

Preliminary Update Scan of Newly-Approved Long-Acting Opioids

Butrans (buprenorphine transdermal)

FDA approval:

- 6/30/2010
- For management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Citations identified in Medline/Cochrane Controlled Trials Register Search (N=4):

Gordon, A., S. Rashiq, et al. "Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain." *Pain Research & Management* **15**(3): 169-78.

OBJECTIVE: The present randomized, double-blinded, crossover study compared the efficacy and safety of a seven-day buprenorphine transdermal system (BTDS) and placebo in patients with low back pain of moderate or greater severity for at least six weeks. METHODS: Prestudy analgesics were discontinued the evening before random assignment to 5 microg/h BTDS or placebo, with acetaminophen 300 mg/codeine 30 mg, one to two tablets every 4 h to 6 h as needed, for rescue analgesia. The dose was titrated to effect weekly, if tolerated, to 10 microg/h and 20 microg/h BTDS. Each treatment phase was four weeks. RESULTS: Fifty-three patients (28 men, 25 women, mean [+/- SD] age 54.5+/-12.7 years) were evaluable for efficacy (completed two weeks or more in each phase). Baseline pain was 62.1+/-15.5 mm (100 mm visual analogue scale) and 2.5+/-0.6 (five-point ordinal scale). BTDS resulted in lower mean daily pain scores than in the placebo group (37.6+/-20.7 mm versus 43.6+/-21.2 mm on a visual analogue scale, P=0.0487; and 1.7+/-0.6 versus 2.0+/-0.7 on the ordinal scale, P=0.0358). Most patients titrated to the highest dose of BTDS (59% 20 microg/h, 31% 10 microg/h and 10% 5 microg/h). There were improvements from baseline in pain and disability (Pain Disability Index), Pain and Sleep (visual analogue scale), Quebec Back Pain Disability Scale and Short-Form 36 Health Survey scores for both BTDS and placebo groups, without significant differences between treatments. While there were more opioid-related side effects with BTDS treatment than with placebo, there were no serious adverse events. A total of 82% of patients chose to continue BTDS in a long-term open-label evaluation, in whom improvements in pain intensity, functionality and quality of life were sustained for up to six months without analgesic tolerance. CONCLUSION: BTDS (5 microg/h to 20 microg/h) represents a new treatment option for initial opioid therapy in patients with chronic low back pain.

Landau, C. J., W. D. Carr, et al. (2007). "Buprenorphine transdermal delivery system in adults with persistent noncancer-related pain syndromes who require opioid therapy: a multicenter, 5-week run-in and randomized, double-blind maintenance-of-analgesia study." *Clinical therapeutics* **29**(10): 2179-93.

OBJECTIVE: This study compared the efficacy and safety profile of buprenorphine transdermal delivery system (BTDS) and placebo in subjects with persistent noncancer-related pain who required opioid analgesics. **METHODS:** This was a multicenter, double-blind, parallel-group study in adult subjects (age ≥ 18 years) with at least a 2-month history of noncancer-related pain for which they received oral opioid combination agents. The study employed a maintenance-of-analgesia, or randomized-withdrawal, design. During a 7- to 21-day open-label run-in phase, all subjects received BTDS, titrated as needed. Subjects who achieved stable pain control and were able to tolerate BTDS in the run-in phase were randomly assigned to continue BTDS at the dose achieved during the run-in phase or to receive placebo for up to 14 days. Acetaminophen 500-mg tablets were provided as escape (rescue) medication. Subjects completed the study on day 14 or when they met predefined criteria for ineffective treatment: requiring >1 g of acetaminophen as escape medication on any day of the double-blind evaluation phase, requiring a change in study drug dose, having difficulty keeping the patch affixed, or discontinuing because of ineffective treatment without meeting any of the first 3 criteria. The primary efficacy variable was the proportion of subjects with ineffective treatment. Secondary efficacy variables were the time to ineffective treatment; the proportion of subjects who reached ineffective treatment or discontinued for any reason other than ineffective treatment; and the amount of escape medication used. Assessment of the safety profile was based on adverse events and changes in vital signs and physical and laboratory findings. **RESULTS:** Five hundred eighty-eight subjects entered the open-label run-in phase, and 267 (129 BTDS, 138 placebo) were subsequently randomized to doubleblind treatment. Demographic characteristics were similar between the double-blind BTDS and placebo groups (61.2% and 63.8% female, respectively; 99.2% and 98.6% white; mean [SD] age, 56.2 [13.3] and 59.2 [11.5] years). In the primary efficacy analysis, the proportion of subjects with ineffective treatment was lower with BTDS than with placebo (51.2% vs 65.0%; 95% CI, 1.09-2.95); the odds of ineffective treatment were 1.79 times greater for placebo relative to BTDS ($P = 0.022$). In the secondary efficacy analyses, the median time from the first dose of double-blind study drug to ineffective treatment was significantly longer with BTDS than with placebo (median, 10 vs 3 days; $P = 0.011$). The proportion of subjects who reached ineffective treatment or discontinued for reasons other than ineffective treatment was lower in the BTDS group compared with the placebo group (55.0% vs 67.9%); the odds of ineffective treatment or discontinuation for a reason other than ineffective treatment was 1.76 times greater with placebo compared with BTDS ($P = 0.028$). The mean amount of escape medication used was significantly lower in the BTDS group than in the placebo group (1.7 vs 2.2 acetaminophen tablets per day; $P = 0.015$). The most common adverse events in the open-label run-in or double-blind phase occurring at a higher incidence with BTDS than with placebo were pruritus at the patch application site (9.3% vs 5.1%, respectively), headache (3.9% vs 2.2%), and somnolence (2.3% vs 0.7%). **CONCLUSION:** In this population of adult subjects with persistent noncancer-related pain who required opioid therapy, BTDS use was associated with analgesic efficacy and was generally well tolerated. Results

