



Naldemedine (Symproic) for the Treatment Of Opioid-Induced Constipation

Kenneth Hu, PharmD; and Mary Barna Bridgeman, PharmD, BCPS, BCGP

INTRODUCTION

Pain, pain management, and the complications associated with interventions intended to mitigate pain are associated with significant direct and indirect health care costs. Beyond the direct costs associated with medications, hospitalizations, provider visits, physical therapy, and rehabilitation, chronic pain places an enormous indirect burden on the affected individual's productivity, quality of life, and mental health. More than 100 million Americans are estimated to suffer from chronic pain, with an estimated 3% of adults in the United States receiving long-term opioid therapy for chronic non-cancer pain, at a national annual estimated cost of approximately \$560 billion to \$630 billion.¹⁻⁴

Opioid analgesics are commonly prescribed for the treatment of chronic pain management. In 2012, prescriptions for opioid pain medications were written by health care providers 259 million times.⁵ While opioids can be useful for alleviating severe pain, the clinical utility of opioids may be limited by an association with adverse effects. Severe adverse effects attributed to opioid use may include physical dependence, respiratory and central nervous system depression, tolerance, and hyperalgesia.² Adverse effects related to sedation, pruritus, nausea and vomiting, and constipation may be perceived

as less severe, but potentially bothersome, and can ultimately contribute to non-compliance with the prescribed regimen. In particular, gastrointestinal (GI) side effects, including nausea, abdominal pain, bloating, abdominal cramping, and constipation, can have an impact on the quality of life, dignity, and health of patients utilizing these agents for chronic pain management. Opioid-induced constipation (OIC), new or worsening constipation occurring when initiating, changing, or increasing opioid use, represents the most common of these GI effects (see Table 1 for a depiction of the ROME IV definition of OIC).⁶

Since tolerance does not develop to the constipating effects of this class, OIC may occur at any point after initiation of the opioids and can be directly attributed to the peripheral effects of the opioid interacting with receptors found within the GI tract. The frequency of OIC increases with prolonged use of opioids, and many patients may reduce the dose or discontinue their opioid treatment due to the effects of constipation, resulting in decreased treatment satisfaction.⁷

Although there are several treatment options for OIC, an unmet clinical need continues to exist for patients utilizing opioids chronically for pain management. Several novel treatment methods are in development.⁸ This review focuses on the safety and efficacy of naldemedine (Symproic, Shionogi), a peripherally acting mu (μ)-opioid receptor antagonist approved by the Food and Drug Administration

(FDA) in March of 2017 for the treatment of OIC in adult patients with chronic non-cancer pain.⁹

PHARMACOLOGY

The mu (μ)-, delta (δ)-, and kappa (κ)-opioid receptors are common in the central nervous system (CNS), but they are also involved with GI function. While the δ - and κ -receptors are primarily found in the proximal colon and stomach, the μ -receptors are widely distributed throughout the GI tract. OIC is largely due to enteric μ -opioid receptor activation, leading to non-peristaltic contractions of the esophagus, reduced gastric motility and emptying, decreased GI secretions, inhibited intestinal propulsion, and greater absorption of water from bowel contents.¹⁰

As a peripheral μ -opioid receptor antagonist, naldemedine works by binding to the μ -, δ -, and κ -opioid receptors and specifically reduces the constipating effects of opioids through its action as an antagonist at the μ -opioid receptors in GI tract tissue.^{9,11} Naldemedine shares a similar chemical structure to that of naltrexone, with an additional side chain increasing the molecular weight and polar surface area.¹¹ Naldemedine also acts as a substrate of the P-glycoprotein (P-gp) efflux transporter. These properties reduce the possibility of naldemedine interfering with centrally mediated opioid analgesia by decreasing its penetration into the CNS at recommended dose levels.⁹

At the time of writing, Dr. Hu was a PharmD Candidate at the Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey; he is now a Global Regulatory Affairs Postdoctoral Fellow at Sanofi in Bridgewater, New Jersey. Dr. Bridgeman is a Clinical Associate Professor at Rutgers University and an Internal Medicine Clinical Pharmacist at Robert Wood Johnson Hospital in New Brunswick, New Jersey. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi and Associates in New York, New York.

