Formulary Drug Review: Naldemedine

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Generic Name: Naldemedine

Proprietary Name: *Symproic* (Shionogi)

Approval Rating: 1S

Therapeutic Class: Detoxification Agents, Antidotes

Similar Drugs: Lubiprostone, Methylnaltrexone, Naloxegol

Sound-/Look-Alike Names: Nalmefene, Nilutamide

Indications

Naldemedine is approved by the US Food and Drug Administration (FDA) for the treatment of opioid-induced constipation (OIC) in adults with chronic noncancer pain.^{1,2} At least 1 study has also evaluated the effects of naldemedine in the treatment of OIC in adults with cancer pain.³

Opioid analgesics are commonly prescribed medications for use in chronic pain management.⁴ The most common adverse events associated with long-term opioid therapy are nausea, vomiting, gas, hardened stool, incomplete evacuation, and constipation.^{5–7} Most effects resolve after continued use of the opioid; however, constipation, which occurs in 15% to 95% of patients receiving opioid therapy, often does not resolve on its own with continued exposure.^{4,7,8} Mu-opioid receptors reduce peristaltic and secretory actions in the bowel, thereby contributing to the development of OIC.^{6,7} Decreased gastrointestinal (GI) motility and secretions cause stools to become hard and dry.^{7,8} Laxative therapy (eg, stool softeners, bowel stimulants, osmotic agents) is commonly used to manage constipation but provides insufficient relief in some patients, especially those taking high doses of opioids.^{4,9} Other drugs approved for the treatment of OIC in adult patients include lubiprostone, methylnaltrexone (oral and subcutaneous injection), and naloxegol.^{10,11}

Clinical Pharmacology

Opiate binding to the mu-receptor in the GI tract leads to decreased propulsive contractions and decreased secretion of water and electrolytes.^{7,12} Several drugs approved for the treatment of OIC are opioid antagonists (eg, methylnaltrexone, naldemedine, naloxegol).^{2,10,11} Naldemedine, a derivative of naltrexone, is a peripherally acting mu-opioid receptor antagonist, but it has binding affinities for the mu-, delta-, and kappa-opioid receptors.^{2,13} In studies with rats, opioid withdrawal symptoms were observed only at doses more than 10 times those required for the anticonstipation effect.¹³ The side chain on naldemedine increases its molecular weight and the polar surface area, thus decreasing its ability to cross the blood-brain barrier.²

Naloxegol is a pegylated derivative of the mu-opioid receptor antagonist naloxone.^{10,12} Pegylation decreases passive blood-brain barrier permeability and increases efflux by the P-glycoprotein transporter, effectively preventing blockade of central opioid receptors.¹⁰

Methylnaltrexone is an opioid antagonist that binds at the mu-opioid receptor. As a quaternary amine, methylnaltrexone's ability to cross the blood-brain barrier is restricted, allowing it to function as a peripherally acting mu-opioid receptor antagonist in tissues such as the GI tract, thereby decreasing the constipating effects of opioids without

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affecting opioid-mediated analgesic effects on the central nervous system (CNS).^{9,11,14}

Unlike the opioid antagonists, lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion. The increased amount of intestinal fluid secretion in the intestine increases GI motility, thereby facilitating the passage of stool and alleviating symptoms associated with opioid-induced and chronic idiopathic constipation.¹⁵

Pharmacokinetics

Peak plasma concentrations occur at 0.75 hours after oral administration of naldemedine in a fasted state.^{2,16} Administration with a high-fat meal does not decrease the extent of absorption but delays peak concentrations to 2.5 hours and decreases the peak plasma concentration by 35%.²

Plasma protein binding is 93% to 94%. The mean apparent volume of distribution is 155 L.² The serum half-life of naldemedine is 5.2 to 9.2 hours after single-dose administration and 37.8 to 45.7 hours after daily administration for 10 days.¹⁶ The terminal elimination half-life is 11 hours.² The primary metabolite of naldemedine is nor-naldemedine, which has opioid antagonistic activity but to a lesser extent than naldemedine.^{2,16} The amount of naldemedine excreted unchanged in the urine is 16% to 18%.²

