Drug Monograph

Drug/Drug Class: **Symproic® (naldemedine)/ GI Motility Agents**
Prepared for: MO HealthNet
Prepared by: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Symproic® is available as a tablet containing 0.2 mg of naldemedine. Manufactured for: Purdue Pharma LP, Stamford, CT, 06901
Summary of Findings:	The effect of Symproic® for the treatment of opioid-induced constipation in patients with noncancer pain was studied in two randomized, double-blind, placebo-controlled, 12-week clinical trials (N=1095). Compared with the response rate of 35% and 34% in patients who received placebo, 48% and 53% of patients who received Symproic® experienced relief of constipation.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Non-Preferred Agent ☐ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [(1)]

Opioid-induced constipation occurs when opioids attach to mu-receptors in the bowel. Opioid-induced constipation is one of the most common side effects of opioid use. The prevalence of constipation in regular opioid users is 21%.

Dosage Form(s) [(1)]

Symproic® is available in a tablet containing 0.2 mg of naldemedine.

Manufacturer [(1)]

Manufactured for: Purdue Pharma LP, Stamford, CT, 06901

Indication(s) [(1)]

Symproic® is indicated for: treatment opioid-induced constipation in adults with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent opioid dosage escalation.

Clinical Efficacy [(1)] (mechanism of action/pharmacology, comparative efficacy)

Symproic® is a derivative of naltrexone and antagonizes mu-, delta-, and kappa-opioid receptors. It reduced the constipation associated with opioid use via mu-opioid antagonism in the gastrointestinal tract.

Pharmacokinetics:

	Symproic®
Distribution	155 L
Half Life	11 hours

Opioid-Induced Constipation

Treatment with Symproic® provided better constipation relief than placebo in patients receiving opioids for chronic noncancer pain.

STUDY DESIGN	Two randomized, double-blind, placebo-controlled, 12-week clinical trials (N=1095)

INCLUSION CRITERIA	Patients with opioid-induced constipation and noncancer pain who were receiving a daily equivalent morphine dose of at least 30mg for at least four weeks
EXCLUSION CRITERIA	Use of laxatives or patients with structural abnormalities of the gastrointestinal tract
TREATMENT REGIMEN	Patients were randomized to receive Symproic® 0.2mg orally once daily or placebo for 12 weeks. Rescue laxative were allowed.
RESULTS	Significantly more patients responded in the Symproic® groups (48% and 53%) compared with the placebo groups (35% and 34%). Clinical response was defined at least 3 spontaneous bowel movements (SBMs) per week, with an increase from baseline of at least 1 SBM/wk for 9 or more of the 12 weeks and for 3 of the last 4 weeks. The mean increase in SBMs/wk from baseline was 3.1 to 3.3 with Symproic® versus 2 o 2.1 with placebo. Patients (mean age, 54 years) had a mean duration of opioid use of 5 years, with a mean daily baseline oral morphine equivalent of 132 mg ad 121 mg.
SAFETY	Not specified

Contraindications [(1)]

- Known or suspected gastrointestinal obstruction or at increased risk for recurrent obstruction; potential for gastrointestinal perforation.
- Hypersensitivity to naldemedine

Warnings and Precautions [(1)]

- Black box warning: Life-threatening and fatal infections (eg, Legionella, Listeria, mycobacterial, invasive fungal, viral, parasitic, and other opportunistic infections) have been reported, especially with concomitant use of immunosuppressants; do not initiate therapy in patients with active infections (including chronic or localized infections); ongoing monitoring recommended both during and after therapy; discontinue if serious infection or sepsis occurs.
- Gastrointestinal perforation has been reported with other opioid antagonists, with increased risk in patients with conditions that may cause reduced structural integrity of the gastrointestinal tract (eg, peptic ulcer disease, Crohn disease, Ogilvie syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies, or peritoneal metastases). Weigh benefits and risks prior to initiation; monitoring required and discontinue therapy if occurs.
- Withdrawal symptoms have been reported during treatment, with increased risk in patients with disruptions to the blood-brain barrier. Weigh benefits and risks prior to initiation; monitoring recommended.
- Avoid use with severe hepatic impairment.
- Avoid concomitant use with strong CYP3A inducers (eg, rifampin, carbamazepine,

phenytoin, St. John's wort).

- May precipitate opioid withdrawal in a fetus when used during pregnancy. Weigh benefits and risks before initiation.
- May precipitate opioid withdrawal in breastfed infants. Weigh benefits and risks. If naldemedine is stopped, breastfeeding may resume 3 days following discontinuation.

Adverse Effects [1]

Most common, ≥ 2%	Naldemedine (n=621)	Placebo (n=619)
Abdominal pain	11%	5%
Diarrhea	7%	3%
Nausea	6%	5%
Vomiting	3%	2%
Gastroenteritis	3%	1%

Drug Interactions [1]

- CYP3A inducers, strong: Rifampin, carbamazepine, phenytoin, St. John's wort
- CYP3A inhibitors, moderate or strong: Fluconazole, diltiazem, ritonavir
- Opioid antagonists
- P-glycoprotein inhibitors: Amiodarone, captopril, cyclosporine, verapamil

Dosage and Administration [1]

The usual FDA recommended dosage is 0.2 mg orally once daily with or without food. Discontinue when treatment with opioid pain medication is discontinued.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	DOSE	COST/ MONTH*
Naldemedine	Symproic	Purdue Pharma LP	0.2 mg tablets	$313.80
Methylnaltrexone bromide	Relistor	Salix	150 mg tablets	$1634.40

* Wholesale Acquisition Cost

Conclusion

Symproic® is an orally administered, peripheral opioid antagonist indicated for the treatment of opioid-induced constipation in adults with chronic noncancer pain. It is a Schedule II controlled substance. In two randomized clinical trials in patients with opioid-induced constipation, patients who received naldemedine experienced more relief of constipation compared with patients who

received placebo. The most common adverse effects are abdominal pain, diarrhea and nausea. Close monitoring for symptoms of opioid withdrawal is recommended.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) Product Information: Symproic®, naldemedine tablets. Purdue Pharma LP, Stamford, CT, 03/2017.

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