of this study were presented in part at the annual meeting of the American Pain Society, March 30-April 2, 2005, Boston, Massachusetts.

Munera, C., M. Drehabl, et al. "A randomized, placebo-controlled, double-blinded, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis." Journal of Opioid Management **6**(3): 193-202.

BACKGROUND: This multicenter, parallel-group, 35-day study in adults with osteoarthritis (OA) pain evaluated the analgesic efficacy and safety of buprenorphine transdermal system (BTDS) designed for 7-day wear. **METHODS:** Patients with OA pain inadequately controlled with nonsteroidal antiinflammatory drugs or patients who had taken opioids for OA pain within the past year entered a 7-day run-in period during which they took ibuprofen only. Patients with pain $>$ or $=$ on a 0-10 scale had their ibuprofen discontinued and were randomized into a 28-day double-blinded period to receive either BTDS at 1 of 3 dose levels (5, 10, or 20 microg/b) or placebo. Doses were titrated to effectiveness over a period of 21 days and maintained for 7 days. No rescue medication was allowed during the study. The primary efficacy measure was the proportion of patients who achieved treatment success, defined as a patient satisfaction score of good, very good, or excellent (on day 28 or at early discontinuation) for those who did not discontinue due to ineffective treatment. **RESULTS:** More BTDS-treated patients experienced treatment success than placebo TDS-treated patients (44 percent and 32 percent; odds ratio = 1.66, $p = 0.036$). Fewer patients taking BTDS titrated to the highest dose compared with placebo ($p < 0.05$). There were two serious adverse events (both in the placebo group) and no deaths. The most common ($>$ or $=5$ percent) adverse events reported in BTDS-treated patients were nausea, headache, dizziness, somnolence, application site pruritus, and vomiting. **CONCLUSION:** Compared with placebo, BTDS treatment was effective in treating patients with moderate to severe pain due to OA of the knee or hip. BTDS was well-tolerated.

Sorge, J. and R. Sittl (2004). "Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study." Clinical therapeutics **26**(11): 1808-20.

BACKGROUND: Buprenorphine, a potent opioid analgesic, has been available in parenteral and oral or sublingual (SL) formulations for >25 years. In 2001, the buprenorphine transdermal delivery system (TES) was introduced at 3 release rates (35, 52.5, and 70 microg/h) for the treatment of chronic cancer and noncancer pain. **OBJECTIVE:** This study compared the analgesic efficacy and tolerability of buprenorphine TES at a release rate of 35 microg/h with those of buprenorphine SL and placebo in patients with severe or very severe chronic cancer or noncancer pain. **METHODS:** This multicenter, double-blind, placebo-controlled, parallel-group trial was 1 of 3 Phase III studies involved in the clinical development of buprenorphine TDS. It comprised a 6-day open-label run-in phase in which patients received buprenorphine SL 0.8 to 1.6 mg/d as needed and a double-blind phase in which patients were randomized to receive 3 sequential patches containing buprenorphine TES 35 microg/h or placebo, each lasting 72 hours. Rescue analgesia consisting of buprenorphine SL 0.2-mg tablets was