Comparative Efficacy

Indication: OIC

Guidelines

Guideline: Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain

Reference: American Pain Society-American Academy of Pain Medicine¹⁷

Comments: The guidelines are focused on the use of opioids in the treatment of chronic noncancer pain, and provide guidance on the prevention and management of opioid-related adverse effects. Based on anecdotal evidence suggesting effectiveness, initiating a bowel regimen that includes increased fluid and fiber intake, stool softeners, and laxatives is recommended in patients at risk for developing OIC. At the time the guideline was written, insufficient information was available to provide recommendations regarding the use of opioid antagonists to treat or prevent OIC. Specific guidelines for the treatment of OIC were not located.

Studies

Drug: Naldemedine versus Placebo

Reference: Ferreira JCA, et al, 2016 (COMPOSE I trial)¹⁸⁻²⁰

Study Design: Randomized, double-blind, multicenter, phase 3 study

Study Funding: Shionogi

Patients: 547 adults with OIC while receiving treatment with an opioid analgesic for chronic noncancer pain. Patients were required to be receiving a stable opioid analgesic dose, with an average total daily dose greater than or equal to 30-mg equivalents of oral morphine sulfate. Patients could not be using laxatives or had to be willing to discontinue laxative therapy. Exclusion criteria included structural abnormalities of the GI tract, or a history of chronic constipation prior to starting analgesic medication or any potential nonopioid cause of bowel dysfunction that may contribute to constipation. Mean patient age was 53 years; approximately 60% of patients were female; 80% were white and 18% were black; and mean body mass index was 31.3 kg/m². The average number of baseline spontaneous bowel movements (SBMs) per week was 1.3, the average total daily dose of opioid at baseline was 125 to 140 mg morphine equivalent, and the average duration of opioid use was 61 months.

Intervention: Patients were randomly assigned to treatment with naldemedine 0.2 mg (n = 273) or placebo (n = 272) orally once daily for 12 weeks. Laxatives could be used as rescue therapy.

Results

Primary End Point(s)

- The proportion of responders was 47.6% with naldemedine and 34.6% with placebo (difference, 13% [95% confidence interval, 4.8%-21.3%]; *P* = .002). A “responder” was defined as a patient having at least 9 positive response weeks within the 12-week treatment period and 3 positive response weeks within the last 4 weeks of the 12-week treatment period. A response week was defined as at least 3 SBMs per week and an increase from baseline of 1 or more SBMs per week for that week.

Comments: Those blinded to the treatment included the patient, caregiver, investigator, and outcomes assessor. The study was conducted in the United States, Austria, Czech Republic, Germany, Poland, Spain, and the United Kingdom. A bowel movement that occurred within 24 hours after rescue laxative therapy was not classified as an SBM. The number needed to treat for the primary end point was 7.7 at week 12.

Limitations: Results are only available as a meeting abstract and in news releases.

Reference: Hale ME, et al, 2016 (COMPOSE II trial)^{19,21,22}

Study Design: Randomized, double-blind, multicenter, phase 3 study

Study Funding: Shionogi

Patients: 553 adults with OIC while receiving treatment with an opioid analgesic for chronic noncancer pain. Patients were required to be receiving a stable opioid analgesic dose, with an average total daily dose greater than or equal to 30-mg equivalents of oral morphine sulfate. Patients could not be using laxatives or had to be

willing to discontinue laxative therapy. Exclusion criteria included structural abnormalities of the GI tract, or a history of chronic constipation prior to starting analgesic medication or any potential nonopioid cause of bowel dysfunction that may contribute to constipation.

Intervention: Patients were randomly assigned to treatment with naldemedine 0.2 mg ($n = 277$) or placebo ($n = 276$) orally once daily for 12 weeks. Laxatives could be used as rescue therapy.

