Drug Use Research & Management
Oregon State University College of Pharmacy

Abbreviated Drug Review

Trade Name (generic)

Symproic® (naldemedine) | Indication not funded

Indications

Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

Dosage

0.2mg orally once a day with or without food.

Background

Naldemedine is an opioid antagonist structurally related to naltrexone and has received Schedule II controlled substance labeling by the U.S. Drug Enforcement Administration (DEA). The removal of the controlled substance scheduling is currently being petitioned by Shionogi Incorporated, the manufacturer of naldemedine.

Efficacy

The FDA approval of naldemedine was based on data from two studies: COMPOSE I and COMPOSE II.COMPOSE I and II were 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies.[1]A third study, COMPOSE III, is an ongoing, 52-week, randomized, double-blind, placebo-controlled, long-term safety study.[2] The studies have not yet been published but are available for review at clinicaltrials.gov.[2-4] COMPOSE I and COMPOSE II evaluated naldemedine in the treatment of adults using opioids to managed chronic non-cancer pain with OIC. The primary endpoint was the proportion of responders who had a positive response in 9 out of the 12 week treatment period. Positive response was defined as at least 3 spontaneous bowel movements (SBMs) per week and an increase from baseline of at least 1 SBM per week. Results from both studies are presented in **Table 1**.

Table 1: Efficacy Responder Rates in COMPOSE I and II in Patients with OIC and Chronic Non-Cancer Pain[2]

	COMPOSE I			**COMPOSE II**		
	Naldemedine 0.2 mg once daily (n = 273)	Placebo (n = 272)	Treatment Difference (95% CI; p-value)	Naldemedine 0.2 mg once daily (n = 276)	Placebo (n = 274)	Treatment Difference (95% CI; p-value)
Proportion of Responders	48% (130/273)	35% (94/273)	13% (5 to 21%; p=0.002)	53% (145/276)	34% (92/274)	19% (11 to 27%; p<0.0001)
Mean change in SBMs/week from baseline to Weeks 11-12	3.1	2.0	1.0 (0.6 to 1.5; p-value not reported)	3.3	2.1	1.2 (0.8 to 1.7; p-value not reported)

Safety

Contraindications:

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

Warnings and Precautions:

- Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue if this symptom develops.
- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with naldemedine.
- Avoid use with strong CYP3A inducers (e.g. rifampin, carbamazepine, phenytoin, St. John's Wort) because it may reduce the efficacy of naldemedine.
- Naldemedine crosses the placenta and may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. Naldemedine should be used during pregnancy only if the potential benefit justifies the potential risk. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Evidence Gaps/Limitations

Long term safety data has been collected over 52 weeks, but not published. No studies found to support evidence for treatment of Oregon Health Plan (OHP) funded conditions or co-morbidities.

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization. Add naldemedine to “Drugs for Constipation” PA criteria.

References

1. Symproic (Naldemedine) Prescribing Information. Florham Park, NJ. Shionogi, March 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208854s000lbl.pdf. Accessed April 5, 2017.
2. Efficacy and Safety of Naldemedine in the Treatment of Opioid-induced Constipation - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01965158?term=naldemedine&rank=3. Accessed April 6, 2017.

3. Efficacy and Safety of Naldemedine in Treating Opioid-induced Constipation - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01993940?term=naldemedine&rank=2. Accessed April 6, 2017.
4. Long Term Safety of Naldemedine - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01965652?term=naldemedine&rank=1. Accessed April 6, 2017.