available as needed throughout the double-blind phase. The main outcome measures were (1) the number of buprenorphine SL tablets required in addition to buprenorphine TES during the double-blind phase compared with the placebo group and compared with the buprenorphine SL requirement during the run-in phase, and (2) patients' assessments of pain intensity, pain relief, and duration of sleep uninterrupted by pain in the double-blind phase compared with the run-in phase. Adverse events were documented throughout the study. **RESULTS:** One hundred thirty-seven patients were included in the double-blind phase (90 buprenorphine TES, 47 placebo). The buprenorphine TES group included 47 men and 43 women (mean [SD] age, 56.0 [12.1] years), and the placebo group included 23 men and 24 women (mean age, 55.7 [12.9] years). Forty-five patients had cancer-related pain and 92 had noncancer-related pain. The 2 treatment groups were comparable with respect to sex distribution, age, height, and body weight. Patients receiving buprenorphine TES significantly reduced their consumption of buprenorphine SL tablets in the double-blind phase compared with patients receiving placebo (reduction of 0.6 [0.4] mg vs 0.4 [0.4] mg; $P = 0.03$). The relationship between the buprenorphine SL dose in the run-in phase and the number of buprenorphine SL tablets required in the double-blind phase was dose dependent in the active-treatment group only. Patients' assessments of pain intensity and pain relief suggested better analgesia with buprenorphine TES than with placebo, although the differences did not reach statistical significance. The proportion of patients who reported sleeping for >6 hours uninterrupted by pain in the double-blind phase compared with the run-in phase increased by 6.4% in the buprenorphine TDS group (35.6% vs 29.2%, respectively), compared with a decrease of 5.9% in the placebo group (40.4% vs 46.3%); no statistical analysis of sleep duration data was performed. Buprenorphine TDS was well tolerated, with adverse events generally similar to those associated with other opioids. The incidence of systemic adverse events in the double-blind phase was similar in the 2 treatment groups (28.9% buprenorphine TDS, 27.6% placebo), with the most common adverse events being nausea, dizziness, and vomiting. After patch removal, skin reactions (mainly mild or moderate pruritus and erythema) were seen in 35.6% of the buprenorphine TDS group and 25.5% of the placebo group. **CONCLUSIONS:** In the population studied, buprenorphine TDS provided adequate pain relief, as well as improvements in pain intensity and duration of pain-free sleep. It may be considered a therapeutic option for the treatment of moderate to severe chronic pain.

Embeda (combination morphine and naltrexone)

FDA approval

- 8/13/2009
- For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Citations identified in Medline/Cochrane Controlled Trials Register (N=3):

Jang, D. H., J. C. Rohe, et al. "Severe opioid withdrawal due to misuse of new combined morphine and naltrexone product (Embeda)." Annals of Emergency Medicine **55**(3): 303-4.

Katz, N., S. Sun, et al. "ALO-01 (morphine sulfate and naltrexone hydrochloride) extended-release capsules in the treatment of chronic pain of osteoarthritis of the hip or knee: pharmacokinetics, efficacy, and safety." Journal of Pain **11**(4): 303-11.

ALO-01 (EMBEDA [morphine sulfate and naltrexone hydrochloride] extended-release capsules [King Pharmaceuticals, Inc, Bridgewater, NJ]), indicated for chronic moderate-to-severe pain, is designed to release naltrexone upon tampering (eg, by crushing), reducing morphine-induced subjective effects. This multicenter, randomized, double-blind, crossover study assessed pharmacokinetics, efficacy, and safety of ALO-01 and compared them with extended-release morphine sulfate (ERMS, KADIAN [morphine sulfate extended-release] capsules [Actavis US, Morristown, NJ]) in adults (N = 113) with osteoarthritis pain. Study periods included washout until pain flare (intensity \geq 5, 0 to 10; 0 = no pain, 10 = worst pain); dose titration with ERMS (20 to 160mg BID); and randomization to 2 (crossover) 14-day treatment periods with ERMS or ALO-01, separated by 7 days of open-label ERMS. Assessments included pharmacokinetics (morphine, naltrexone), pain scores (0 to 10), Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index; Patient Global Assessment of Medication (1 to 5; poor to excellent). Mean score at pain flare was 7.1. Morphine exposure from both formulations at steady state was similar. Plasma naltrexone concentrations were below limit-of-quantification for most patients and, when present, did not impact pain scores. During treatment, mean pain intensity (day 14: ERMS, 2.4; ALO-01, 2.3, P = .31), WOMAC change-from-baseline (mean pain, physical function, composite scores), and adverse event frequency were similar. ALO-01 and ERMS provided similar relief of osteoarthritis pain. PERSPECTIVE: We present data demonstrating that ALO-01 has steady-state morphine exposure, efficacy, and safety similar to marketed ERMS capsules. Results highlight the potential for morphine in ALO-01 to manage moderate-to-severe osteoarthritis pain, while the sequestered naltrexone does not interfere with efficacy. Copyright 2010 American Pain Society. Published by Elsevier Inc. All rights reserved.