Results

Primary End Point(s)

- The proportion of responders was 52.5% with naldemedine and 33.6% with placebo (difference, 18.9% [95% confidence interval, 10.8%-27%]; $P < .001$). A “responder” was defined as a patient having at least 9 positive response weeks within the 12-week treatment period and 3 positive response weeks within the last 4 weeks of the 12-week treatment period. A response week was defined as at least 3 SBMs per week and an increase from baseline of 1 or more SBMs per week for that week.

Secondary End Point(s)

- Details regarding secondary end points (eg, number of complete SBMs per week, number of SBMs without straining per week during the last 2 weeks of the study) were not provided.

Comments: This trial used the same study design and evaluation criteria as COMPOSE I but was conducted only in the United States.^{18,20} The number needed to treat for the primary end point was 5.3 at week 12. The clinical efficacy and safety results observed in COMPOSE I and II are similar to those in phase 2 clinical studies.^{23,24}

Limitations: Results are available only as published abstracts and in news releases.

Reference: Webster L, et al, 2016 (COMPOSE III trial)^{25,26}

Study Design: Randomized, double-blind, multicenter, phase 3 study

Study Funding: Shionogi

Patients: 1,240 adults with OIC while receiving treatment with an opioid analgesic for chronic noncancer pain. Patients were required to be receiving a stable opioid analgesic dose, with an average total daily dose greater than or equal to 30-mg equivalents of oral morphine sulfate. Patients were required to have 4 or fewer SBMs in a 14-day qualifying period and 3 or fewer SBMs per week during the qualifying period. Exclusion criteria included structural abnormalities of the GI tract, no prior use of laxatives for OIC, and a history of chronic constipation prior to starting analgesic medication or any potential nonopioid cause of bowel dysfunction that may contribute to constipation.

Intervention: Patients were randomly assigned to treatment with naldemedine 0.2 mg ($n = 620$) or placebo ($n = 620$) orally once daily for 52 weeks. Laxative therapy was allowed.

Results

Primary End Point(s)

- Long-term safety and tolerability: Naldemedine was not associated with signs and symptoms of opioid withdrawal based on the Subjective Opioid Withdrawal Scale and Clinical Opioid Withdrawal Scale, nor were the analgesic effects of the opioids affected, as assessed by the Numerical Rating Scale.
- The frequency of bowel movements per week was greater in the naldemedine group than in the placebo group at weeks 12, 24, 36, and 52 ($P < .001$); no details were provided.

Comments: This is an ongoing phase 3 clinical study being conducted in the United States, Australia, Austria, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Poland, South Africa, Spain, Sweden, and the United Kingdom. The trial used a study design similar to COMPOSE I and COMPOSE II but for a longer duration (52 weeks instead of 12 weeks).

Limitations: Results are available only as a published abstract.

Contraindications, Warnings, and Precautions

Contraindications

Naldemedine is contraindicated in patients with known or suspected GI obstruction and in those at increased risk of recurrent obstruction due to the potential for GI perforation. It is also contraindicated in patients with a history of hypersensitivity reaction (eg, bronchospasm, rash) to naldemedine or other product ingredients (D-mannitol, croscarmellose sodium, magnesium stearate, hypromellose, talc, and yellow ferric oxide).²

Methylnaltrexone and naloxegol have similar contraindications.^{10,11}

Warnings and Precautions

GI perforation may occur with the use of peripherally acting opioid antagonists in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract (eg, peptic ulcer disease, Ogilvie syndrome, diverticular disease, infiltrative GI tract malignancies, peritoneal metastases). Patients should be monitored for the development of severe, persistent, or worsening abdominal pain, and naldemedine should be discontinued in patients who develop this symptom.²

Clusters of 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.²

Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using naldemedine in such patients. Monitor for symptoms of opioid withdrawal in such patients.²

