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RESEARCH**

APPLICATION NUMBER:

208854Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA	208854
Applicant	Shionogi, Inc.
Date of Submission	March 23, 2016
PDUFA Goal Date	March 23, 2017
Proprietary Name / Non-Proprietary Name	Symproic naldemedine
Dosage Form(s) / Strength(s)	Tablet/0.2 mg
Applicant Proposed Indication(s)/Population(s)	Opioid-induced constipation in adult patients with chronic non-cancer pain
Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Lauren Weintraub, MD/Anil Rajpal, MD
Statistical Review	George Kordzakhia, PhD and Lin Lan, PhD/Yeh-Fong Chen, PhD
Pharmacology Toxicology Review	Tracy Behrsing, PhD/Sushanta Chakder, PharmD/Abigail Jacobs, PhD
OPQ Review	See table below.
DAAAP	Elizabeth Kilgore, MD/Joshua Lloyd, MD/Ellen Fields, MD, MPH/Sharon Hertz, MD
DPMH/MHT	Christos Mastroyannis, MD/Tamara Johnson, MD/Lynne Yao, MD
Clinical Pharmacology Review	Sandhya Apparaju, PhD/Justin Earp, PhD/Yuching Yang, PhD/Nitin Mehotra, PhD/ Ping Zhao, PhD/ Edward Bashaw, PhD TqT: Moh Jee Ng
COA	Sarrit M. Kovacs, PhD/Elektra Papadopoulos, MD, MPH
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OSE/DEPI	Joel Weissfeld, MD, MPH/Kira Leishear White, PhD, MS/Michael Nguyen, MD/ Simone Pinheiro, ScD
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OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 COA=Clinical Outcome Assessment
 CSS=Controlled Substance Staff
 DAAAP= Division of Anesthesia, Analgesia, and Addiction Products
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DPMH = Division of Pediatric and Maternal Health
 MHT=Maternal Health Team

Quality Review Team

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1. Benefit-Risk Assessment

I concur with the reviewers' conclusions that the benefit/risk of naldemedine is favorable in the population for which this product will be approved and that the risks can be managed with labeling.

The applicant proposed the following indication for naldemedine, an orally administered peripheral mu opioid receptor antagonist:

Symproic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

The FDA reviewers found that two randomized, controlled clinical trials submitted to the NDA (Study V9231 and Study V9232) supported naldemedine's approval for the proposed indication. I concur.

The following Benefit-Risk Summary and Assessment is reproduced and modified from the CDTL review.

Benefit-Risk Summary and Assessment

Naldemedine is an opioid antagonist with binding affinities for mu-, delta-, and kappa-opioid receptors. Naldemedine functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, decreasing the constipating effects of opioids. Opioid induced constipation (OIC) is a frequent complication of chronic opioid use. Naldemedine is a derivative of naltrexone to which a side chain has been added, increasing the molecular weight and the polar surface area, and reducing its ability to cross the blood-brain barrier (BBB). It is also a substrate of the P-glycoprotein (P-gp) efflux transporter. Based on these properties, the CNS penetration of naldemedine is expected to be negligible at the recommended dose levels, decreasing the potential for interference with centrally-mediated opioid analgesia.

Currently, there are three drugs specifically approved for treatment of OIC: Amitiza (lubiprostone), Relistor (methylnaltrexone), and Movantik (naloxegol). Relistor and Movantik are peripherally active opioid antagonists. Amitiza is a chloride channel activator. All three are available as oral formulations; Relistor is also available as a subcutaneous formulation.

- Amitiza was approved in April 2013 for an OIC indication in adults with chronic non-cancer pain.
- Movantik was approved in September 2014 for an OIC indication in adults with chronic non-cancer pain.
- Relistor (subcutaneous formulation) was approved in April 2008 for an OIC indication in patients who are receiving palliative care; Relistor (subcutaneous formulation) was approved in September 2014 for an OIC indication in adult patients with chronic non-cancer pain.
- Relistor (oral formulation) was approved in July 2016 for the same indications as Relistor (subcutaneous formulation).

In addition, a wide variety of over-the-counter and prescription products are used to treat constipation, including: stool softeners (docusate), bulk-forming laxatives (psyllium, methylcellulose, polycarbophil), stimulant laxatives (bisacodyl, senna, and castor oil), saline osmotic laxatives (sodium phosphate, magnesium citrate, and magnesium hydroxide), osmotic laxatives (lactulose and sorbitol), lubricants (mineral oil, glycerin), and other osmotic agents like polyethylene glycol (PEG)-3350 (with and without electrolytes).

The efficacy and safety of naldemedine as a treatment of OIC in adult patients with chronic non-cancer pain has been adequately assessed. Efficacy of naldemedine was established in two replicate, 12-week, randomized, double-blind, placebo-controlled trials in patients with OIC and chronic non-cancer pain; naldemedine was used without laxatives with the exception of bisacodyl rescue treatment. Efficacy was measured by the proportion of patients with 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 study weeks and 3 out of the last 4 weeks. This endpoint was considered clinically

meaningful. The treatment difference relative to placebo was 13% in the first trial and 19% in the second trial.

A 52-week randomized double-blind, placebo-controlled trial was also conducted in this population; however, approximately half of patients in both arms were on a laxative regimen at baseline and continued it on the study, concomitantly with study drug. The primary objective of the trial was assessment of safety. Secondary analyses (without alpha control) of change from baseline in stool frequency (not SBM) revealed changes that appeared similar to those observed in secondary analyses of SBM changes in the two 12-week efficacy trials.

Naldemedine was shown to be safe and well-tolerated in adult OIC patients with chronic non-cancer pain. The safety profile was generally comparable to the known safety profile described in the product labels for other peripherally-acting mu-opioid receptor antagonist (PAMORA) medications approved for treatment of OIC. No new or unexpected safety signals or serious reactions were identified.

The most common adverse reactions¹ in the two 12-week trials were abdominal pain (naldemedine 8% vs. placebo 2%) and diarrhea (7% vs. 2%). These were also the most common adverse reactions in the first 12 weeks of the third trial (abdominal pain: 11% vs. 5%; diarrhea: 7% vs. 3%) and the full 52 weeks of the third trial (diarrhea: 11% vs. 5%; abdominal pain: 8% vs. 3%). Additionally, in the latter trial, over the full 52 weeks, 8% of naldemedine subjects reported nausea vs. 6% in the placebo arm.

Overall adverse reactions led to discontinuation in 5% (naldemedine) vs. 2% (placebo) in the combined data from the two 12-week trials, and 6% vs. 5% (over the full 52 weeks in Study V9235).² In the first 12 weeks of Study V9235, the discontinuation rate for adverse reaction was similar to that observed in the two 12 week trials, 5% naldemedine vs. 2.5% placebo. In all three trials, gastrointestinal (GI) disorders were the most common reason for study discontinuation. GI disorders led to discontinuation in 3% (naldemedine) vs. 1% (placebo) in the two 12-week trials, and 4% vs. 1%, respectively, in the 52-week trial.³

There was a single death (naldemedine arm) in the two 12-week phase 3 trials, and the death was not considered treatment related. Deaths specifically related to treatment emergent adverse events occurred in 0.2% naldemedine arm vs. 0.5% placebo arm subjects in the 52-week trial (Study V9235);⁴ none of the deaths were considered treatment-related. However, there were also unwitnessed sudden deaths in Study V9235, and if those are counted, there were 4/621 (0.6%) naldemedine subjects and 4/619 (0.6%) placebo subjects who died on study.

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¹ Adverse reactions were defined as adverse events occurring at a higher rate in the naldemedine group compared to placebo.
² Table 14.3-1.1.2 of Integrated Summary of Safety
³ Table 14.3-1.5.2 of Integrated Summary of Safety
⁴ Table 14.3-1.1.2 of Integrated Summary of Safety

Serious adverse reactions (SAEs) occurred in 4% (naldemedine) vs. 3% (placebo) in the two 12-week trials, and 9% vs. 11%, respectively, in the overall 52-weeks of Study V9235.⁵ Specific SAEs occurred with similar frequency in both treatment groups, were distributed across multiple System Organ Classes (SOCs) and, in general, occurred in 2 or less subjects per group. One case of serious hypersensitivity reaction (bronchospasm) was reported and resulted in hospitalization and treatment discontinuation. There were no gastrointestinal perforations.

