FDA Approves 7-Day Buprenorphine Pain Patch

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July 8, 2010 — The US Food and Drug Administration (FDA) has approved a once-weekly buprenorphine transdermal system (Butrans; Purdue Pharma LP) for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period. The patches will be available in 5, 10, and 20 μg/hour strengths.

Buprenorphine is a schedule III controlled substance with partial agonist activity at the μ-opioid receptor and competitive antagonist activity at the kappa opioid receptor. The patch represents a new formulation for the opioid, which previously was available as an intramuscular/intravenous injection (Buprenex; Reckitt Benkiser Pharmaceuticals, Inc) for the relief of moderate to severe pain.

"Healthcare professionals now have an important new option for appropriate adult patients suffering from moderate to severe chronic pain when an opioid may be needed to manage their pain," said Lynn R. Webster, MD, FACPM, FASAM, medical director of the Lifetree Clinical Research and Pain Clinic in Salt Lake City, Utah, in a company news release.

Buprenorphine patches should only be used in patients requiring continuous opioid therapy for an extended time; use is contraindicated in the management of acute or short-term pain, postoperative pain, mild pain, and intermittent pain.

Clinical Study Findings

FDA approval of the product was based on data from 2 randomized, double-blind, clinical studies of patients with moderate to severe chronic lower back pain who underwent an open-label dose-titration phase before randomization to a 12-week study period.

In the first study, 53% of 1024 opioid-naive patients achieved a tolerable and effective dose of 10 or 20 μg/hour buprenorphine — 23% discontinued use because of adverse events, 14% discontinued use because of lack of therapeutic effect, and 10% were dropped for various administrative reasons. The remaining 539 patients were randomly assigned to continued treatment or placebo for 12 weeks.

Results showed that the mean pain score during the last 24 hours at the end of the study (week 12/early termination) was significantly lower for patients on the buprenorphine patch relative to placebo, as evaluated on an 11-point, 0 to 10 numerical rating scale. Of 256 patients receiving buprenorphine, 9% discontinued use because of lack of efficacy, and 16% discontinued use because of adverse events (vs placebo, 13% and 7%, respectively).

In the second study, 57% of 1160 opioid-tolerant enrollees were able to titrate to, and tolerate, a 20 μg/hour buprenorphine patch during the open-label phase after taper of prior opioids; 12% of patients discontinued use because of adverse events, and 21% discontinued use because of lack of therapeutic effect. The remaining patients were randomly assigned to receive either continued treatment with the 20 μg/hour patch or a low, 5 μg/hour, dose.

Results showed that the 20 μg/hour buprenorphine patch yielded a significant decrease in mean pain score relative to the 5 μg/hour patch, and a higher proportion of those receiving 20 μg/hour buprenorphine achieved a 30% or greater reduction in pain score from baseline (49% vs 33%). During the treatment phase, 11% of patients receiving 20 μg/hour buprenorphine discontinued use because of lack of efficacy and 13% discontinued use because of adverse events (vs 5 μg/hour dose, 24% and 6%, respectively).

Two additional studies were conducted of the buprenorphine patch: one low back pain study failed to show efficacy, and an osteoarthritis study failed to show efficacy for both the patch and the active comparator.

The most commonly reported treatment-related adverse events (incidence ≥ 5%) included nausea, headache, application-site pruritus, dizziness, constipation, somnolence, vomiting, application-site erythema, dry mouth, and application-site rash. Rare cases of severe application-site reactions with signs of marked inflammation, including burn, discharge, and vesicles, have occurred within days to months of treatment initiation.
Administration of Drug

Buprenorphine patches should be applied on a rotating basis to sites on the outer arm, upper chest, upper back, or side of chest once every 7 days. Because of the risk for QTc interval prolongation, the dose should not exceed a single 20 μg/hour patch. Patch exposure to direct heat sources should be avoided because temperature-dependent increases in buprenorphine exposure can lead to overdose and death.

For opioid-naive patients and those with mild to moderate hepatic impairment, buprenorphine therapy should be initiated with a 5 μg/hour patch.

When converting opioid-tolerant patients to buprenorphine patches, current around-the-clock therapy should be tapered for up to 7 days to no more than 30 mg oral morphine or equivalent daily. Patients originally requiring less than 30 mg oral morphine equivalents daily should start buprenorphine therapy with a 5 μg/hour patch; those requiring between 30 and 80 mg oral morphine equivalents daily should start with a 10 μg/hour patch.

Up-titration may be instituted at a minimum interval of 72 hours; the 20 μg/hour patch may not provide adequate analgesia for patients requiring more than 80 mg/day oral morphine equivalents.

Warnings/Precautions and Adverse Events

As cited in the black-box safety labeling warning for the product, buprenorphine patches are linked to a risk for misuse, abuse, and diversion, particularly in patients with a history of substance abuse or mental illness. As a consequence, the company and FDA have developed a risk evaluation and mitigation strategy that includes a medication guide, elements to ensure safe use (eg, clinician training), and a timetable for submitting required assessments.

Because respiratory depression is the chief hazard of buprenorphine and other opioids, extreme caution is advised when treating patients with significant chronic obstructive pulmonary disease or cor pulmonale; other risks for substantially decreased respiratory reserve include asthma, severe obesity, sleep apnea, myxedema, clinically significant kyphoscoliosis, central nervous system depression, hypoxia, hypercapnia, and preexisting respiratory depression. Treatment is contraindicated in those with significant respiratory depression and severe bronchial asthma.

Additive effects on central nervous system depression should be expected with coadministration of alcohol, other opioids, benzodiazepines, skeletal muscle relaxants, or illicit drugs. Buprenorphine should not be used within 2 weeks of monoamine oxidase inhibitors.

Because of the potential for QTc interval prolongation, buprenorphine should not be used in patients with long QT syndrome or a family history thereof and those taking class 1A or class 3 antiarrhythmic medications.

In patients with head injury, buprenorphine may worsen increased intracranial pressure and obscure its signs, such as level of consciousness or miosis.

Treatment with buprenorphine can cause severe hypotension and should be approached with caution in patients at increased risk and those in circulatory shock.

Buprenorphine may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Postoperative patients should be monitored for decreased bowel motility.

Sublingual tablets containing 2 mg and 8 mg buprenorphine alone (Subutex; Reckitt Benkiser Pharmaceuticals, Inc) and 0.5 mg and 2 mg naloxone, respectively (Suboxone; Reckitt Benkiser), previously were approved for the treatment of opioid dependence.