Stauffer, J., B. Setnik, et al. (2009). "Subjective effects and safety of whole and tampered morphine sulfate and naltrexone hydrochloride (ALO-01) extended-release capsules versus morphine solution and placebo in experienced non-dependent opioid users: a

randomized, double-blind, placebo-controlled, crossover study." Clinical Drug Investigation **29**(12): 777-90.

BACKGROUND AND OBJECTIVE: Given the dual public health challenges of undertreated pain and opioid abuse, there is a need to reduce attractiveness of opioid analgesics to drug abusers. ALO-01 (morphine sulfate and naltrexone hydrochloride) extended-release capsules, indicated for treatment of chronic, moderate to severe pain, contain polymer-coated pellets of morphine, each with a core of sequestered naltrexone intended for release only upon tampering (crushing). The purpose of this study was to assess the pharmacodynamic effects (including drug-liking and euphoria) of whole and crushed ALO-01 versus morphine sulfate solution (MSS) and placebo. **METHODS:** This was a randomized, double-blind, placebo-controlled, triple-dummy, four-way crossover study carried out at a clinical research centre. Participants were experienced non-dependent opioid users. Subjects were given either two ALO-01 60 mg capsules, crushed pellets from two ALO-01 60 mg capsules, MSS 120 mg or placebo; there was a 14- to 21-day washout between treatments. The primary endpoints were drug-liking visual analogue scale score, scores on items from the Addiction Research Center Inventory (ARCI) and Cole/ARCI scales characterizing abuse potential and euphoria, and pupil diameter as measured by pupillometry. **RESULTS:** Morphine plasma concentrations were similar after ALO-01 crushed and MSS, with a median time to reach maximum plasma concentration (t(max)) of 1.1 and 1.2 hours, respectively; the plasma naltrexone median t(max) was 1.1 hours after ALO-01 crushed. By comparison, the median t(max) for morphine with ALO-01 whole was 8.1 hours. The maximum effect (E(max)) of MSS was significantly greater than placebo on pupillometry and the subjective measures (all $p < 0.001$). ALO-01 whole and crushed produced lower E(max) values and flatter effect-time profiles for subjective measures and caused less pupillary constriction than MSS. **CONCLUSION:** The results of this study demonstrated that ALO-01, whether taken orally whole as intended or tampered with by crushing and taken orally, had reduced desirability compared with MSS.

Exalgo (hydromorphone extended release)

FDA approval:

- 3/1/2010
- For management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.

Citations identified in Medline/Cochrane Controlled Trials Register (N=2)

Grosset, A. B., M. S. Roberts, et al. (2005). "Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone in patients with persistent moderate to severe pain: two randomized controlled trials." Journal of Pain & Symptom Management **29**(6): 584-94.

Two multicenter, randomized, double-blind, crossover studies with identical designs evaluated the efficacy of oral extended-release hydromorphone (HHER) administered q24h compared with immediate-release hydromorphone (HHER) dosed four times daily in patients with persistent moderate to severe pain. Patients titrated to a stable HHER dose were randomized to individualized doses of HHER or HHER for 3 to 7 days before crossover to the second treatment. Primary efficacy end point was the mean of average pain intensity (API) scores, rated on a 0- to 10-point numeric scale, over the last 2 days before the pharmacokinetics/pharmacodynamics day of each double-blind period. Difference between treatments (HHER - HHER) in study 1 was 0.17 with a 90% confidence interval (CI) (-0.01, 0.34); in study 2, difference was 0.07 with a 90% CI (-0.12, 0.26). There were no significant differences between treatments in API scores or amount of rescue medication used at any time interval within the 24-hour dosing period. No reduction in pain control occurred in patients administered HHER at the end of the 24-hour dosing period. Most treatment-emergent adverse events were opioid-related. In these studies, HHER administered q24h and HHER dosed four times daily provided comparable analgesia at an equivalent total daily dose.