Specific safety assessments were conducted to assess the risk of major adverse cardiac events (MACE) and included prospective adjudication by an independent committee. A class-wide safety concern of increased risk of MACE arose from safety data with another member of this class – Entereg (alvimopan)].⁶ In the naldemedine clinical trials, no increased risk of MACE was identified; however, because the extent of exposure may not have been sufficient to identify a signal of this risk, a postmarketing study should be required to identify an unexpected serious risk of MACE in patients with chronic non-cancer pain taking naldemedine for OIC [see discussion of Postmarketing Requirement (PMR) below], similar to the PMR that was a condition of approval for the other PAMORAs.

Pooling the two 12-week trials, the incidence of adverse reactions of opioid withdrawal was 2% (8/542) for naldemedine and 1% (3/546) for placebo. In the 52-week trial, the incidence was 3% (20/621) for naldemedine and 1% (9/619) for placebo. Patients with disruptions to the blood-brain barrier (BBB) may be at increased risk for opioid withdrawal or reduced analgesia when taking naldemedine. In such patients, the overall risk-benefit profile should be considered, and healthcare practitioners should monitor for symptoms of opioid withdrawal. In addition, healthcare practitioners should advise females of reproductive potential, who become pregnant or are planning to become pregnant, that the use of naldemedine during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped BBB.

There is no information available regarding the presence of naldemedine in human milk, the effects on the breastfed infant, or the effects on milk production. However, a study revealed the presence of naldemedine in the milk of rats. 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. If drug is discontinued in order to minimize drug exposure to a breastfed infant, women should be advised that breastfeeding may be resumed 3 days after the final dose of naldemedine.

⁵ Table 14.3-1.1.2 of Integrated Summary of Safety

⁶ On June 11-12, 2014, there was a general matters meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) to discuss the potential cardiovascular risk associated with products in the class of peripherally-acting opioid receptor antagonists; and the necessity, timing, design and size of cardiovascular outcomes trials to support approval of products in the class for the proposed indication of OIC in patients taking opioids for chronic pain. The AADPAC recommended that sponsors assess the potential for a cardiovascular risk through postmarketing requirements (PMR) observational studies. Meeting materials are available at

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm390304.htm>

Concomitant use of strong CYP3A inducers may decrease the efficacy of naldemedine by decreasing naldemedine's systemic exposure; strong CYP3A inducers should be avoided. Concomitant use of other opioid antagonists may have the potential for additive effect of opioid receptor antagonism and increased risk of opioid withdrawal; use with another opioid antagonist should be avoided. Concomitant use of moderate CYP3A inhibitors may increase plasma naldemedine concentration; monitoring for potential naldemedine-related adverse reactions should be performed when naldemedine is administered with moderate CYP3A inhibitors. A thorough QT study, which evaluated a supratherapeutic naldemedine dose associated with an exposure that exceeds that expected with concomitant administration of a potent CYP3A inhibitor revealed no clinically relevant QT prolongation.

Naldemedine is currently a Schedule II drug under the Controlled Substances Act (CSA), based on a provision in the CSA that places all derivatives of opium and opioids, including thebaine, into Schedule II. The Controlled Substances Staff Reviewer concluded, based on review of the nonclinical and clinical abuse-related data submitted in this NDA, that naldemedine is primarily a full opioid antagonist with limited CNS activity, and as such, does not have abuse potential that is similar to controlled substances in the CSA. However, the DEA decision regarding scheduling remains pending at the time of this review.

The benefit-risk profile for naldemedine is favorable, and similar to other drugs in this class. A REMS is not necessary for naldemedine to ensure the benefits outweigh the risks. Risks associated with this product will be managed with labeling, consistent with class labeling for PAMORAs, including: a contraindication for history of hypersensitivity reaction and for use in patients with a known or suspected GI obstruction or at increased risk of recurrent obstruction; a Warning and Precaution for opioid withdrawal and gastrointestinal perforation. There will also be a medication guide.

A post-marketing, observational epidemiologic study comparing naldemedine to other treatments of opioid induced constipation in patients with chronic non-cancer pain will be required as a condition of approval. This PMR study is consistent with the PMR observational study that was a condition of each of the approvals of other PAMORAs for OIC in patients with chronic non-cancer pain (i.e., Movantik, Relistor subcutaneous formulation, and Relistor oral formulation) and is intended to evaluate for and detect a signal of increased risk for MACE. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately.

A waiver of pediatric studies will be granted as studies are impossible or highly impractical. Based on the limited available literature, few pediatric patients in all age groups receive round-the-clock opioids for greater than four weeks. There is also a lack of consensus on the use of opioids for the treatment of chronic non-cancer pain in pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	Opioid analgesics are commonly prescribed for the management of moderate to severe pain and represent one of the most prescribed classes of medications worldwide. In 2014, approximately 3-4% of adults in the US (equal to 9.6 to 11.5 million persons) were prescribed opioid therapy >3 weeks duration (Dowell, 2016). Another source reports an estimated prevalence of chronic opioid use of >4 million US adults. Opioid induced constipation (OIC) is a frequent opioid side effect, with reported rates as high as 80-90% among patients with chronic, non-cancer pain (Panchal, 2007). Opioids exert constipating effects on the gastrointestinal (GI) tract. Patients do not experience tolerance to the constipating effects of opioids. OIC often impacts quality of life and can lead to complications, such as fecal impaction and pseudo-obstruction (Leppert, 2012).	Chronic opioid use for non-cancer pain is increasing in the US and worldwide. Because OIC is a common adverse reaction, OIC is also increasing. Although OIC is rarely life-threatening, this condition is associated with morbidities and reduced quality of life.
<u>Current Treatment Options</u>	Currently, three drugs are approved for the treatment of OIC in patients with chronic non-cancer pain: two peripherally-acting mu-opioid receptor antagonists (PAMORAs)—Relistor (methylnaltrexone bromide, available in both subcutaneous and oral formulations) and Movantik (naloxegol, available as an oral tablet)—and lubiprostone (Amitiza), a chloride channel activator that is also approved for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome (IBS). Standard-of-care management of OIC includes laxatives, fiber supplementation, and lifestyle interventions, such as increased fluid intake and physical activity. Though not specifically indicated for OIC, laxatives of all classes (i.e., stool softeners, bulk-forming agents, stimulants, osmotic agents, saline solutions, and lubricants) are extensively used to treat OIC. Approximately half of the subjects who entered the 52 week phase 3 safety	Naldemedine is a peripherally-acting mu-opioid receptor antagonist (PAMORA). There are currently two drugs in this class (Relistor and Movantik) approved for treatment of OIC in patients with chronic non-cancer pain. Another drug (Amitiza), a chloride channel activator, is also approved for treatment of OIC in patients with chronic non-cancer pain.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	trial submitted in this NDA were taking a routine/regular laxative regimen for their OIC and continued it on the trial. Even on that baseline regimen, those patients met entry criteria of having ≤ 4 spontaneous bowel movements over 14 consecutive days during the screening period.	
<u>Benefit</u>	aldemedine's effectiveness for treatment of OIC in adults with chronic non-cancer pain was evaluated based primarily on data from two replicate multicenter, randomized, double-blind, placebo-controlled clinical trials, each with a treatment and evaluation period of 12 weeks in duration. The combined efficacy analysis database from the two trials included 1095 subjects with OIC (based on pre-specified diagnostic criteria) and ≥ 4 weeks of opioid use with a stable dosage regimen, who were randomized 1:1 to receive either naldemedine 0.2 mg once daily (n=549) or matching placebo (n=546). The primary endpoint was the difference in proportion of responders between groups, using a responder definition of the proportion of patients with 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 study weeks and 3 out of the last 4 weeks. The proportion of responders was higher among naldemedine-treated patients than placebo-treated patients (a 13% and 19% treatment difference relative to placebo in the respective trials), and achieved statistical significance in both trials (p=0.002 and <0.0001). Sensitivity analyses of primary endpoint data yielded comparable results. A third placebo controlled trial, in which approximately half of subjects entered the trial on a laxative regimen to manage their OIC and continued the regimen concomitantly with study drug, provided additional supportive efficacy data. The trial's primary objective was safety assessment, and alpha was not controlled for the prespecified secondary efficacy analyses. However, the mean change in stool frequency (bowel movement, not SBM which defined the endpoint in the efficacy trial) from	The effectiveness of naldemedine for treatment of OIC in patients with chronic, non-cancer pain was demonstrated in two adequate and well-controlled clinical trials. The eligibility criteria were considered appropriate to ensure a study population sufficiently representative of the target patient population and interpretability of efficacy assessments. The primary endpoint was considered an appropriate measure of a clinically meaningful treatment benefit upon which to base efficacy assessments. The difference in proportion of responders between treatment and placebo in the two trials was comparable to what was observed in the clinical trials that supported approval of other PAMORAs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	baseline observed in this trial appeared similar to the mean change from baseline in SBM observed in the secondary analyses of the two efficacy trials. Subgroup efficacy analyses of the two efficacy trials (based on the primary endpoint <u>responder analysis</u>) by sex suggested lower treatment effect in females relative to males in one of the two trials; however, this was not observed in the other 12-week trial. Subgroup analysis of the <u>mean change from baseline in stool frequency (bowel movement, not SBM)</u> in the third phase 3 trial (the safety trial), revealed a numerically slightly lower mean change in bowel movements in females relative to males; however the difference was very small and unlikely to be clinically relevant. Therefore, there are no persuasive data establishing that the treatment effect of naldemedine is lower in females than in males. Similarly, there is some uncertainty regarding efficacy in Black subjects, as subgroup analyses of the phase 3 trials revealed the response relative to placebo was much lower in Black subjects relative to White subjects. In fact, in Study V9232, the placebo response in Black subjects was higher than that observed in the naldemedine arm. The placebo response in Black subjects in both trials was higher than the placebo response observed in White subjects. The very small sample size of the Black subgroup makes it impossible to draw firm conclusions regarding relative efficacy of this product between the two races. The applicant also submitted a subgroup analysis of the bowel movement (not SBM) data from the safety trial, Study V9235, using repeated measures analysis of change in frequency of bowel movements/week. They reported that the change from baseline relative to placebo in Black subjects was lower than in White subjects: 0.43 vs. 1.45. The mean change from baseline of bowel movements at Week 12 was higher in Black subjects treated with placebo than in White subjects treated with placebo (3.20 vs. 2.23). The sample size of Black subjects in this trial was larger than in the other two trials,	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	but was <25% that of the White subjects. The distribution of use of baseline concomitant laxative regimens between arms within this subgroup was similar (48%). “Regular/routine” concomitant laxative use in the White subgroup was numerically somewhat higher, 50% in the naldemedine group and 55.5% in the placebo group. Given that this exploratory subgroup analysis examined a secondary endpoint of uncertain meaningfulness (relative to the endpoint in the two efficacy trials) and there was no alpha control, the observed difference is not reliable and of questionable meaningfulness.	
<u>Risk</u>	The naldemedine safety population consisted of 1163 subjects with chronic, non-cancer pain who received ≥ 1 dose of naldemedine in phase 3 clinical trials, as well as a similar population of placebo-treated subjects (total 2328 subjects). The primary sources of safety data included the two 12-week studies, as well as a long-term, dedicated safety trial with a planned 52-week treatment period. The latter trial, addresses the recommendations from the June 11-12, 2014 meeting of the Anesthesia and Analgesia Drug Products Advisory Committee Drugs for the PAMORA drug class, which was held to discuss whether there was a need to conduct CV safety outcome trials to support their approval (either pre or post approval). Based on the discussion at the AC meeting, FDA determined that the <u>premarketing</u> safety assessment for drugs in this class should be a 12 month trial, ideally controlled, with a sample size similar to the Movantik and Entereg safety databases, i.e., not a dedicated CVOT, but with a pre-specified plan to adequately capture/assess/adjudicate MACE events to assure the data are interpretable for assessment of a CV signal when the NDA is reviewed. A l t h o u g h a sample size in the range of the trial included in the Movantik NDA had limited capability to detect a signal, unless the incremental increase in risk was quite large, reviewers agreed that such a 12 month trial is valuable for evaluating general safety of a PAMORA, which will be used chronically.	The safety profile was generally comparable to the known safety profile of other PAMORA medications approved for treatment of OIC. GI reactions comprised the majority of adverse reactions, and led to study discontinuation in 5% of all naldemedine-treated subjects (30% of subjects experiencing GI ARs). However, serious GI events were rare, and symptoms resolved without sequelae upon treatment discontinuation. The naldemedine safety evaluation did not identify any new or unexpected safety signals or serious reactions. The naldemedine safety database is a large, prospectively collected dataset from randomized, double-blind trials. Safety assessments for all phase 3 trials included prospective identification and adjudication of MACE. Although the safety data did not

