Novel Agent Helps Cut Opioid-Induced GI Adverse Events

BY ROXANNE NELSON
Contributing Writer

SAN ANTONIO — Alvimopan is effective in relieving gastrointestinal adverse events associated with opioid administration, according to preliminary data.

"We were able to demonstrate that alvimopan, a μ-opioid receptor antagonist that is taken orally, was able to increase bowel function significantly," lead investigator Dr. Lynn Webster reported in a poster during the annual meeting of the American Pain Society Meeting. "At several different doses, the side effects were similar to what was seen with placebo."

Patients using opioids to treat chronic moderate to severe pain often develop gastrointestinal adverse events, including constipation, abdominal pain and discomfort, and bloating. These side effects can prevent some patients from adequately managing their pain.

"There is a very significant need for this type of agent," said Dr. Webster, medical director of a group practice in Salt Lake City. "About 50% of my patients have a significant bowel dysfunction from opioid use, and it sometimes limits the amount of opioids that they can be given."

The problem can be life threatening, causing complications such as bowel perforation in some patients, he added.

'About 50% of my patients have a significant bowel dysfunction from opioid use, and it sometimes limits the amount of opioids that they can be given' for their pain.

The efficacy of alvimopan was evaluated in a 6-week study of 522 patients receiving opioid treatment for persistent noncancer pain. The phase IIb double-blind design randomized patients to 0.5 mg alvimopan twice daily, 1 mg alvimopan once daily, 1 mg alvimopan twice daily, or placebo.

Patients in all of the groups reported an average frequency of one spontaneous bowel movement (SBM) per week during the baseline period. The average increase in SBMs per week during the treatment period was about 3.5 in the two daily alvimopan groups, and 4.3 in the twice daily group; the increases were significantly greater than the 1.7 increase seen among patients given placebo.

The increase in SBMs was apparent within the first week of the study, was sustained throughout the entire treatment period, and returned toward baseline when alvimopan was discontinued.

Patients on active therapy also reported improvements in straining, stool consistency, completeness of evacuation, and abdominal pain and bloating, compared with placebo. Overall, 40% of the patients who received alvimopan reported moderate to substantial improvement in constipation, vs. 14% with placebo. Patients using alvimopan also reported a significantly lower need for rescue laxatives.

The most common adverse events reported in the trial were abdominal pain, nausea, and diarrhea, occurring in 30%-43% of patients on active therapy and 36% of those on placebo. Overall, withdrawal rates for adverse events were 13% or lower across all treatment groups. The best benefit-to-risk profile was seen with the 0.5 mg twice-daily dose.

"The important thing is that we demonstrated efficacy with a low risk of adverse events," Dr. Webster said. "Any opportunity that we have to restore as much normal bowel function as possible, with very little side effect and risk, presents a great opportunity." ■

No Needle Needed: Postop Pain Controller Gains FDA Approval

BY ELIZABETH MECHCATIE
Senior Writer

A patient-activated transdermal product for short-term management of acute postoperative pain in adults requiring opioid analgesia has received Food and Drug Administration approval.

The fentanyl iontophoretic transdermal system, marketed under the trade name IONSYS by Alza Corp., was approved for use only in hospitalized patients.

In an interview, Dr. Eugene R. Viscusi, director of regional anesthesia and acute pain management at the medical school of Thomas Jefferson University, Philadelphia, described IONSYS as a compact, preprogrammed, needle-free system that provides an alternative to administering morphine via intravenous patient-controlled analgesia (PCA).

Each unit is about 2 by 3 inches, with adhesive backing and a dosing button. The patient double clicks the button when analgesia is needed, and 40 mcg of fentanyl is delivered over 10 minutes.

The approval of IONSYS and of DepoDur, a sustained-release injectable morphine for epidural use approved in 2004, illustrates the movement of postoperative analgesia "into this realm of less invasive and less burdensome technologies" that are more user-friendly and less cumbersome for patients and nursing staff, noted Dr. Viscusi. He has served as a scientific adviser to Alza, which has provided research support to Thomas Jefferson University.

IONSYS is applied to intact, nonirritated, nonirradiated skin on the chest or upper outer arm, and is replaced every 24 hours or when 80 doses have been administered. A maximum of 6 doses per hour and 80 doses over 24 hours can be administered; no more than 1 dose every 10 minutes can be released. Patients should be titrated to comfort before starting treatment, the label says.

IONSYS was compared with placebo or with IV PCA morphine in seven studies of 3,392 patients (2,114 using IONSYS) aged 18-90 years, with body types ranging from very thin to obese. In those studies, IONSYS provided effective acute pain management after a variety of surgical procedures, including orthopedic, general, and gynecologic surgery, according to Dr. Viscusi. The most common adverse effects among those treated with IONSYS included nausea, vomiting, application site–related erythema, fever, and headache.

Dr. Viscusi was the lead author of a study in which more than 600 postoperative adult patients were randomly assigned to either IONSYS or IV PCA. The patients rated the two approaches "as basically therapeutically equivalent" in terms of pain control after 24 hours of treatment, he said. Opioid-related side effects were comparable in the study (JAMA 2004;291:1333-41).

Other aspects of the transdermal system have not been directly compared with IV PCA, but because IONSYS is compact, self-contained, and needle-free, Dr. Viscusi believes that it should be easier to use, won't impede physical therapy or patient activity, and will reduce the risk of medication errors, compared with IV PCA.

Fentanyl is a schedule II drug with a high potential for abuse. ■

ORTHO-MCNEIL, INC.

IONSYS is a compact, preprogrammed, needle-free system that provides an alternative to administering morphine intravenously.

Tysabri Is Back, With Black Box Warning

BY ELIZABETH MECHCATIE
Senior Writer

Safety information that has been added to the revised label of natalizumab is highlighted in a "dear healthcare professional" letter and timed to coincide with the reintroduction of the monoclonal antibody in the United States as monotherapy for people with relapsing forms of multiple sclerosis.

The letter, released in July by Biogen Idec and Elan, the companies that market natalizumab as Tysabri, includes a copy of the black box warning about the risk of progressive multifocal leukoencephalopathy (PML) associated with treatment. It also refers to the two cases of PML diagnosed in 1,869 patients with MS who were treated with natalizumab for a median of 120 weeks, and a third case in a patient with Crohn's disease who had received 8 doses, among 1,043 patients with Crohn's who received the treatment.

The warning also includes the recommendation that health care professionals monitor patients on natalizumab for any new sign or symptoms "that may be suggestive of PML," and that treatment should be immediately stopped at the first sign or symptom suggestive of PML.

Because of this risk, which cannot be precisely estimated, the Food and Drug Administration approved the reintroduction of natalizumab under a restricted distribution program, called the TOUCH Prescribing Program, which requires prescribing physicians, infusion centers, and pharmacies associated with infusion centers to register with the program to prescribe, distribute, or infuse the product.

Natalizumab was approved in November 2004, and withdrawn by the manufacturer in February 2005 after two cases of PML were reported. Earlier this year, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee recommended that natalizumab should become available again, with a stringent risk management program, and that it be limited to patients with relapsing features of the disease, only as monotherapy. ■

The dear doctor letter is available on the FDA's Medwatch site at www.fda.gov/medwatch/safety/2006/safety06.htm#Tysabri. The letter advises health professionals to report serious adverse events possibly associated with natalizumab to Biogen Idec at 1-800-456-2255, or to the FDA's MedWatch adverse event reporting program by phone (1-800-FDA-1088), online at www.fda.gov/medwatch, or by mail to MedWatch, HF-2, 5600 Fishers Lane, Rockville, Md. 20852-9787.