Disclosure: The authors report no commercial or financial interests in regard to this article.

Table 1 Characteristics of OIC According to the ROME IV Criteria⁶

New or worsening symptoms when initiating, changing, or increasing opioid therapy that must include two or more of the following in $\geq 25\%$ of defecations:

- Straining to pass a bowel movement
- Passing lumpy or hard stools
- Experiencing the sensation of incomplete evacuation, obstruction, or blockage of stool
- Requiring manual maneuvers to facilitate evacuation of stool
- Fewer than three spontaneous bowel movements per week

AND

Rarely experiencing loose stools without laxative use

Table 2 Comparison of FDA-Approved Medications for the Treatment of OIC^{9, 11-14}

Features	Naldemedine ^{9,11}	Methylnaltrexone ¹²	Naloxegol ¹³	Lubiprostone ^{14*}
Mechanism	μ-, δ-, and κ-opioid receptor antagonist	μ-opioid receptor antagonist	μ-opioid receptor antagonist	Chloride channel activator
Route of Administration	Oral	Subcutaneous; Oral	Oral	Oral
Absorption (Time to Peak)	0.75 hours; 2.5 hours (with food)	Subcutaneous: 30 minutes; Oral: ~1.5 hours (delayed by 2 hours with high-fat meal)	<2 hours; in majority of subjects, a secondary C _{max} occurs ~0.4 to 3 hours after the first C _{max}	M3: ~1.1 hours
Distribution	Vz/F: 155 L	Vss: 1.1 L/kg	Vz/F: 968–2,140 L	Minimal beyond GI tissues
Metabolism	CYP3A	Conversion to methyl-6-naltrexol isomers and methylnaltrexone sulfate	CYP3A	Carbonyl reductase
Elimination	t _{1/2} : 11 hours	t _{1/2} : 8 hours	t _{1/2} : 6–11 hours	M3 t _{1/2} : 0.9–1.4 hours
Side Effects	<ul style="list-style-type: none"> Abdominal pain Diarrhea Nausea Gastroenteritis 	<ul style="list-style-type: none"> Abdominal pain Flatulence Nausea Dizziness 	<ul style="list-style-type: none"> Abdominal pain Diarrhea Nausea Flatulence 	<ul style="list-style-type: none"> Abdominal pain Diarrhea Nausea Flatulence

*Low systemic availability of lubiprostone after oral administration, with concentrations below the level of quantitation (10 pg/mL). Pharmacokinetic parameters of M3 (its only measurable active metabolite) have been characterized.

C_{max} = peak concentrations, Vz/F = mean apparent volume of distribution during terminal phase, Vss = steady-state volume of distribution, t_{1/2} = half-life.

PHARMACOKINETICS

A summary of the pharmacokinetic characteristics of the FDA-approved treatments for OIC can be found in Table 2.^{9,11-14}

Absorption and Distribution

When taken orally, naldemedine is absorbed from the GI tract, with peak concentrations (C_{max}) occurring at approximately 0.75 hours (T_{max}) in the fasted state. There is a dose-proportional, or near dose-proportional, increase for both C_{max} and the area-under-the-plasma-concentration-time curve (AUC) and multiple daily doses of naldemedine result in minimal accumulation. A high-fat meal decreases C_{max} by approximately 35% and T_{max} is extended to approximately 2.5 hours when taken with food; however, the AUC does not experience a significant change as high-fat meals lower the speed, but not the degree, of naldemedine absorption.^{9,11} Naldemedine is 93% to 94% bound to human plasma proteins when taken orally and has a mean apparent volume of distribution of 155 L.^{9,11}

Metabolism

Naldemedine undergoes hepatic metabolism via CYP3A to nor-naldemedine. Naldemedine also undergoes metabolism to a lesser degree through