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	As with other PAMORAs, gastrointestinal (GI) events represented the majority of adverse reactions associated with naldemedine treatment (i.e., events reasonably attributable to treatment). Two-hundred thirty-six (236) of 1163 (10.3%) naldemedine-treated subjects experienced ≥ 1 of the 4 major GI reactions (abdominal pain, diarrhea, nausea, and vomiting), of which >50% reported onset of symptoms within the first seven days of treatment (n=122, 10.4), and >30% reported onset on Day 1 (n=71, 6.1%). The most common adverse reactions⁷ in the combined safety data from the two 12-week trials were abdominal pain (naldemedine 8% vs. placebo 2%) and diarrhea (7% vs. 2%). These were also the most common adverse reactions in the first 12 weeks of Study V9235 (abdominal pain: 11% vs. 5%; diarrhea: 7% vs. 3%) and the full 52 weeks of the third trial (diarrhea: 11% vs. 5%; abdominal pain: 8% vs. 3%). Additionally, in the latter trial, over the full 52 weeks, 8% of naldemedine subjects reported nausea vs. 6% in the placebo arm. Overall adverse reactions led to discontinuation in 5% (naldemedine) vs. 2% (placebo) in the two 12-week trials combined, and 6% vs. 5% in the overall 52-week duration of the safety trial, Study V9235.⁸ The rate of discontinuation for adverse reactions in the first 12 weeks of the 52 week trial was similar to that observed in the two 12 week trials combined (5% naldemedine vs. 2.5% placebo). In all three trials, gastrointestinal (GI) disorders were the most common reason for study discontinuation. GI disorders led to discontinuation in 3% (naldemedine) vs. 1% (placebo) in the two 12-week trials, and 4% vs. 1%, respectively, in the 52-week trial.⁹ A single death occurred (in a naldemedine arm subject) in the combined two	demonstrate an increased frequency of MACE compared to placebo, the safety database from controlled phase 3 trials of naldemedine was too small to yield an event frequency high enough to statistically rule out an increased risk of MACE with naldemedine treatment.

⁷ Adverse reactions were defined as adverse events occurring at a higher rate in the naldemedine group compared to placebo.

⁸ Table 14.3-1.1.2 of Integrated Summary of Safety

⁹ Table 14.3-1.5.2 of Integrated Summary of Safety

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	12-week trials, 0.2% (naldemedine) vs. 0 (placebo). Deaths specifically related to treatment emergent adverse events occurred in 0.2% naldemedine arm vs. 0.5% placebo arm subjects in the 52-week trial (Study V9235);¹⁰ none of the deaths were considered to be treatment-related. However, there were also unwitnessed sudden deaths in Study V9235, and if those are counted, there were 4/621 (0.6%) naldemedine subjects and 4/619 (0.6%) placebo subjects who died on study. Serious adverse reactions (SAEs) occurred in 4% (naldemedine) vs. 3% (placebo) in the two 12-week trials, and 9% vs. 11%, respectively, over the full 52 week treatment period in the 52-week trial.¹¹ Specific SAEs occurred with similar frequency in both treatment groups, were distributed across multiple System Organ Classes (SOCs) and, in general, occurred in 2 or less subjects per group. Pooling the two 12-week trials, the incidence of opioid withdrawal was 2% (8/542) for naldemedine and 1% (3/546) for placebo. In the 52-week trial, the incidence was 3% (20/621) for naldemedine and 1% (9/619) for placebo. No significant difference in pain (either pain scores or AEs) between groups was determined; however, methodology was not adequate for conclusive assessments. Regarding other labeled class-wide safety concerns: 1) one serious case of hypersensitivity (bronchospasm) was reported and resulted in hospitalization and treatment discontinuation; 2) No gastrointestinal perforations occurred, although two naldemedine subjects were diagnosed with gastric ulcerations (vs. 0 placebo subjects); and 3) An increased frequency of MACE with naldemedine compared to placebo was not observed in the naldemedine phase	

