Naldemedine Tosylate (Symproic®) New Drug Update

April 2017

Drug Name:	**naldemedine tosylate**
Trade Name (Manufacturer):	**Symproic (Shionogi, Purdue)**
Form:	Oral tablets, C-II
Strength:	0.2 mg
FDA Approval:	March 23, 2017
Market Availability:	Anticipated mid-summer 2017
FDA Approval Classification:	Standard
Classification:	Specific Therapeutic Class (HIC3): Gastrointestinal Agents—Opioid Antagonist (anticipated)

INDICATION[1]

Naldemedine tosylate (Symproic), an opioid antagonist, is indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain.

CONTRAINDICATIONS/WARNINGS

Naldemedine tosylate is contraindicated in patients with known or suspected gastrointestinal (GI) obstruction or at increased risk of recurrent obstruction, and in patients with a history of a hypersensitivity reaction to naldemedine tosylate. Reactions reported include bronchospasm and rash.

Warnings associated with naldemedine tosylate include GI perforation and opioid withdrawal.

DRUG INTERACTIONS

Concomitant use of naldemedine tosylate should be avoided with strong cytochrome P450 3A4 (CYP3A) inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) due to resulting decreased concentrations of naldemedine.

Administration with other opioid antagonists could potentiate additive effect and increase the risk of opioid withdrawal, therefore concomitant use should be avoided.

Coadministration with moderate CYP3A4 inhibitors such as fluconazole, atazanavir, aprepitant, diltiazem, and erythromycin and strong CYP3A4 inhibitors such as itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir can increase naldemedine tosylate concentrations, therefore, patients must be monitored for adverse reactions.

Increased plasma naldemedine tosylate concentrations can also occur when given with P-gp inhibitors (e.g., amiodarone, captopril, and cyclosporine) and it is necessary to monitor patients for naldemedine-related adverse reactions.

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COMMON ADVERSE EFFECTS

The most common adverse reactions (incidence ≥ 2%) reported in clinical trials were abdominal pain, diarrhea, and nausea.

SPECIAL POPULATIONS

Pregnancy

When used in pregnancy, naldemedine tosylate can cause opioid withdrawal in a fetus. While no data are available with naldemedine tosylate in pregnant women to inform a drug-associated risk of major birth defects and miscarriage, it should be used during pregnancy only when the potential benefit outweighs risk.

Pediatrics

The safety and effectiveness of naldemedine tosylate have not been established in pediatric patients.

Geriatrics

Of 1,163 patients treated with naldemedine tosylate, 16% were 65 years of age and over and 3% were 75 years and over. Even though no significant differences in safety and effectiveness were observed in this population compared to the younger population, greater sensitivity to naldemedine tosylate may be experienced by older individuals.

Hepatic Impairment

Naldemedine tosylate should be avoided in patients with severe hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment.

Renal Impairment

Naldemedine tosylate dosage adjustments are not needed in patients with mild, moderate, or severe renal impairment. Plasma concentrations of naldemedine tosylate in patients with end stage renal disease (ESRD) on hemodialysis were similar regardless of whether naldemedine tosylate was administered either before or after hemodialysis, indicating that naldemedine tosylate was not removed from the blood by hemodialysis.

DOSAGES

The recommended dose is 0.2 mg orally taken once-daily without regard to food. Patients receiving opioids for less than 4 weeks may be less responsive to naldemedine tosylate. When the opioid is discontinued, naldemedine should also be discontinued.

CLINICAL TRIALS[2,3]

A literature search was performed using "naldemedine" and "opioid-induced constipation".

Two replicate, 12-week, randomized, double-blind, placebo-controlled, phase 3 trials, COMPOSE 1 (Study 1) and COMPOSE 2 (Study 2), evaluated the safety and efficacy of naldemedine for the treatment of OIC in patients 18 to 80 years of age with chronic non-cancer pain.[2,3,4] In COMPOSE 1, 547 patients were randomized 1:1 to naldemedine 0.2 mg or placebo daily. In COMPOSE 2, 553 subjects were

