioid withdrawal symptoms could be expected to result from the action of these drugs on peripheral opioid receptors (i.e., in the gastrointestinal tract). No association was seen between symptoms potentially related to opioid withdrawal and adverse cardiovascular events. Although patients suspected of having clinically important disruptions to the blood-brain barrier were not enrolled in clinical trials of naldemedine, these patients may be at increased risk for opioid withdrawal or reduced analgesia. I concur with the inclusion of a Warning in product labeling for naldemedine regarding the risk of opioid withdrawal, and with the recommendation to monitor patients suspected of having clinically important disruptions to the blood-brain barrier for symptoms of opioid withdrawal. **Drug Interactions.** Clinically important interactions are notable when naldemedine is co-administered with: Strong CYP3A4 inducers: A significant decrease in plasma naldemedine concentrations which may reduce efficacy was observed with co-administration of rifampin; use of naldemedine with strong CYP3A4 induces should be avoided; Strong and moderate CYP3A4 inhibitors: An increase in plasma naldemedine concentrations was observed with co-administration of fluconazole or itraconazole; monitor for naldemedine-related adverse reactions when the drug is co-administered with strong or moderate CYP3A4 inhibitors; P-gp inhibitors: An increase in plasma naldemedine concentrations was observed with co-administration of cyclosporine; monitor for naldemedine-related adverse reactions when the drug is co-administered with P-gp inhibitors; Other opioid antagonists: The potential for additive effects and increased risk of opioid withdrawal exists with co-

[4] Adverse reactions consistent with opioid withdrawal were based on investigator assessment and adjudicated based upon the occurrence of at least 3 adverse reactions occurring on the same day or within one day of each other.

Dimension	Evidence, Uncertainties and Conclusions
	administration of naldemedine and other opioid antagonists; use of naldemedine with other opioid antagonists should be avoided. **Major Adverse Cardiovascular Events (MACE).** Trial V9235, a 52-week randomized, double-blind, controlled trial, was conducted to evaluate the long-term safety of daily administration of naldemedine 0.2 mg versus placebo in adults with OIC and chronic non-cancer pain. The incidence of MACE[5] in the first 12 weeks of this trial was low and similar for both naldemedine and placebo. When the 12-week results of Trials V9231, V9232 and V9235 are combined, the incidence of MACE in naldemedine-treated patients was 0.2% (2/1163) and 0.3% (3/1165) in placebo-treated patients. Pooling data from all three trials (from Day 1 to end of study), the incidence of MACE remained comparable between the two treatment groups (i.e., naldemedine: 0.4% or 8.3 events per 1000 patient-years vs. placebo: 0.5% or 9.9 events per 1000 patient-years).[6] ***Comment.*** I concur that there is no direct evidence in the submitted data for a MACE risk for naldemedine in adults with OIC and chronic non-cancer pain. Consistent with the Agency's requirements of other manufacturers of peripherally acting mu-opioid receptor antagonists, Shionogi will be required to conduct a postmarketing observational study comparing naldemedine to other treatments for OIC in patients with chronic non-cancer pain to assess the potential risk of MACE.[7] This study will help further quantify the potential risk of MACE in real world settings and with larger numbers of patients. **Abuse Potential.** Naldemedine is derived from naltrexone, a derivative of thebaine, a Schedule II opium derivative. As a derivative of thebaine, naldemedine is currently also a Schedule II substance. CDER's Controlled Substances Staff concluded,

[5] MACE is defined as the occurrence of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death.

[6] *See* statistical review by George Kordzakhia, PhD, dated December 9, 2016.

[7] See my Office Director memorandum, dated September 16, 2014 for Movantik (NDA 204760), for a summary of the discussion at the June 11-12, 2014, meeting of the Anesthesia and Analgesia Drug Products Advisory Committee convened to assess the potential risk of MACE associated with the use of peripherally acting mu-opioid receptor antagonists. An imbalance in myocardial infarctions with the drug Entereg (alvimopan) relative to placebo was observed in a single 12-month trial in OIC patients with chronic non-cancer pain. Committee members were split regarding whether this finding represented a real cardiovascular signal. Those who believed it was a signal described it as weak, at best, but not ignorable given the seriousness of the adverse event. These members also acknowledged that 1) the finding had not been replicated in a second trial, and 2) there was insufficient evidence to establish a biologic mechanism by which Entereg or other opioid receptor antagonists could cause myocardial infarction in chronic opioid users. Subsequent to this meeting, FDA determined that manufacturers of peripherally acting mu-opioid receptor antagonists would be required to conduct a postmarketing observational study to further quantify the potential MACE risk with their drug in real world settings and with larger numbers of patients.

Dimension	Evidence, Uncertainties and Conclusions
	based on review of submitted non-clinical and clinical abuse-related data, that naldemedine has no abuse potential and that naldemedine be recommended for decontrol from the Controlled Substances Act. **Other Serious Adverse Reactions.** Two patients developed symptoms of hypersensitivity following a single dose of Symproic (naldemedine). One patient reported bronchospasm and another rash.
Risk Management	**Labeling.** The prescribers of Symproic (naldemedine) will likely be general practitioners and gastroenterologists familiar with the need to optimize control of OIC in patients with chronic non-cancer pain, and with the attendant risks of available treatments for OIC, including those associated with members of this drug class, namely Movantik (naloxegol) and Relistor (methylnaltrexone bromide). Consistent with product labeling for other drugs in this class, labeling for Symproic (naldemedine) will warn about: • Gastrointestinal perforation • Opioid withdrawal Use of Symproic (naldemedine) will be contraindicated in: • Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction • Patients with a history of a hypersensitivity reaction to naldemedine. In addition, a Medication Guide will be required as part of approved labeling to provide important safety information to patients; routine pharmacovigilance will be conducted in the postmarket setting. **Risk Mitigation.** A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Symproic (naldemedine). It is likely that practitioners who will prescribe Symproic (naldemedine) for OIC will be aware of the attendant risks of treatment with peripherally acting mu-opioid receptor antagonists, given the previous marketing experience with other FDA-approved products in this class. **Postmarketing Required Studies.**

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	Pediatric Research Equity Act (PREA) The Agency is waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Based on the limited available literature, few pediatric patients in any group receive round-the-clock opioids for greater than 4 weeks. There is also a lack of consensus on the use of opioids for the treatment of chronic non-cancer pain in pediatric patients. ***Food and Drug Administration Amendments Act (FDAAA)*** The applicant will be required to conduct a postmarketing observational study comparing Symproic (naldemedine) to other treatments for OIC in patients with chronic non-cancer pain to assess the risk of MACE. ***Comment.*** The safety concerns identified with use of Symproic (naldemedine) in clinical trials can be adequately managed by professional labeling, a Medication Guide, that will be required as part of approved labeling to communicate important safety information to patients, and routine pharmacovigilance in the postmarketing setting. The results of a required postmarketing study will inform product labeling regarding the potential risk of MACE with use of Symproic (naldemedine).

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/s/

JULIE G BEITZ
03/23/2017