¹⁰ Table 14.3-1.1.2 of Integrated Summary of Safety

¹¹ Table 14.3-1.1.2 of Integrated Summary of Safety

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	3 trials [adjudicated MACE cases: 5/1163 (naldemedine) vs. 6/1165 (placebo); RR=0.84; 95% CI: 0.26, 2.73]. The trials in this is application included specific safety assessments for major adverse cardiac events (MACE), which were prospectively adjudicated by an independent committee, in order to address a class-wide safety concern arising from the long-term safety trial of Entereg (alvimopan), a PAMORA not indicated for OIC and approved (with a REMS) only for short-term use.	
Risk Management	Product labeling will address the safety concerns of naldemedine and other PAMORAs, including a Contraindication and class-wide Warnings and Precautions. (See above.) Though not observed in clinical trials of naldemedine, this includes a warning of gastrointestinal perforation. Product labeling for the PAMORAs indicated for OIC, including naldemedine, does not include safety information specific to risk of MACE. However, the concern for a potential increased risk of MACE with these products has not been resolved, and postmarketing evaluations evaluating for a signal of MACE were required as a condition of approval of the other PAMORAs currently marketed. A PMR to obtain similar postmarketing data for naldemedine will also be a condition for its approval. This observational study will evaluate postmarketing data for evidence of a signal of increased risk of MACE.	Overall, clinical trial data support the finding of a favorable benefit-risk profile for naldemedine. The product labeling adequately reflects the overall safety profile of naldemedine and class-wide safety concerns for PAMORAs approved for treatment of OIC. There is no established class-wide increased risk of MACE (for PAMORAs) and there was no evidence of a signal for increased risk in the naldemedine safety database. However, a postmarketing observational epidemiologic study comparing naldemedine to other treatments of OIC in patients with chronic non-cancer pain will be required as a condition of approval, similar to the PMRs for the other PAMORAs approved for OIC. The letter will state that the study will be required to identify an unexpected serious risk of MACE:

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

References for Benefit-Risk Table:

- Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States 2016. JAMA 2016; 315(15):1624-45.
- Leppert W. The impact of opioid analgesics on the gastrointestinal tract function and the current management possibilities. Contemporary Oncology. 2012;16(2):125-131.
- Nelson AD, Camilleri M. Chronic opioid induced constipation in patients with nonmalignant pain: challenges and opportunities. Therapeutic Advances in Gastroenterology. 2015;8(4):206-220. doi:10.1177/1756283X15578608.
- Panchal SJ, Müller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. International Journal of Clinical Practice. 2007;61(7):1181-1187.

2. Background

Naldemedine, a new molecular entity, is a derivative of naltrexone. It is an antagonist of opioid binding to mu-, delta-, and kappa-opioid receptors. It is intended to function as a peripherally-acting mu-opioid receptor antagonist (PAMORA), specifically in the gastrointestinal (GI) tract; polar groups in its chemical structure and its molecular weight impact its ability to cross the blood brain barrier. Furthermore, it is a substrate for p-glycoprotein (pGP).

The regulatory history of naldemedine's development is documented in the Clinical Review. The reviewers have recommended approval. I concur. My review summarizes key review findings.

3. Product Quality

The OPQ reviewers determined sufficient CMC information was provided to assure the identity, strength, purity and quality of the drug product. The Office of Process and Facilities made a final overall "Approval" recommendation for the facilities involved in the application. A Categorical Exclusion for the Environmental Assessment was granted. All CMC labeling issues were resolved. OPQ recommended approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

No approvability issue was identified by the Pharmacology/Toxicology reviewers. They recommended the label's Section 12.1 Mechanism of Action should state that naldemedine is an opioid antagonist with binding affinities for mu-, delta- and kappa-opioid receptors. (The K_i values are 0.34, 0.43 and 0.94, respectively.)

The Ames assay, a chromosomal aberration assay with cultured Chinese hamster lung cells, and an *in vivo* micronucleus assay with rat bone marrow cells revealed no evidence of genotoxicity. The carcinogenicity studies (mice and rats) were negative.

A six month, repeat dose toxicity study in rats achieved systemic exposures approximately 3600 times the human exposure associated with the naldemedine dose that will be approved (0.2 mg once daily). A 9-month repeat dose toxicity study in dogs achieved systemic exposures approximately 345 times the human exposure associated with naldemedine 0.2 mg. There were no deaths in rats, and the key clinical findings were decreased weight gain and abnormal eating behavior. No histopathological lesions were reported. In the dog study, the liver was identified as the target organ. Increases in ALT, ALP and GGT were noted in both sexes. Histopathological examination revealed single hepatic cell necrosis and increases in Kupffer cells in dogs administered the high dose. There were no deaths.

5. Clinical Pharmacology

The Clinical Pharmacology reviewers found the information submitted to the NDA “acceptable from a Clinical Pharmacology perspective.” Their labeling recommendations were incorporated in final labeling. They did not recommend any PMRs or PMCs.

The reviewers concurred with the dose and dosing schedule proposed by the applicant, i.e., 0.2 mg PO once daily. The terminal half life is 9-11 hours. The product is hepatically and renally cleared. Naldemedine is primarily metabolized by CYP3A4. A multidose PK study conducted in OIC patients revealed no meaningful accumulation. A food effect study revealed that a high fat meal increases the C_{max} by 35%, but AUC wasn’t altered. The drug was administered without regard to food in the clinical trials; the reviewers recommended the label’s Dosage and Administration section should state the product can be taken with or without food.

The applicant submitted hepatic impairment and renal impairment studies. There were no data on the effects of severe hepatic impairment on naldemedine PK. Based on the submitted data, the product label will state that the naldemedine dose doesn’t have to be altered (b) (4) for mild and moderate hepatic impairment. Given the absence of data for severe hepatic impairment, the label (in Section 8.6 Hepatic Impairment) will state that naldemedine should be avoided in patients with severe hepatic impairment.

The reviewers’ recommendations for labeling regarding co-administration of CYP3A4 inducers and inhibitors, as well as P-gp inhibitors, were accepted by the applicant.

Thorough QT (tQT) study. The tQT study included a moxifloxacin 400 mg arm, a naldemedine 0.2 mg arm, and a naldemedine 1.0 mg arm. The supratherapeutic naldemedine dose level produces a C_{max} 5-fold higher than the dose that will be approved and concentrations that exceed those predicted when it is coadministered with strong CYP3A inhibitors. Assay sensitivity was established. The largest upper bound of the 2-sided 90%CI for the mean difference between naldemedine 1 mg and placebo was less than 10 ms.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

I concur with the recommendations of both the Clinical and Statistical reviewers that the clinical trials submitted in this NDA establish that naldemedine 0.2 mg dosed once daily is efficacious in the treatment of OIC in adults with chronic noncancer pain. The applicant submitted two replicate randomized, placebo controlled trials of 12 weeks duration which revealed a similar naldemedine response relative to placebo in both trials (Studies V9231 and V9232). Only one naldemedine dose level was studied in the phase 3 trials. Patients entered the two trials if they had been on a stable opioid dose of at least 30 mg morphine equivalents for at least 4 weeks AND had OIC, defined as no more than 2 spontaneous bowel movements/week during a 2 week run-in period (and no more than a total of 4 spontaneous bowel movements (SBMs) during the entire 2 week run-in period). The responder definition was the same definition that has been used in the clinical trial that supported approval of

another peripherally active mu opioid antagonists (Movantik), i.e., a patient is a responder if for at least 9/12 weeks AND for at least 3 of the last 4 weeks in the 12-week treatment period they had ≥ 3 spontaneous bowel movements (SBM) per week and an increase from baseline of ≥ 1 SBM. SBM was defined as a bowel movement (BM) that occurred without rescue laxative use within the past 24 hours. Laxatives used for OIC prior to study entry were discontinued. Patients were allowed to use rescue bisacodyl on study if they had had no BM in 72 hours. If they didn't have a BM within 24 hours after rescue bisacodyl, a rescue enema was permitted.

The most common underlying etiology of chronic pain in Study V9231 and Study V9232 was back pain, 62% and 53%, respectively. The population was predominantly female and the median age was 53 and 54 in the two trials. Approximately half had hypertension, approximately 40% had dyslipidemia and approximately 16% had diabetes. Fifty four percent and 60%, in the respective trials, were taking opioid doses in the range of ≥ 30 and ≤ 100 morphine equivalents. Oxycodone and hydrocodone were the most common opioids.

The following table, which will be presented in the product label, summarizes the results of the primary efficacy endpoint in the two replicate phase 3 trials. Results were similar between trials, although there was a slightly numerically higher response rate relative to placebo in Study V9232. The demographics were similar between trials (majority female and white), and there was a similar mean morphine equivalent opioid dose between trials. The mean baseline number of SBMs/week in Study V9231 was similar to Study V9232 (approximately 1.3 and 1.2, respectively). The median baseline number of SBMs/week was slightly higher in Study V9231 than in Study V9232, 1.5 vs. 1.1.

Table 1: Efficacy Responder Rates in Studies 1 and 2 in Patients with OIC and Chronic Non-Cancer Pain

	Study V9231			Study V9232		
	SYMPROIC 0.2 mg once daily (N=273)	Placebo (N=272)	Treatment Difference [95% CI]	SYMPROIC 0.2 mg once daily (N=276)	Placebo (N=274)	Treatment Difference [95% CI]
Responder [#]	130 (48%)	94 (35%)	13% [5%, 21%]	145 (53%)	92 (34%)	19% [11%, 27%]
p value*			0.0020			<.0001

[#]The primary endpoint was defined as a patient who had 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 weeks.