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randomized 1:1 to naldemedine 0.2 mg or placebo daily. Patients were required to either not be using laxatives or willing to discontinue laxative use prior to study enrollment. During the treatment period, bisacodyl was allowed as a rescue laxative if patients did not have a bowel movement (BM) for 72 hours. In addition, subjects were allowed 1-time use of an enema if after 24 hours of taking bisacodyl there was not a BM. The primary endpoint was assessed using a responder analysis. A responder was defined as a patient who had at least 3 spontaneous bowel movements (SBMs) per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks. Primary outcome data were available from 273 patients randomized to naldemedine and 272 patients randomized to placebo in COMPOSE 1 and 276 patients randomized to naldemedine and 274 patients randomized to placebo in COMPOSE 2. In both studies, a significantly greater proportion of patients responded to naldemedine versus placebo (COMPOSE 1: 47.6% versus 34.6%, respectively, p=0.002; COMPOSE 2: 52.5% versus 33.6%, p<0.0001). Abdominal pain (8% versus 2%), diarrhea (7% versus 2%), nausea (4% versus 2%), and gastroenteritis (2% versus 1%) were reported with naldemedine versus placebo use, respectively.

OTHER DRUGS USED FOR CONDITION

OIC is a common adverse effect of opioid therapy. Other opioid antagonists, oral or subcutaneous methylnaltrexone (Relistor®) and oral naloxegol (Movantik®), also are indicated for treatment of non-cancer OIC.

Oral lubiprostone (Amitiza®) is approved for the treatment of OIC in adults with chronic, non-cancer pain. However, its effectiveness in the treatment of OIC in patients taking diphenylheptane opioids (e.g., methadone) has not been established.

PLACE IN THERAPY

The 2009 American Pain Society (APS) and American Academy of Pain Medicine (AAPM) clinical guidelines for chronic opioid therapy in patients with non-cancer pain recommend that common adverse effects, including constipation, should be anticipated and addressed appropriately.[4] The 2012 American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain recommend that prescribers initiate a prophylactic bowel regimen even before the development of constipation and after its development.[5,6] A guideline on management of OIC from the American Gastroenterological Association (AGA) is anticipated for early 2018.[7]

Naldemedine tosylate is a once-daily oral peripherally acting mu-opioid receptor antagonist and offers another treatment option for adults with OIC in chronic non-cancer pain. It is currently designated by the Drug Enforcement Agency (DEA) as a Schedule II controlled substance, because of structural similarity to naltrexone. The manufacturer has petitioned to deschedule naldemedine; it is under DEA evaluation.

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SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Gastrointestinal Motility, Chronic
Clinical Edit	▪ Patient is at least 18 years old; **AND** ▪ Patient is diagnosed with OIC related to chronic non-cancer pain; **AND** ▪ Patient is currently on opioids (discontinue if patient not on opioids); **AND** ▪ Patient has been using opioids for at least 150 days within past 180 days; **AND** ▪ Trial and failure of at least 1 preferred product, if naldemedine tosylate is considered non-preferred; **AND** ▪ Trial of both polyethylene glycol (PEG) and lactulose (without adequate response); **AND** ▪ Patient does not have the following conditions: - Known or suspected gastrointestinal obstruction, **OR** - Hypersensitivity to naldemedine tosylate, **OR** - Pregnancy, **OR** - Severe hepatic impairment (Child-Pugh Class C)
Quantity Limit	30 tablets per 30 days
Duration of Approval	1 year
Drug to Disease Hard Edit	None

REFERENCES

1 Symproic [prescribing information]. Florham Park, NJ; Shionogi; February 2017.
2 Hale, ME, Wild J, Reddy, J et al. Efficacy and safety of naldemedine for the treatment of opioid-induced constipation in subjects with chronic non-cancer pain receiving opioid therapy: results from two phase 3 clinical trials. Gastroenterology, 2016, 150 (4): S121–S122.
3 Symproic [prescribing information]. Florham Park, NJ; Shionogi; February 2017.
4 Chou R , Fanciullo GJ , Fine PG, et al. American Pain Society- American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009; 10: 113 – 30. Available at: http://www.jpain.org/article/S1526-5900(08)00831-6/pdf. Accessed April 19, 2017.
5 Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part I – Evidence Assessment. Pain Physician. 2012; 15:S1-S66.
6 Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part I – Evidence Assessment. Pain Physician. 2012; 15:S1-S66.
7 American Gastroenterological Association. Guidelines. Available at: http://www.gastro.org/guidelines. Accessed April 19, 2017.

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