Methylnaltrexone and naloxegol have similar warnings and precautions to naldemedine.^{10,11}

Naldemedine does not cause QTc prolongation at therapeutic or supratherapeutic doses.^{2,27}

The use of opioid antagonists during pregnancy may precipitate opioid withdrawal in a fetus.^{2,10,11}

A decision should be made to discontinue breastfeeding or use of naldemedine. If naldemedine is discontinued to minimize drug exposure to a breastfed infant, breastfeeding should be delayed for 3 days after the final dose of naldemedine.²

The safety and effectiveness of naldemedine have not been established in pediatric patients.²

Adverse Reactions

The most common adverse reactions with naldemedine (incidence of at least 5% and occurring at a greater frequency than with placebo) in clinical trials were abdominal pain (ie, abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, GI pain; 5.2%-11% vs 1.1%-5%), diarrhea (6.6%-11% vs 1.8%-5.3%), nausea (4%-6% vs 2%-5%), vomiting (3% vs 2%), and gastroenteritis (2%-3% vs 1%).^{2,18,19,25} Serious and important adverse reactions include GI perforation and opioid withdrawal.²

Drug Interactions

Administration with strong CYP3A inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort) significantly decreases plasma naldemedine concentrations and efficacy; therefore, coadministration should be avoided.²

Administration with moderate (eg, aprepitant, atazanavir, diltiazem, erythromycin, fluconazole) or strong (eg, clarithromycin, itraconazole, ketoconazole, ritonavir, saquinavir) CYP3A inhibitors significantly increases plasma naldemedine concentrations, which increases the risk of naldemedine-related adverse reactions.²

Administration with P-glycoprotein inhibitors (eg, amiodarone, captopril, cyclosporine, quercetin, quinidine, verapamil) may increase plasma naldemedine concentrations and increase the risk of naldemedine-related adverse reactions.²

Coadministration with other opioid antagonists has the potential for an additive effect on naldemedine's opioid receptor antagonism and increases the risk of opioid withdrawal.²

In *in vitro* studies, naldemedine at clinically relevant concentrations did not inhibit the major CYP enzymes (including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A11 isozymes), inhibit transporters (including OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, BCRP, or P-gp), or cause significant induction of CYP1A2, CYP2B6, CYP3A4, UGT1A2, UGT1A6, or UGT2B7 isozymes.²

Recommended Monitoring

No special safety monitoring is recommended, with the exception of monitoring for acute opiate withdrawal.

Dosing

The recommended dose is naldemedine 0.2 mg orally once daily with or without food. There are no dosage adjustment recommendations based on age or organ function; however, naldemedine therapy should be avoided in patients with severe hepatic impairment. Alteration of analgesic dosing is also not required; however, if the opioid pain medication is discontinued, naldemedine therapy should be discontinued.²

Patients receiving opioids for less than 4 weeks may be less responsive to naldemedine therapy.²

Product Availability

The New Drug Application (NDA) for naldemedine was accepted by the FDA in June 2016. The Prescription Drug User Fee Act (PDUFA) target action date was March 23, 2017.²⁸ *Symproic* was approved by the FDA on March 23, 2017.¹

Naldemedine 0.2 mg is available as a film-coated tablet in bottles of 90.²

Store naldemedine in a light-resistant container at 20°C to 25°C (68°F-77°F); excursions are permitted to 15°C to 30°C (59°F-86°F).²

Drug Safety/REMS

No Risk Evaluation and Mitigation Strategy (REMS) is required for naldemedine.

Conclusion

Naldemedine is an opioid antagonist approved for the treatment of OIC in adults with chronic noncancer pain. In clinical trials, naldemedine improved the frequency of SBMs and did not affect opioid analgesic effects. Similar to naloxegol and methylnaltrexone, naldemedine is available as oral tablets. There are no head-to-head studies comparing these drugs, and none are intended for the treatment or management of OIC in cancer patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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