CI=Confidence Interval

* Cochran-Mantel-Haenszel test adjusted for opioid dose strata (30 to 100 mg; greater than 100 mg)

The results of the analyses of all 4 prespecified key secondary endpoints (which compared group mean changes in SBMs between study arms) in both trials were statistically significant, favoring naldemedine. Section 14 of the label will include the results of all 4 analyses. The COA staff was consulted to evaluate whether the observed changes were clinically meaningful. They stated the lack of data from adequate patient-reported global impression of severity or change scales to use as anchors made it impossible to explore what constitutes a meaningful change. The Subject Global Satisfaction Scale, was not considered an appropriate anchor scale for exploration of meaningful changes, as the data generated with the scale were considered uninterpretable. Some patients who experienced a very small treatment effect in terms of change in bowel movement frequency reported high satisfaction, and vice versa.

Ultimately, the reviewers agreed to include the difference in mean change from baseline between naldemedine and placebo for each of the 4 secondary endpoints. The baseline mean SBM/week for each study will be included in the label, to provide context for health care providers' interpretation of the meaningfulness of these group mean changes. The other drugs in the class evaluated different key secondary endpoint analyses, so their labels do not present similar secondary analyses. CSBM data have been presented in IBS-C and CIC labels. Change from baseline in frequency of "SBMs without straining", one of the key secondary endpoints that will appear in the naldemedine label, has not been presented in previous non-OIC labels. Analyses of straining in non-OIC drug development programs have been based on measuring incremental shifts in straining severity, and the Division has questioned whether measurement tools for severity have been adequate for this use. However, if one assumes patients understand what straining is, it seems reasonable to conclude that patients can reliably report the absence of straining. Therefore, it seems reasonable to include the SBM without straining secondary analysis results in the label.

Section 14 of the product label will state the following, after presentation of the primary efficacy analysis data (Study 1 and 2 refer to Studies V9231 and V9232, respectively):

In Studies 1 and 2, the mean increase in frequency of SBMs per week from baseline to the last 2 weeks of the 12-week treatment period was 3.1 for SYMPROIC vs. 2.0 for the placebo (difference 1.0, 95% CI 0.6, 1.5), and 3.3 for SYMPROIC vs. 2.1 for the placebo (difference 1.2, 95% CI 0.8, 1.7), respectively.

During week 1 of the treatment period, the mean increase in frequency of SBMs per week from baseline was 3.3 for SYMPROIC vs. 1.3 for placebo (difference 2.0, 95% CI 1.5, 2.5) in Study 1 and 3.7 for SYMPROIC vs. 1.6 for placebo (difference 2.1, 95% CI 1.5, 2.6) in Study 2.

The mean increase in the frequency of complete SBM (CSBM) per week from baseline to the last 2 weeks of 12-week treatment period was 2.3 for SYMPROIC vs. 1.5 for placebo (difference 0.8, 95% CI 0.4, 1.2) in Study 1 and 2.6 for SYMPROIC vs. 1.6 for placebo, (difference 1.1, 95% CI 0.6, 1.5) in Study 2. A CSBM was defined as a SBM that was associated with a sense of complete evacuation.

The change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period was 1.3 for SYMPROIC vs. 0.7 for placebo

(difference 0.6, 95% CI 0.2, 0.9) in Study 1 and 1.8 for SYMPROIC vs. 1.1 for placebo (difference 0.7, 95% CI 0.3, 1.2) in Study 2.

The first two secondary endpoints evaluate change from baseline at two different time points: one week on study and during the last two weeks on study. Although the change from baseline relative to placebo is numerically lower in the last two weeks than in the first week (difference of approximately 1 SBM per week), this appears related to the higher placebo SBM frequency at the end of 12 weeks than in the first week in both trials.

An additional large placebo controlled trial of 12 months duration was submitted for review, Study V9235. Its primary objective was to assess long term safety relative to placebo, including capturing MACE events; however, the applicant also assessed efficacy as secondary endpoints (change in frequency of BMs from baseline across multiple various time points). Given that the efficacy assessments were not primary endpoints and alpha was not controlled for the efficacy analyses, (b) (4)

Furthermore, unlike the two trials described above, the patients in this trial were allowed to stay on baseline laxative regimens as concomitant therapy with naldemedine (or placebo). Randomization was not stratified for whether patients entered the trial continuing a baseline “routine/regular” laxative regimen. Even on this baseline regimen, the subjects had to qualify for study participation by having ≤ 4 bowel movements over 14 consecutive days during the screening period. Half the patients entered the trial taking a “stable” concomitant laxative regimen and continued the regimen on the trial (50.6% in the naldemedine arm and 54.2% in the placebo arm). The most commonly used concomitant laxative category was “stimulant laxative.” The mean and median baseline stool frequency was slightly higher in the placebo arm of Study V9235 than in the naldemedine arm (Mean: 1.62 vs. 1.59, respectively; Median: 1.62 vs. 1.56, respectively). The baseline stool frequency was higher in this trial than in the two phase 3 trials described above. The safety of concomitant ongoing laxative administration was explored in the safety dataset. (See Section 8 Safety, below.)

Subgroup efficacy analyses by demographics. The Statistical review presents the efficacy analyses by demographic subgroup. The table below is reproduced from that review.

Table 2: Statistical Reviewer’s Subgroup Efficacy Analyses by Demographics.

	Study V9231		Study V9232	
	Naldemedine 0.2mg	Placebo	Naldemedine 0.2mg	Placebo
Gender				
Male	55.4% (62/112)	34.6% (36/104)	56.8% (63/111)	39.6% (42/106)
Female	42.2% (68/161)	34.5% (58/168)	49.7% (82/165)	29.8% (50/168)
Race				
Black	49.1% (26/53)	41.7% (20/48)	40.8% (20/49)	46.2% (18/39)
White	47.2 % (102/216)	33.2% (73/220)	54.5% (121/222)	31.3% (71/227)
Age				
< 65 years	48.7% (114/234)	35.6% (80/225)	50.9% (118/232)	31.4% (74/236)
≥ 65 years	41.0% (16/39)	29.8% (14/47)	61.4% (27/44)	47.4% (18/38)
Region				
US	45.2% (104/230)	34.9% (80/229)	53.9% (130/241)	32.6% (78/239)
Non-US	60.5% (26/43)	32.6% (14/43)	42.9% (15/35)	40.0% (14/35)

N=number of patients; SE=Standard Error

In Study V9231, there was a numerically higher response to naldemedine relative to placebo in males compared to females: 20.8% vs. 7.7%. The placebo response rate was nearly identical between sexes in this trial. The responses relative to placebo in the second trial, Study V9232, were similar between sexes: 19.9% vs. 17.2%. However, in the latter trial the placebo response rate was lower in females than in males. A responder analysis was not conducted in safety trial, Study V9235. Exploratory analyses of the mean change from baseline in number of bowel movements (not SBM) were conducted at multiple time points. The FDA Statistical reviewer compared change from baseline data in bowel movements (not SBM) at the 12 week point in the trial in the naldemedine arm vs. placebo in each of the subgroups (male/female), and found that the difference between arms in males was 1.36 bowel movements vs 1.23 bowel movements in females. The applicant presented a similar repeated measures analysis of change in frequency of bowel movements/week, and the results were similar to the Statistical reviewer's analysis: 1.37 in males and 1.25 in females, at Week 12. Although the number of bowel movements is numerically lower, by a fraction, in females, it is not clear that the small magnitude of difference is clinically relevant. The publically available FDA Statistical review for Movantik reveals that, in the single trial submitted to support its approval, the responder rate in females was numerically lower than in males. The Relistor SQ FDA review's subgroup analysis suggests a similar response between sexes (using a different endpoint).

The response relative to placebo was similar between age subgroups (<65 vs. ≥65 years of age) in Study V9231. It was somewhat numerically higher in the younger subgroup of Study V9232: 19.5% vs. 14.0%. The placebo response rate in the latter study in the older subgroup was higher than the younger subgroup of that trial, and higher than both age subgroups of Study V9231. The very small sample size of the ≥65 year old subgroup in both trials relative to the overall population makes it impossible to draw firm conclusions from these data. Section 8.5 Geriatric Use of the product label will state, "No overall differences in safety or effectiveness between [patients 65 years of age and over] and younger patients were observed....."