UGT1A3 to form naldemedine 3-G. Both metabolites have shown antagonistic activity for opioid receptors but to a lesser extent than naldemedine. Naldemedine is also cleaved to benzamidine and naldemedine carboxylic acid within the GI tract.^{9,11} When [¹⁴C]-labeled naldemedine was taken orally, nor-naldemedine was the primary metabolite in plasma, with approximately 9% to 13% relative exposure compared to naldemedine. As a minor metabolite in plasma, naldemedine 3-G had a relative exposure of less than 3%.⁹

Elimination

When [¹⁴C]-labeled naldemedine was taken orally, 57% and 35% of the radio-labeled dose was excreted in the urine and feces, respectively. In the urine, approximately 16% to 18% of the administered dose of naldemedine was excreted unchanged. There is no estimate at this time for the degree of change in naldemedine excreted in the feces. As the primary metabolite excreted in the urine and feces, benzamidine represented approximately 32% and 20% of the administered dose of naldemedine, respectively.^{9,11}

Hepatic and Renal Impairment

The pharmacokinetic properties of naldemedine given once at a dose of 0.2 mg in subjects with normal hepatic

and renal (estimated creatinine clearance ≥ 90 mL/min) function were similar to those in subjects with mild (estimated glomerular filtration rate [eGFR] of 60 to 89 mL/min/1.73 m²), moderate (eGFR, 30 to 59 mL/min/1.73 m²), or severe (eGFR < 30 mL/min/1.73 m²) renal impairment, subjects with end-stage renal disease requiring hemodialysis, and subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No adjustments are required when dosing naldemedine for patients with mild to moderate hepatic impairment, although there have been no studies of the effect on the pharmacokinetic properties of naldemedine in subjects with severe hepatic impairment (Child-Pugh Class C) and use should be avoided in these types of patients.^{9,11}

CLINICAL TRIALS

A summary of the clinical trials leading to the approval of naldemedine can be found in Table 3.^{11,15, 17-20}

NCT01122030

Webster et al. conducted a single-center, randomized, double-blind, placebo-controlled, single ascending-dose phase 2a study evaluating the safety and efficacy of naldemedine at doses of 0.01 mg, 0.03 mg, 0.1 mg, 0.3 mg, 1.0 mg,

Table 3 Naldemedine Clinical Trials^{11,15,17-20}

Clinical Trial Number	NCT01122030 ^{11, 15}	NCT01443403 ^{11, 17}	NCT01965158 (COMPOSE I) ^{11, 18}	NCT01993940 (COMPOSE II) ^{11, 18}	NCT01965652 (COMPOSE III) ^{11, 19, 20}
Design	<ul style="list-style-type: none"> Phase 2a Single center, randomized, double-blind, placebo-controlled, single ascending-dose study 	<ul style="list-style-type: none"> Phase 2b Multicenter, randomized, double-blind, placebo-controlled, parallel-group study 	<ul style="list-style-type: none"> Phase 3 Multicenter, randomized, double-blind, placebo-controlled, parallel-group study 	<ul style="list-style-type: none"> Phase 3 Multicenter, randomized, double-blind, placebo-controlled, parallel-group study 	<ul style="list-style-type: none"> Phase 3 Multicenter, randomized, double-blind, placebo-controlled study
Primary Endpoint	Number of participants with adverse events	Mean change in weekly SBM frequency from baseline to last 2 weeks of treatment	Percentage of participants with a SBM response	Percentage of participants with a SBM response	Number of participants with adverse events
Results	<ul style="list-style-type: none"> Naldemedine: n = 54 Placebo: n = 18 81.5% frequency of TEAE with naldemedine vs 50.0% frequency with placebo Abdominal pain most frequent Frequency generally increased with dose 	<ul style="list-style-type: none"> Naldemedine: n = 183 Placebo: n = 61 Statistically significant increase in mean weekly SBM frequency in 0.2-mg group and 0.4-mg group compared with placebo No significant difference in frequency between 0.2-mg and 0.4-mg doses No significant difference in frequency between 0.1-mg dose and placebo 	<ul style="list-style-type: none"> Naldemedine: n = 274 Placebo: n = 273 47.6% responders in naldemedine group vs. 34.6% responders in placebo group 	<ul style="list-style-type: none"> Naldemedine: n = 277 Placebo: n = 276 52.5% responders in naldemedine group vs. 33.6% responders in placebo group 	<ul style="list-style-type: none"> Naldemedine: n = 621 Placebo: n = 619 68.4% incidence of TEAEs in naldemedine group vs. 72.1% incidence in placebo group GI TEAEs more frequent in naldemedine group than in placebo group
Conclusions	<ul style="list-style-type: none"> Single doses generally well tolerated Best benefit–risk profile observed with 0.3-mg dose 	<ul style="list-style-type: none"> 0.2 mg once daily is optimal dose for future confirmatory trials in OIC due to improved safety profile over 0.4-mg dose 	<ul style="list-style-type: none"> Supports that naldemedine could be a new option for OIC in patients with chronic non-cancer pain 	<ul style="list-style-type: none"> Supports that naldemedine could be a new option for OIC in patients with chronic non-cancer pain 	<ul style="list-style-type: none"> Treatment with naldemedine generally well tolerated

