CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Symproic®

GENERIC NAME
Naldemedine

MANUFACTURER
Shionogi Inc.

DATE OF APPROVAL
March 23, 2017

PRODUCT LAUNCH DATE
Anticipated to launch mid-summer 2017

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
Symproic is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

OFF-LABEL USES
Not applicable

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3Q17 July – August

CLINICAL EFFICACY[12345]

The efficacy of Symproic was evaluated in two replicate, 12-week, randomized, double-blind, placebo-controlled trials (Study 1 and Study 2) in which Symproic was used without laxatives in patients with OIC and chronic non-cancer pain. A total of 547 patients in Study 1 and 553 patients in Study 2 were randomized in a 1:1 ratio to receive Symproic 0.2 mg once daily or placebo for 12 weeks.

Patients receiving a stable opioid morphine equivalent daily dose of at least 30 mg for at least 4 weeks before enrollment and self-reported OIC were eligible for clinical trial participation. In Studies 1 and 2, patients had to either be not using laxatives or willing to discontinue laxative use at the time of screening and willing to use only the provided rescue laxatives during the screening and treatment periods. Patients with evidence of significant structural abnormalities of the GI tract were not enrolled in these trials.

In Studies 1 and 2, OIC was confirmed through a two-week run in period and was defined as no more than 4 spontaneous bowel movements (SBMs) total 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 conditions: (1) straining; (2) hard or lumpy stools; (3) having a sensation of incomplete evacuation; and (4) having a sensation of anorectal obstruction/blockage. An SBM was defined as a bowel movement (BM) without rescue laxative taken within the past 24 hours. Patients with no BMs over the 7 consecutive days prior to and during the 2 week screening period or patients who have never taken laxatives were excluded.

The primary endpoint of theses studies was the proportion of responders in each treatment group. A responder was defined as a subject 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.

The efficacy responder rates in studies 1 and 2 in patients with OIC and chronic non-cancer pain are shown in the table below.

	Study 1			Study 2		
	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% Cl]
Responder	130 (48%)	94 (35%)	13% [5%, 21%]	145 (53%)	92 (34%)	19% [11%, 27%]
p value			0.0020			<0.0001

Secondary efficacy endpoints for these studies included: change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period; change in the frequency of SBMs

per week from baseline to the first week of the treatment period; change in the frequency of complete SBMs (CSBMs) per week from baseline to the last 2 weeks of the treatment period; and change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period.

CONTRAINDICATIONS
Symproic is contraindicated in:

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

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS

Strong CYP3A Inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort)	
Clinical Impact	Significant decrease in plasma naldemedine concentrations, which may reduce efficacy
Intervention	Avoid use of Symproic with strong CYP3A inducers.
Other Opioid Antagonists	
Clinical Impact	Potential for additive effect of opioid receptor antagonism and increased risk of opioid withdrawal.
Intervention	Avoid use of Symproic with another opioid antagonist.
Moderate (e.g., fluconazole, atazanavir, aprepitant, diltiazem, erythromycin) and Strong (e.g., itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir) CYP3A4 Inhibitors	
Clinical Impact	Increase in plasma naldemedine concentrations
Intervention	Monitor for potential naldemedine-related adverse reactions
P-glycoprotein (P-gp) Inhibitors (e.g., amiodarone, captopril, cyclosporine, quercetin, quinidine, verapamil)	
Clinical Impact	Increase in plasma naldemedine concentrations
Intervention	Monitor for potential naldemedine-related adverse reactions

ADVERSE REACTIONS
Most common adverse reactions (≥2%) are: abdominal pain, diarrhea, and nausea.

DOSAGE AND ADMINISTRATION
The recommended dosage of Symproic is 0.2 mg orally once daily with or without food.

- Alteration of analgesic dosing regimen prior to initiating Symproic is not required.
- Patients receiving opioids for less than 4 weeks may be less responsive to Symproic
- Discontinue Symproic if treatment with the opioid pain medication is also discontinued.

CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

PRODUCT AVAILABILITY
Tablets: 0.2 mg naldemedine

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Lubiprostone (Amitiza)	24 mcg PO twice daily with food and water*	Chloride channel activator
Methylnaltrexone (Relistor)	Oral: 450 mg PO once daily in the morning* Subcutaneous: 12 mg subcutaneously once daily*	Peripheral Mu-opioid Receptor Antagonist
Naloxegol (Movantik)	25 mg PO once daily, taken on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal. Reduce dose to 12.5 mg PO once daily if patient is unable to tolerate full dose*	Peripheral Mu-opioid Receptor Antagonist
Docusate sodium (Colace)	50—300 mg/day PO given in single or divided doses	Stool softener
Lactulose	10 to 20 g (15 to 30 mL or 1 to 2 packets) daily; may increase to 40 g (60 mL or 2 to 4 packets) daily if necessary	Osmotic laxative
Polyethylene glycol 3350 (MiraLax)	17 g (approximately 1 heaping tablespoon) of powder in 120 to 240 mL of fluid given PO once daily	Osmotic laxative
Bisacodyl (Dulcolax) **(bisacodyl)**	Oral: 5 to 15 mg once daily Rectal: Enema, suppository: 10 mg (1 enema or suppository) once daily	Stimulant laxative
Senna (Senokot)	1 to 2 tablets (8.6 to 17.2 mg sennosides) PO twice daily.	Stimulant laxative
Magnesium citrate	150-300 mL PO as a single or divided dose (roughly 1/2 to 1 full bottle)	Saline laxative
Magnesium hydroxide (Milk of Magnesia)	15-60 mL PO per day, preferably at bedtime or in divided doses	Saline laxative

***** *Dosage regimen for opioid-induced constipation in adults with chronic non-cancer pain*
Boldface indicates generic availability

CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

Utilization Management Recommendation[67]
• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): i) To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes. (1) Symproic is approved for use only in the treatment of OIC in patients with chronic non-cancer pain. (2) Opioid antagonists, such as Symproic, are usually reserved for patients who continue to experience OIC despite treatment with conventional first-line agents (e.g., laxatives). ii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☒ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison
• CPAC score: 57 vs. Movantik - Equal therapeutic outcomes anticipated • Equal therapeutic outcomes are anticipated for Symproic, Movantik, Relistor, and Amitiza; therefore, it would be appropriate to provide equal access to all or to require a trial of one before the other. • It would be clinically appropriate to require a trial of non-bulk forming laxatives (e.g., bisacodyl, senna, polyethylene glycol) prior to initiation of Symproic.

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REFERENCES

[1] Symproic Prescribing Information. Florham Park, NJ: Shionogi Inc.; March 2017. Available at: http://www.shionogi.com/. Accessed March 31, 2017.
[2] Kumar L, Barker C, Emmanuel A. Opioid-Induced Constipation: Pathophysiology, Clinical Consequences, and Management. Gastroenterology Research and Practice. 2014;2014:141737. doi:10.1155/2014/141737.
[3] Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: http://www.clinicalpharmacology-ip.com/.
[4] Pergolizzi JV, Raffa RB, Pappagallo M, et al. Peripherally acting μ-opioid receptor antagonists as treatment options for constipation in noncancer pain patients on chronic opioid therapy. Patient preference and adherence. 2017;11:107-119. doi:10.2147/PPA.S78042.
[5] Nelson AD, Camilleri M. Chronic opioid induced constipation in patients with nonmalignant pain: challenges and opportunities. Therap Adv Gastroenterol. 2015 Jul;8(4):206-20.
[6] Nelson AD, Camilleri M. Opioid-induced constipation: advances and clinical guidance. Ther Adv Chronic Dis. 2016 Mar; 7(2): 121–134.
[7] Argoff CE, Brennan MJ, Camilleri M, et al. Consensus Recommendations on Initiating Prescription Therapies for Opioid-Induced Constipation. Pain Med. 2015 Dec;16(12):2324-37.