The response relative to placebo was much lower in Black subjects relative to White subjects. In fact the placebo response in Black subjects was higher than the response observed in the naldemedine arm of Study V9232. The placebo response in Black subjects in both trials was higher than the placebo response observed in White subjects. The very small sample size of the Black subgroup makes it impossible to draw firm conclusions regarding relative efficacy of this product between the two subgroups. (b) (4)

The applicant submitted a subgroup analysis of the bowel movement (not SBM) data from the safety trial, Study V9235, using repeated measures analysis of change in frequency of bowel movements/week. They reported that the change from baseline relative to placebo in Black subjects was lower than in White subjects: 0.43 vs. 1.45. The mean change from baseline in number of bowel movements at Week 12 was higher in Black subjects treated with placebo than in White subjects treated with placebo (3.20 vs. 2.23). The sample size of Black subjects in this trial was larger than in the other two trials, but was <25% that of the White subjects. The distribution of baseline "routine/regular" concomitant laxative regimens between arms within this subgroup was similar (48%). The proportion of White subjects on "routine/regular" concomitant laxative regimens in this trial was somewhat numerically higher

than in the Black subgroup – 50% in the naldemedine arm and 56% in the placebo arm. This subgroup efficacy analysis was an exploratory analysis of a secondary endpoint of uncertain meaningfulness (relative to the endpoint in the two efficacy trials) for which there was no alpha control; therefore, the observed difference is not reliable. The publically available FDA Statistical reviews for Movantik reveals that in the single trial submitted to support its approval, the responder rate in ‘Non-Caucasians’ was numerically lower than in ‘Caucasians’.

8. Safety

Among the two 12 week placebo controlled efficacy trials (Study V9231 and Study V9232) and the 12 month placebo controlled safety trial (Study V9235), 1163 patients were exposed to naldemedine, including 387 patients with exposures exceeding 6 months and 203 with 12 month exposures. (There were 1165 placebo control subjects in these combined trials.)

There was one death (in a naldemedine arm) in the two phase 3 efficacy trials, and 8 deaths (4 naldemedine and 4 placebo) in the 12-month randomized, controlled safety trial (Study V9235). With the exception of a death attributed to Stage 4 lung adenocarcinoma (naldemedine; Study V9235), a death attributed to exacerbation of COPD (naldemedine; Study V9235), and a death from a basilar artery thrombotic stroke (placebo; Study V9235), the deaths (3 naldemedine and 3 placebo) were unwitnessed events and attributed to a cardiovascular (CV) event or overdose. The deaths, by treatment arm, are briefly summarized below:

Naldemedine:

Study V9232 – Pt. 22359-018: 37 yo female with osteoarthritis, disc disease, bipolar disorder, ADHD, hypertension, Mirena IUD. Unwitnessed death on Day 9 of study. Attributed to drug overdose. No drug levels described from emergency room. Patient had a history of a methadone overdose.

Study V9235 – Pt. 52415-004: 52 yo female. Diagnosed with Stage IV lung adenocarcinoma while on study. Presented with dyspnea on Day 63 of study. Reported chest pain and dyspnea on Day 72. Naldemedine d/c'd on Day 72. Underwent venacavagram and filter placement on Day 73. Had an MI on Day 74. Diagnostic work up found patient had Stage IV adenocarcinoma. Death occurred on Day 94.

Study V9235 – Pt. 52387-009: 58 yo female. History of COPD, cardiac catheterization, hypothyroidism, collapsed femoral head, osteomyelitis, fibromyalgia, tobacco use. Presented with exacerbation of COPD on Day 155. Died from exacerbation of COPD on Day 162.

Study V9235 – Pt. 52449-005: 49 yo male. History of back pain, radiculopathy, spinal fixation device, COPD, diabetes, hypercholesterolemia. Unwitnessed death. Found in his bathroom on Day 350. Presumed to have died on Day 346.

Study V9235 – Pt. 52375-007: 53 yo female. History of leg pain and depression. Unwitnessed death on day 350. No autopsy. Presumed CVA.

Placebo:

Study V9235 – Pt. 52437-005: 64 yo male. History of a fib, COPD, disk disease, depression, hypercholesterolemia, hypertension, osteoarthritis, tobacco use. Unwitnessed death on Day 28.

Study V9235 – Pt. 52442-017: 49 yo female. History of asthma, COPD, diabetes, neuropathy, lumbar disc disease. Unwitnessed death on Day 28.

Study V9235 – Pt. 52446-013: 78 yo female. History of degenerative joint disease, hypercholesterolemia, hypertension. Found unresponsive on Day 175. Basilar artery thrombosis diagnosed. Intervention unsuccessful and patient died.

Study V9235 – Pt. 52352-002: 52 yo male. History of back pain, diabetes, hypercholesterolemia, neuropathy, required epidural pain medication. Unwitnessed death. Found deceased in bed. Attributed to overdose.

In the combined safety data from the three phase 3 trials, limited to first 12 weeks of the 52 week Study V9235, there was a similar proportion of overall serious adverse events (SAEs) between naldemedine and placebo: 4.0% vs. 3.4%. Within trials, the incidence rate of SAEs was balanced between arms, with the exception of a numerically higher rate of SAEs in the naldemedine arm of Study V9231 compared to placebo: 4.1% vs. 1.8%, respectively. The percentage of SAEs increased in V9235 when the full 52 weeks were considered: 9% naldemedine vs. 11% placebo. A numerically higher proportion of patients on the naldemedine arm of Study V9231 had SAEs that led to discontinuation: 1.1% vs. 0. A similar proportion of patients had SAEs that led to discontinuation during 12 weeks between arms in each of Study V9232 (1.1% both arms) and Study V9235 (0.5% both arms). When the full 52 weeks of Study V9235 were considered, 2% of placebo arm subjects discontinued due to an SAE vs. 1 % on the naldemedine arm. On the naldemedine arm of each of the three trials (Studies V9231, V9232, and 9235, respectively), 3/13, 3/14 and 3/16 SAEs led to discontinuation (during first 12 weeks of Study V9235).

Review of the list of SAEs in the ISS revealed no specific pattern or clustering of SAEs by specific type. Among the three trials, there were 3 abdominal pain SAEs in subjects enrolled in a naldemedine arm vs. 1 in the placebo arm. Two of the abdominal pain SAE subjects in the naldemedine arm discontinued from the trials due to the SAE. Both had onset of pain on Day 1. The pain was associated with nausea and vomiting [Pt 52216-005] in one of these subjects, and in the other, the pain was associated with nausea, yawning, increased bowel movements, and restlessness. In the latter subject, drug withdrawal syndrome was diagnosed. In the remaining naldemedine arm subject with an abdominal pain SAE, onset occurred on Day 28 and was associated with diarrhea. The abdominal pain SAE in the placebo arm (which occurred on Day 43 of the study), occurred in a subject who had associated diarrhea; this

subject had stopped opioid medication entirely on Day 26 of the study. Given the opioid discontinuation, the subject was discontinued from the trial.

Abdominal pain non-SAEs also led to study discontinuation. There were 17 subjects on a naldemedine arm among the three phase 3 trials who had non-SAE abdominal pain adverse events that led to discontinuation (vs. 2 placebo subjects). Among those 17 subjects, 7 had concomitant adverse events of diarrhea reported as cause for discontinuation (vs. 1/2 placebo subjects), 1 had concomitant nausea (vs. 1/2 placebo subjects) and 1 had symptoms that could have reflected manifestations of withdrawal.

There was one vomiting SAE in a naldemedine arm subject and two in placebo arm subjects. There were two dehydration SAEs in naldemedine arm subjects, but none in the placebo arm. The dehydration SAE subjects did not have vomiting SAEs. There were no “diarrhea” SAEs; however, there was one naldemedine subject with an SAE of duodenitis and gastritis, one naldemedine arm subject with an SAE of “ischemic colitis”, and one naldemedine arm subject with an SAE of “enterocolitis”. There was one SAE of “viral gastroenteritis” on placebo.

There were 4 (and possibly 5; a loss of consciousness) SAE overdoses in naldemedine subjects vs. 1 in placebo arm subjects. Of these subjects with an overdose SAE, one naldemedine arm subject is also described above as a death from overdose [**Pt. 22359-018**].

There were no SAEs specifically coded as “withdrawal”. DAAAP was consulted to evaluate naldemedine safety related to opioid withdrawal. They noted that this is the first PAMORA in which the sponsor incorporated DAAAP advice for prospectively assessing opioid withdrawal in the phase 3 trial designs. All 3 trials assessed for withdrawal using the Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), change in pain intensity (Numeric Rating Scale), and change in opioid dose. Adverse events consistent with opioid withdrawal were based on investigator assessment using SMQ defined terms and adjudicated cases based on the occurrence of at least 3 adverse events 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. Given that the drug is designed to induce local opioid withdrawal limited to the GI tract, DAAAP had advised the sponsor prior to NDA submission to analyze the withdrawal data with and without GI terms.