SBM = spontaneous bowel movement; TEAE = treatment-emergent adverse event; OIC = opioid-induced constipation; GI = gastrointestinal.

and 3.0-mg tablets compared to placebo. A total of 72 patients aged 18 to 65 years with chronic non-cancer pain and opioid-induced bowel dysfunction (no more than five spontaneous bowel movements [SBMs] during the two weeks prior to receiving study drug) were enrolled. Nine were assigned to each naldemedine dose in the fasted state, and 18 were given placebo in the fasted state.^{11,15}

The primary objective was to evaluate the safety of single doses of oral naldemedine in opioid-dependent patients. This was assessed by identifying the number of participants with adverse events during the study time frame, from the first dose of study drug on Day 15 to Day 24.^{15,16} Patients in the naldeme-

dine groups reported more treatment-emergent adverse events (TEAEs) (81.5%) than those in the placebo group (50.0%). Increasing doses generally lead to increased frequency of specific TEAEs, with abdominal pain being the most frequently reported (16.7% of those on placebo and 46.3% of those on any dose of naldemedine). Greater than 10% of patients also experienced nausea, diarrhea, hyperhidrosis, vomiting, chills, dizziness, flatulence, and headache. Severe TEAEs were reported with naldemedine 1.0 mg (drug withdrawal syndrome occurring in one patient) and 3.0 mg (six occurrences of abdominal pain, diarrhea, nausea/vomiting, or chills).¹⁵

Change in the number of SBMs per

day was also assessed as a secondary outcome measure of efficacy. The change in the number of SBMs per day from baseline to 24 hours post-dose was 1.83, 3.76, and 4.77 in the naldemedine 0.3-mg, 1.0-mg, and 3.0-mg groups, respectively, and 0.29 in the placebo group ($P < 0.0001$ for all naldemedine groups versus placebo). However, the change in the naldemedine 0.01-mg, 0.03-mg, and 0.1-mg mg groups was not significant.^{6,10} These findings indicate that patients with opioid-induced bowel dysfunction generally tolerate single doses of naldemedine well, with naldemedine 0.3 mg having the best benefit–risk profile.¹⁵

NCT01443403

Webster et al. conducted a subsequent four-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2b study evaluating the safety and efficacy of naldemedine 0.1-mg, 0.2-mg, and 0.4-mg tablets once daily in patients with OIC on long-term opioid therapy for chronic non-cancer pain. A total of 244 patients aged 18 years or older were randomized, evenly distributed among the three naldemedine groups and a fourth placebo group.¹⁷