Hale, M., I. C. Tudor, et al. (2007). "Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, noninferiority analysis." Clinical Therapeutics **29**(5): 874-88.

OBJECTIVE: This study compared the efficacy and tolerability of a once-daily controlled-release formulation of hydromorphone (OROS) hydromorphone, Janssen-Cilag, Beerse, Belgium) and twice-daily extended-release (ER) oxycodone in patients with chronic, moderate to severe osteoarthritis (OA) pain. OROS hydromorphone is currently available only in Europe. **METHODS:** Adults who met American College of Rheumatology clinical criteria for OA of the knee or hip with moderate to severe mean daily pain intensity despite chronic use of stable doses of NSAIDs or other nonsteroidal, nonopioid therapies were eligible for participation in this randomized, open-label study. The study consisted of a 14-day dose-titration and stabilization phase and a 28-day maintenance phase. OROS hydromorphone and ER oxycodone were initiated at dosages of 8 mg QD and 10 mg BID, respectively. Patients maintained diaries in which they rated their

pain (from 0 = none to 3 = severe) and pain relief (from 0 = no relief to 4 = complete relief). Other assessments completed every 14 days included patient and investigator global evaluations of treatment effectiveness (scale from 1 = poor to 5 = excellent), the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, and the Medical Outcomes Study (MOS) Sleep Scale. Adverse events (whether observed by study personnel, identified in response to questioning, or spontaneously reported) and vital signs were monitored throughout the study. The primary efficacy measures were the mean pain relief score at end point and the time from initiation of treatment to the third day of moderate to complete pain relief, as reported in the patient diary. Noninferiority analyses were conducted on all primary and secondary efficacy variables.

RESULTS: One hundred thirty-eight patients (71 OROS hydromorphone, 67 ER oxycodone) received treatment (safety population), and 83 (60.1%) completed the study. Data from 124 patients were included in the efficacy analyses; the majority of these patients were white (85.5%) and female (69.4%), with a mean age of 63.6 years. The most commonly affected joint was the knee (79.8 %). At end point, the OROS hydromorphone group had a mean pain relief score of 2.3 (median, 2.0) and the ER oxycodone group had a mean pain relief score of 2.3 (median, 2.3) (95% CI, -0.30 to infinity). The mean time to the third day of moderate to complete pain relief was 6.2 days (median, 4.0) in the OROS hydromorphone group and 5.5 days (median, 5.0) in the ER oxycodone group (95% CI, -0.31 to infinity). Mean pain intensity decreased from baseline to end point by 0.6 point in the OROS hydromorphone group and by 0.4 point in the ER oxycodone group. Mean scores on the patient global evaluation improved by a respective 1.2 and 1.0 points (median, 1 in both groups). Approximately two thirds of patients in each group (67.2% and 66.7%) rated the overall effectiveness of treatment as good to excellent at end point. There were no statistically significant differences between groups in total WOMAC scores at end point, and similar improvements from baseline in the WOMAC physical function, stiffness, and pain scales were observed in both groups. Whereas MOS sleep outcomes scores improved from baseline in both groups, OROS hydromorphone was associated with a significantly greater improvement on the MOS Sleep Problems Index I compared with ER oxycodone ($P < 0.045$). Adverse events were comparable in both groups; the most frequently reported adverse events were nausea (35.2% and 29.9%), constipation (29.6% and 25.4%), somnolence (25.4% and 17.9%), vomiting (16.9% and 11.9%), and dizziness (14.1% and 22.4%). Adverse events led to study discontinuation in 35.2% (25/71) of patients in the OROS hydromorphone group and 32.8% (22/67) in the ER oxycodone group. Discontinuations due to adverse events during the titration phase were numerically greater in the OROS hydromorphone group (29.6% [21/71]) than in the ER oxycodone group (19.4% [13/67]). Only 1 serious adverse event (diarrhea in a patient receiving OROS hydromorphone)