The DAAAP consultants reviewed these data and found no clinically meaningful changes in total COWS and SOWS scores in the trials relative to placebo. They noted the mean NRS score remained “generally stable” through the end of the trials, and there was a similar proportion of outliers of NRS between the study arms in all 3 trials. However, they pointed out the NRS data were limited by the frequency of assessment (only performed at clinic visits). The opioid doses remained generally unchanged relative to baseline in both treatment groups throughout the trials. The following table, which is reproduced from the DAAAP review, summarizes the treatment emergent adverse events (TEAEs) potentially related to opioid withdrawal and with a frequency $\geq 2\%$ in the phase 3 trials. Each event was numerically higher in the naldemedine arm than in placebo; however, the DAAAP reviewer noted that in isolation, the individual TEAEs do not necessarily constitute evidence of withdrawal syndrome.

Table 3. TEAEs potentially related to Opioid withdrawal with incidence $\geq 2\%$

Preferred Term	Study V9231		Study V9232		Study V9235	
	Naldem N=271	Placebo N=272	Naldem N=271	Placebo N=274	Naldem N=621	Placebo N=619
Abdominal pain*	30 (11)	7 (2)	26 (10)	12 (4)	99 (16)	53 (8)
Diarrhea	18 (7)	8 (3)	24 (9)	5 (2)	62 (10)	31 (5)
Nausea	13 (5)	7 (3)	13 (5)	9 (3)	46 (7)	33 (5)
Vomiting	3 (<1)	2 (<1)	5 (2)	5 (2)	33 (5)	18 (3)
Hyperhidrosis	6 (2)	2 (<1)	2 (<1)	1 (<1)	10 (2)	6 (1)
Pyrexia	2 (<1)	1 (<1)	6 (2)	0	5 (<1)	2 (<1)
Anxiety	2 (<1)	2 (<1)	3 (<1)	3 (<1)	11 (2)	13 (2)

Reviewer, modified from Applicant's tables 14.3-1.2.1; *Abdominal pain terms included under

abdominal pain include: abdominal discomfort, abdominal distension, lower abdominal pain, upper abdominal pain, and abdominal tenderness. Naldem=naldemedine.

Numbers in parentheses represent %.

When the safety data were analyzed for evidence of possible cases of withdrawal syndrome based on presence of ≥ 3 predefined preferred terms potentially related to opioid withdrawal on the same day or onset within one day of each other, there was a higher number of subjects identified in a naldemedine arm than in placebo in each of the 3 phase 3 trials; however, when this analysis was limited to only non GI terms, 0 vs. 1 subject (naldemedine vs placebo) met the criteria in the three phase 3 trials combined. When the analyses was limited to only GI terms, 11 vs. 2 subjects (naldemedine vs. placebo) met the criteria. The following table, reproduced from the DAAAP review, summarizes the number of subjects with possible withdrawal syndrome, based on having any of GI alone sign/symptoms, non-GI alone, and combination.

Table 4. Summary of withdrawal syndrome events in the three phase 3 trials with the defining preferred terms identifying the event.

Study	Naldemedine N	Placebo N
V9231	2 (both GI only)	1 (GI only)
V9232	5 (1: GI only; 4 non GI+GI)	2 (both non GI +GI)
V9235	14 (8 GI only; 6 non GI+GI)	4 (1: GI only; 1: non GI only; 2: nonGI+GI)

The DAAAP reviewer noted that most Standardized MedDRA Query (SMQ) identified events were described as mild and occurred on Day 1 of study. The DAAAP reviewer identified a subject (Pt. 52375-003) with an SAE of abdominal pain and drug withdrawal and another subject (Pt. 52216-005) who had abdominal pain and met criteria for withdrawal syndrome but had confounding possible infection as cause of the symptoms (colitis). She noted there were 2 subjects whose non-SAE withdrawal events were graded as “severe”, but the narratives didn’t

explain why the events were severe. In the naldemedine arm, based on SMQ identified withdrawal cases, 6/13 discontinued, and among possible opioid withdrawal cases 13/21 subjects discontinued.

The DAAAP reviewer didn't agree with the applicant's proposal

(b) (4)

She recommended the label include cases of possible opioid withdrawal using all terms. The following will appear in Section 6 Adverse Reactions of the label:

"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 (b) (4)% (8/542) for SYMPROIC and (b) (4)% (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."

The DAAAP reviewer clarified that

(b) (4)

The label will also include a Warning and Precaution related to withdrawal (5.2 Opioid Withdrawal), which is consistent with other drugs in the PAMORA class.

Cardiovascular events. Review of the SAE table in the ISS revealed that in the three phase 3 trials, there were 3 SAE events consistent with MACE (CVA and 2 acute MIs) in naldemedine arm subjects and 3 in placebo arm subjects (CVA, cardiac arrest, MI). There were two CHF SAEs in the naldemedine subjects vs. 1 in the placebo arm subjects. There were also unwitnessed deaths in the dataset that were attributed to overdose, but could have reflected sudden death from a CV event. Of note, one of the placebo arm subjects listed here as a MACE event (cardiac arrest) was an unwitnessed death, which could have been due to overdose. Moving this subject from MACE to overdose changes the relative MACE SAE count to 3 naldemedine vs. 2 placebo. There were also two unwitnessed deaths in the naldemedine arm that could have been secondary to overdose or MACE [*Pt. 52449-005* and *Pt. 52375-007*] and two additional unwitnessed deaths in the placebo arm [*Pt. 52442-017* and *Pt. 52352-002*] that could have been secondary to overdose or MACE.

The phase 3 program included a prospective plan for adjudication of MACE (major adverse cardiovascular events) events. The following table, reproduced from the ISS, summarizes the MACE events from the three phase 3 trials:

Table 5. Summary of MACE events in the three phase 3 trials.

	V9231+V9232		V9235		Overall	
	Naldemedine	Placebo	Naldemedine	Placebo	Naldemedine	Placebo
	N=542	N=546	N=621	N=619	N=1163	N=1165
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
MACE	1 (0.2%)	1 (0.2%)	2 (0.3%)	5 (0.8%)	3 (0.3%)	6 (0.5%)
CV Death	0	0	0	3 (0.5%)	0	3 (0.3%)
MI	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.3%)	2 (0.2%)	3 (0.3%)
CVA	0	0	1 (0.2%)	0	1 (0.1%)	0

Review of the list of adjudicated subjects revealed that 2/3 naldemedine arm events in the table above were included in the SAE list (an MI in a 59 yo male on Day 82 of study and a CVA in a 52 yo female on Day 245 of study). One of the events in the table above appears in the SAE list and discontinuation for AE list as “SVT”, which would not as a free standing term qualify as MACE; however, the adjudication panel determined this patient had an acute MI. (The patient was a 65 yo female who presented on Day 17 with chest pain and rapid heart rate. Troponin was elevated.) There is also an acute MI on the SAE list for naldemedine that does not appear on the adjudicated MACE event list [Pt 52415-004].

Review of the list of adjudicated subjects from placebo arms of the phase 3 trials revealed that 3/6 appeared in the SAE list with terms consistent with MACE events. The remaining 3 all appeared in the SAE list, but with non-MACE terms. Those 3 were adjudicated as MACE: one was a syncope SAE in a 44 year old male on Day 19 of Study V9232; one was an unstable angina SAE in a 63 yo female on Day 246 of Study V9235; one was an “arteriosclerosis” SAE in a 49 year old female who experienced sudden death on Day 31.

In the 120 day safety update, 2 additional subjects with adjudicated MACE events were identified in Study V9235, in subjects who were on the naldemedine arm. This brings the overall cases to : 5/1163 (naldemedine) vs. 6/1165 (placebo).

There is no signal of increased risk of MACE in this NDA for a new PAMORA. The Cardiorenal consultant for previous PAMORAs reviewed by the division noted that all three opioid receptor subtypes are present in the heart. Cardioprotective effects of endogenous opioids have been widely studied, particularly related to delta opioid receptors (for which naldemedine has receptor antagonist activity. There has been a great interest in preconditioning protocols, which have produced some data (primarily animal models) indicating that short ischemic periods reduce tissue damage resulting from subsequent ischemic periods of longer duration.² Based on this, systemic exposure to opioid receptor blockade could theoretically remove an endogenous opioid mediated cardioprotective system; however, this remains theoretical.