The primary efficacy endpoint was the change from baseline to the last two weeks of treatment in weekly SBM frequency. While the increase in frequency of weekly SBMs was not significant with naldemedine 0.1 mg (1.98, $P=0.3504$), it was significantly higher with naldemedine 0.2 mg (3.37, $P=0.0014$) and 0.4 mg (3.64, $P=0.0003$), compared with placebo recipients (1.42). Secondary endpoints included the percentage of SBM responders (patients with ≥ 3 SBMs per week and a ≥ 1 SBM per week increase from baseline over the last two weeks of treatment). While the increase in percentage of SBM responders was not significant with naldemedine 0.1 mg (52.5%, $P=0.1461$), the percentage of responders was significantly higher with naldemedine 0.2 mg (71.2%, $P=0.0005$) and 0.4 mg (66.7%, $P=0.003$), compared with placebo (39.3%).^{11,17}

The study also evaluated safety measures such as incidence of adverse events, impact on analgesia, and symptoms of opioid withdrawal. The incidence of TEAEs increased with naldemedine dose, with TEAEs generally being mild to moderate in severity and GI disorders such as abdominal pain, diarrhea, flatulence, and nausea being the most common. No clinically meaningful changes were seen among other safety measures.¹⁷

These findings indicate that the use of naldemedine 0.2 mg and 0.4 mg once daily to relieve OIC in patients with chronic non-cancer pain on long-term opioid therapy is efficacious without compromising analgesia or causing opioid withdrawal symptoms. Because naldemedine 0.2 mg had an improved safety profile in the study over naldemedine 0.4 mg, the 0.2-mg once daily dose was used in future confirmatory trials in OIC.¹⁷

NCT01965158 (COMPOSE I) and NCT01993940 (COMPOSE II)

Hale et al. conducted two multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 studies evaluating the efficacy and safety of naldemedine for the treatment of OIC in patients with chronic non-cancer pain in 68 outpatient sites in seven countries (COMPOSE I) and 69 outpatient sites in six countries (COMPOSE II) in Europe and the United States. The studies evaluated 547 patients in COMPOSE I and 553 patients in COMPOSE II aged 18 to 80 years with OIC and chronic non-cancer pain treated with opioids for at least three months and with at least one month of an average total daily dose equivalent to ≥ 30 mg of oral morphine sulfate prior to screening. At screening, patients were required to discontinue all laxative therapy until the end of the study. Patients could use rescue laxative therapy if they did not have a SBM during screening and treatment for a 72-hour period. Patients were evenly distributed between naldemedine 0.2 mg or placebo once daily for 12 weeks.^{11,18}

The primary endpoint was the percentage of responders with at least nine positive-response weeks (at least three SBMs per week and an increase from baseline of at least one SBM per week) of the 12-week study and three or four positive-response weeks of the previous four weeks. The naldemedine group had a significantly greater percentage of responders than the placebo group in both studies, with 130 responders out of 273 patients (47.6%) in the naldemedine group compared to 94 responders out of 272 patients (34.6%) in the placebo group in COMPOSE I (difference of 13.0% [95% CI, 4.8–21.3]; $P=0.002$) and 145 out of 276 patients (52.5%) in the naldemedine group compared to 92 out of 274 patients (33.6%) in the placebo group in COMPOSE II (difference of 18.9% [95% CI, 10.8–27.0]; $P<0.0001$).^{11,18}

The studies included a safety population consisting of patients who received at least one dose of naldemedine, and patients were analyzed by the treatment actually received. Adverse events occurred with a similar frequency between the naldemedine group and the placebo group, with 132 of 271 patients (49%) in the naldemedine group compared to 123 out of 272 patients (45%) in

the placebo group in COMPOSE I and 136 out of 271 patients (50%) in the naldemedine group compared to 132 out of 274 patients (48%) in the placebo group in COMPOSE II. Observable TEAEs occurred in 59 out of 271 patients (22%) in the naldemedine group compared to 45 out of 272 (17%) in the placebo group in COMPOSE I and in 54 (20%) of 271 patients in the naldemedine group compared to 31 out of 274 patients (11%) in the placebo group of COMPOSE II. GI disorders were more common with naldemedine than with placebo, with 40 patients (15%) in the naldemedine group compared to 18 patients (7%) in the placebo group in COMPOSE I and 42 patients (16%) in the naldemedine group compared to 20 patients (7%) in the placebo group in COMPOSE II.¹⁸

Naldemedine use in both trials led to a much higher percentage of responders than use of placebo did, with comparable rates of adverse events. This supports the use of naldemedine as a new option for treating OIC in patients with chronic non-cancer pain.¹⁸

NCT01965652 (COMPOSE III)

Webster et al. conducted a multicenter, randomized, double-blind, placebo-controlled phase 3 study evaluating the long-term safety and efficacy of naldemedine over 52 weeks in patients with chronic non-cancer pain and OIC.¹⁹ A total of 1,240 patients aged 18 to 80 years with chronic non-cancer pain for at least three months, reporting OIC, and on a stable opioid regimen (≥ 30 mg morphine-equivalent) for at least one month were equally divided between naldemedine 0.2-mg tablets or placebo once daily.^{19,20} Patients may have been on laxatives and were required to have had no more than four SBMs in a 14-day qualifying period and no more than three SBMs per week in any given week in those 14 days in order to be enrolled.^{11,19}

The primary objective was to assess the long-term safety of naldemedine versus placebo. The occurrence of TEAEs was similar for both groups, with a 68.4% frequency with naldemedine and a 72.1% frequency with placebo. TEAEs reported for more than 5% of subjects and more frequently in the naldemedine group than the placebo group included abdominal pain, diarrhea, and vomiting.¹⁹

Secondary endpoints assessing the

efficacy of naldemedine versus placebo included the number of SBMs per week over time, change in opiate withdrawal scales, and the impact on opiate-mediated analgesia. A larger increase from baseline in the frequency of SBMs per week was seen in the treatment group than with placebo and was statistically significant at all assessed time points (weeks 12, 24, 36, and 52 [nominal $P \leq 0.0001$]).^{11,19} Signs and symptoms of opioid withdrawal were not seen following use of naldemedine. Opiate-mediated analgesia was also not affected by the use of naldemedine.¹⁹

This study demonstrated that the use of naldemedine was generally well tolerated, with a frequency of TEAEs similar to that for placebo. Naldemedine treatment resulted in a larger increase in frequency of SBMs per week from baseline and did not cause opioid withdrawal or affect opiate-mediated analgesia.¹⁹

SAFETY AND TOLERABILITY

Naldemedine is generally well-tolerated. Comparable rates of TEAEs were seen between naldemedine and placebo groups in the COMPOSE I-III trials. GI disorders, such as abdominal pain, nausea, and vomiting, occurred more frequently in the naldemedine group.^{18,19} An earlier study (NCT01122030) observed more TEAEs in the naldemedine groups (81.5%) than the placebo group (50.0%). A patient in the study also experienced drug withdrawal syndrome on naldemedine 1.0 mg and six patients developed more severe abdominal pain, diarrhea, nausea, vomiting, or chills on naldemedine 3.0 mg.¹⁵

The incidence of TEAEs generally increases with dose. The use of naldemedine to relieve OIC among patients with chronic non-cancer pain in study NCT01443403 at a dose of 0.2 mg once daily for 4 weeks was efficacious without compromising analgesia or causing opioid withdrawal symptoms.¹⁷

CONTRAINDICATIONS, PRECAUTIONS, AND SPECIAL PATIENT POPULATIONS

Known or suspected GI obstruction and increased risk of recurrent obstruction are contraindications for use of naldemedine, due to the potential risk of GI perforation. Patients with a history of hypersensitivity reactions to naldemedine, such as bronchospasm and rash,

are also contraindicated. Patients with conditions that may result in weakened integrity of the walls of the GI tract have had cases of perforation of the wall following use of another peripherally acting opioid antagonist.⁹ The COMPOSE I and II trials had occurrences of possible opioid withdrawal based on investigator assessment in 1% of both naldemedine and placebo groups. In COMPOSE III, 3% of recipients on naldemedine and 1% of recipients on placebo experienced possible opioid withdrawal. Symptoms of hypersensitivity (bronchospasm or rash) occurred in two patients following a single dose of naldemedine.¹¹