Drugs in the PAMORA drug class were subject to a previous Advisory Committee meeting (Anesthesia and Analgesia Drug Products Advisory Committee; June 11-12, 2014) to discuss whether there was a need for conducting CV safety outcome trials to support their approval (either pre or post approval). The AC members were generally unwilling to dismiss the numerically higher MACE events in a 12 month Entereg trial conducted in an OIC population (7 vs. 0, in the context of a 2:1 randomization), which had been the basis of a REMS designed to mitigate a serious risk of MI for Entereg. Committee member recommended requiring evaluation of PAMORAs in post marketing, controlled, observational safety studies, to more definitively evaluate for a signal of increased CV risk. Subsequent to the AC, both Relistor and Movantik were approved with a PMR observational epidemiologic study to evaluate for MACE. At the time of approval of Relistor and Movantik, based on the AC discussion, I concluded the MIs and deaths observed in the Relistor uncontrolled, extension study (Study 3358) did not constitute a signal of increased CV risk associated with the drug. I also concluded that a post-approval controlled, observational study could be a means of identifying a CV signal.

The OSE reviewers concluded during this review cycle, "...risk mitigation measures beyond professional labeling are not warranted for naldemedine." The OSE Division of Epidemiology-1 reviewers evaluated OND's recommendation to require, as a condition for approval, the same post-marketing controlled, observational study required for the previous PAMORAs. The Division of Epidemiology-1 reviewers determined that Sentinel ARIA is currently insufficient to evaluate naldemedine-associated risk of MACE, "given the determination that new information in NDA 208854 does not change the level of concern regarding the cardiovascular safety of this product class." The approval letter will state: "...to identify an unexpected serious risk of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 3174-1 A post-marketing, observational epidemiologic study comparing Symproic (naldemedine) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Ensure an adequate number of patients with at least 12 months of Symproic (naldemedine) exposure at the end of the study.

The timetable you submitted on February 27, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2017
Study Completion:	11/2023
Final Report Submission:	11/2025"

Liver. Across the phase 3 program (three trials), there were 8 subjects in naldemedine arms and 7 subjects in placebo arms that met predefined definitions of a “liver event” (ALT or AST >5xULN; ALT or AST >3xULN and total bilirubin >2 xULN or INR >1.5; ALT or AST >3xULN with signs/symptoms of hepatitis or hypersensitivity; ALT or AST >5xULN and subject not followed up weekly). None of the patients met criteria for Hy’s Law. Only one patient in the three trials developed hyperbilirubinemia, a placebo arm patient in Study V9231.

Common adverse reactions. The most common adverse reactions observed in the phase 3 trials will be presented in the product label as pooled data for the two 12 week trials (Studies V9231 and V9232, referred to below as Study 1 and Study 2, respectively) separately from the data from the first 12 weeks of the 52 week safety trial (Study V9235, referred to below as Study 3), as shown in the tables below.

Table 6: 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 7: 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

The placebo controlled, long term safety trial, Study V9235, allowed subjects to continue their baseline laxative regimens concomitantly with naldemedine. No clear signal of a significant safety issue related to concomitant laxative use was identified, although the discontinuation rate due to adverse events in the naldemedine arm in Study V9235 during the overall 52 week study period of that trial was slightly numerically higher than that reported in the two 12- week phase 3 trials: 6.3% in the overall 52 weeks of Study V9235 vs. 5 % in Study V9231 and 5% in Study V9232. (The proportion of placebo arm subjects who discontinued for adverse events was numerically higher in the overall 52 week period of Study V9235 vs. the 12 week trials: 4.7% in Study V9235; 1.5% in Study V9231; and 3.3% in Study V9232.) However, when only the first 12 weeks of Study V9235 is compared, the discontinuation rate in the naldemedine arm of that trial is numerically the same (5%) as that observed in the two 12 week trials, (placebo rate in the first 12 weeks of Study V9235 was 2.5%). Concomitant use of naldemedine with another laxative or laxative combination regimen might be anticipated to be associated with diarrhea and/or abdominal pain. Cross study comparison of treatment emergent diarrhea that led to discontinuation revealed that among the 20 naldemedine arm subjects who discontinued treatment due to diarrhea on one of the three phase 3 trials, severe diarrhea was reported in 3/20 and two of those 3 (Pt. 52421-004 and Pt 52437-004) were enrolled in Study V9235 (0.3% in Study V9235 vs. 0.4% in Study V9232, i.e., a similar percentage between trials), and only one of those two subjects in Study V9235 was taking concomitant stable laxative regimen with study drug. The diarrhea that led to continuation in the 20 subjects was rapid in onset, and occurred after the first dose in 12/20. Discontinuations triggered by abdominal pain adverse reactions were also explored. Among 16 naldemedine treated subjects across the three trials who discontinued due to abdominal pain, the events were graded “severe” in 5; three of the 5 occurred in Study V9235 (Pts: 52321-022, 52428-011 and 52437-004), representing 0.5% of the naldemedine arm subjects in Study V9235. Two of those 3 were taking stable laxative regimen concomitantly with study drug and the other was not. The two severe events in the other two trials were distributed equally between the trials,

representing 0.4% of the naldemedine treated subjects. The reviewers concluded that given there was no serious safety signal associated with concomitant use of a laxative regimen in Study V9235, it was not necessary for the product label to state that baseline laxative regimens should be discontinued when initiating naldemedine treatment.

A summary of the long term safety data from Study V9235 will be presented in narrative format in the label:

“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).”

9. Advisory Committee Meeting

There was no advisory committee convened to discuss this application because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease and outside expertise was not necessary.

10. Pediatrics

The Maternal Health Team from the Division of Pediatrics and Maternal Health worked with the Pharmacology/Toxicology and Clinical reviewers from DGIEP to ensure the Pregnancy and Lactation Labeling Rule (PLLR) requirements were met. The Maternal Health Staff and Clinical reviewers discussed concerns regarding the potential for opioid withdrawal in a fetus when naldemedine is used in pregnant women taking opioids. They ultimately aligned on including the following clinical consideration information in the product label’s Section 8.1 Pregnancy:

“There are no available data with naldemedine in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. There is a potential for opioid withdrawal in a fetus when SYMPROIC is used in pregnant women [*see Clinical Considerations*]. SYMPROIC should be used during pregnancy only if the potential benefit justifies the potential risk..... Naldemedine crosses the placenta, and may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier.”

Data presented in the NDA revealed naldemedine was present in milk of rats after administration. The Maternal Health Staff reviewers noted that drug presence in breast milk is species specific. There are no data available regarding naldemedine levels in human milk. The Maternal Health Staff and Clinical reviewers discussed their concerns about the potential for opioid withdrawal in breastfed infants if naldemedine is present in breast milk. The reviewers aligned on including the following information in Section 8.2 Lactation of the label:

“There is no information regarding the presence of naldemedine in human milk, the effects on the breastfed infant, or the effects on milk production. Naldemedine was present in the milk of rats [*see Data*]. 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. If drug is discontinued in order to minimize drug exposure to a breastfed infant, advise women that breastfeeding may be resumed 3 days after the final dose of SYMPROIC.”

The pediatric study requirement under PREA will be waived for this application because necessary studies are impossible or highly impracticable. Based on information from the limited available literature, few pediatric patients in all age groups 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..

11. Other Relevant Regulatory Issues

Financial disclosure – The Clinical reviewer stated in her review that none of the investigators who participated in the major phase 3 trials that supported this NDA had disclosable financial interests.

OSI - Six clinical investigator sites (all in the U.S.) and the sponsor were inspected. Four clinical sites and the sponsor site had classifications of no action indicated. Two clinical investigator sites had final classifications of voluntary action indicated. The violations at those sites were not considered to have an impact on data integrity. The OSI reviewers stated, “The studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.”

CSS – Naldemedine is derived from naltrexone, which is a derivative of thebaine. Thebaine is a Schedule II opium derivative, which makes naldemedine a Schedule II substance. The applicant submitted an abuse assessment; CSS reviewed the data and concluded that the drug doesn’t have abuse potential. They recommend that the Assistant Secretary for Health should make a recommendation to decontrol naldemedine to DEA. As of the time of completion of my review, DEA had not made a decision on whether to decontrol naldemedine. For this reason, the product label will be approved with Section 9.1 Controlled Substance stating “SYMPROIC contains naldemedine, a Schedule II controlled substance.” If and when DEA makes a decision to decontrol naldemedine, Section 9 can be removed from the product label.

12. Labeling

DMEPA found the proprietary name, Symproic, acceptable.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies – none necessary
- Other Postmarketing Requirements and Commitments – See Section 8 Safety in this review for a description of the PMR observational study that will be required as a condition of approval.

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/s/

DONNA J GRIEBEL
03/23/2017