No data are available regarding the risk of major birth defects and miscarriage associated with naldemedine use in pregnancy, due to a lack of data regarding use in this population; however, it should be noted that the fetus of a pregnant woman using naldemedine may experience opioid withdrawal. Use of naldemedine during pregnancy should only be considered if the predicted benefit outweighs the possible risk.⁵ In a rat embryo-fetal development study, there were no observable abnormalities in development after naldemedine was given by mouth during organogenesis at doses leading to systemic exposure approximately 23,000 times the human AUC at recommended human doses of 0.2 mg per day. After giving naldemedine to rabbits by mouth during organogenesis at doses leading to systemic exposure approximately 226 times the human AUC at the recommended human dose, no adverse effects on embryo-fetal development were seen.⁹

There is also a lack of information regarding the effect of naldemedine on human milk production, the effect on breastfed infants, or its presence in human milk. Due to the possibility of serious adverse reactions, health care providers should discuss with patients the options of discontinuing breastfeeding or naldemedine, with consideration to the importance of the medication to the mother. If administration of the medication is ceased to reduce exposure to an infant being breastfed, women may resume breastfeeding three days after the final dose of naldemedine is given.⁹

The safety and effectiveness of naldemedine in pediatric patients has not been determined, whereas no overall differences in safety and effectiveness of nal-

medine have been observed in patients aged 65 years or older compared to younger patients. In older adults, however, there is a possibility for increased sensitivity in certain individuals, as this has not been studied. No age-related differences in the pharmacokinetics of the medication were seen during a population pharmacokinetic analysis.⁹

Drug Interactions

Concomitant use of strong hepatic CYP3A inducers, such as rifampin, carbamazepine, phenytoin, and St. John's Wort, leads to significant reductions in plasma concentrations of naldemedine, which may reduce its efficacy. Alternatively, an increase in plasma concentrations of naldemedine will result if given with moderate or strong CYP3A inhibitors or P-gp inhibitors, such as amiodarone, captopril, cyclosporine, quercetin, quinidine, and verapamil. There is a potential for additive opioid receptor antagonism and increased potential for opioid withdrawal if naldemedine is given concurrently with other opioid antagonists.⁹

DOSAGE AND ADMINISTRATION

It is recommended that naldemedine be given by mouth without regard to food at a dose of 0.2 mg once each day. The product is supplied as yellow, round, film-coated tablets.⁹

COST AND P&T COMMITTEE CONSIDERATIONS

In a retrospective cohort study of 434,304 hospital patients, 2,493 of 19,373 patients receiving oral opioid treatment also received medication for constipation and 477 patients received medication for nausea, vomiting, and constipation. The average cost of treatment was \$8,554 for patients receiving medication for constipation and \$8,054 for patients receiving medication for nausea, vomiting, and constipation in this study. Patients who did not receive medication for nausea, vomiting, or constipation had an average treatment cost of \$5,831.²¹ For OIC not responding to laxatives: lubiprostone, methylnaltrexone, and naloxegol are also available. There are limited comparative data and no head-to-head studies of naldemedine with these other agents utilized in the treatment of OIC. The choice of agents will therefore depend on patient and prescriber preference, as well as

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cost considerations. The Average Wholesale Price (AWP) for a 30-day supply of lubiprostone 24 mcg orally twice daily is \$445.32; methylnaltrexone 450 mg (three 150-mg tablets) orally once daily is \$1,962.00; and naloxegol 25 mg orally once daily is \$414.04 (as of September 6, 2018).^{22, 23} By comparison, the AWP for a 30-day supply of naldemedine 0.2 mg orally once daily is \$376.74.²²

CONCLUSION

For patients experiencing OIC after taking an opioid medication for chronic non-cancer pain, naldemedine is available as a treatment option. For P&T committees considering naldemedine for addition to the formulary, naldemedine represents an alternative to increase bowel movements among patients experiencing OIC, without compromising analgesia or causing opioid withdrawal symptoms.

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