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(388) A novel formulation of ibuprofen sodium is absorbed faster than standard ibuprofen tablets

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Ibuprofen (IBU) is a widely used, safe and effective, over-the-counter (OTC) analgesic. Rapid onset of action is a desirable attribute of OTC analgesics; therefore, faster-absorbed formulations have been developed. The objective of the 2 randomized, single-dose, open-label, 5-way crossover, pharmacokinetic studies conducted in 71 healthy adults (n=36 and n=35, respectively) described herein was to evaluate the rate and extent of IBU absorption from a novel IBU sodium (IBU_{Na}) tablet compared with several marketed IBU formulations. IBU_{Na} (2×256mg; each equivalent to 200mg IBU free acid) was bioequivalent to Advil® Liqui-Gels® (IBU_{LG}; 2×200mg) in the fasted and fed states, and to Advil® Fastgel® (IBU_{FG}; 2×200mg) and IBU lysine (Nurofen® Express [IBU_{Lys}]; 2×342mg; each equivalent to 200mg IBU free acid) in the fasted state for rate (maximum concentration [C_{max}]) and extent (area under the concentration-time curves to last measurement [AUC_L]) of IBU absorption. In the fasted state, IBU_{Na} was bioequivalent to Motrin®IB (IBU_{Mot}), Advil (IBU_{Adv}), and Nurofen (IBU_{Nur}; each 2×200mg) for extent of absorption, but was absorbed significantly faster than all 3 standard IBU tablets. In the fasted state, the median IBU_{Na} time to maximum concentration (T_{max}) was 30-35 minutes, comparable to IBU_{LG}, IBU_{FG}, and IBU_{Lys} (median T_{max}= 40, 40, and 35 minutes, respectively), but much shorter than IBU_{Mot}, IBU_{Nur}, and IBU_{Adv} (median T_{max}= 120, 120, and 82 minutes, respectively). In the fed state, IBU_{Na} and IBU_{LG} had the same median T_{max} (90 minutes). Adverse events (AEs) were balanced across treatments and mostly mild in severity. The most common AEs were headache and dizziness. These data demonstrate that IBU_{Na} is absorbed at a faster rate, but to a similar extent, as standard IBU tablets. Moreover, IBU_{Na} reaches peak concentrations in 30-35 minutes, comparable to other faster-absorbed IBU formulations, and >45 minutes faster than standard formulations. Funded by Pfizer Consumer Healthcare.

(389) A randomized, multi-Center, double-blind, placebo-controlled phase II/III trial to evaluate the efficacy, tolerability and safety of MRX-7EAT Etodolac-Lidocaine Topical Patch in the treatment of pain

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MRX-7EAT Etodolac-Lidocaine Topical Patch (4.4% w/w) is a novel, selective COX-2 inhibitor, non-steroidal anti-inflammatory drug (NSAID) patch, developed by using a novel transdermal delivery system based on a proprietary ionic liquid technology, ion-pair formulation paired with appropriate counter ion presence which allows for efficient transdermal delivery to local tissues. Etodolac-lidocaine is a new salt of etodolac with equimolar amounts of lidocaine. Phase I study of MRX-7EAT showed that Etodolac-Lidocaine patch has higher skin permeability than Etodolac-alone patch for local transdermal administration. No serious adverse event or death occurred. We conducted a Phase II/III, randomized, multi-center, double-blind, placebo controlled study in the U.S. to evaluate the safety and the efficacy of MRX-7EAT Etodolac-Lidocaine Topical Patch once daily application for 14 days in relieving shoulder acute pain due to recent onset of supraspinatus, subacromial bursitis/tendonitis and/or subdeltoid bursitis as described for > 24 hours and < 7 days and a Current Pain Intensity (CPI) of > 6 but < 8 on an 11-point Numeric Pain Rating Scale (NPRS) at the time study entry. The efficacy primary endpoint is a Mean of all 16 CPI scores collected on Days 11 through 14 on a 0-10 NPRS at four time points. This study enrolled approximately 210 subjects aged in 14 years old or older at 30 sites to achieve 95 evaluable subjects per group for 11 months, from December 2011 to October 2012. Currently, this study has been completed the enrollments. However, any result is not obtained because the data has not been locked. At this moment when all patients were completed this study, no serious adverse event has been occurred. The final study result plans to be presented at 32nd Annual Scientific Meeting of American Pain Society, 2013.

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(390) A prospective study of withdrawal-associated hyperalgesia in opioid dependent volunteers

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Spontaneous opioid withdrawal can affect opioid efficacy during both addiction and chronic pain treatment. Buprenorphine is approved for the office-based treatment of opioid dependence and chronic pain. Although there is some evidence that buprenorphine spontaneous withdrawal is mild, controlled comparisons to full mu opioid receptor agonists (i.e., morphine) are lacking. Six out-of-treatment opioid dependent male volunteers were admitted for a 59-day within-subject residential study of spontaneous opioid withdrawal from morphine versus buprenorphine. Volunteers were stabilized either on double-blind intramuscular (IM) buprenorphine (32 mg/day) or morphine (120 mg/day) administered in 4 divided doses for 9 days. They then underwent an 18-day period of spontaneous withdrawal during which double-blind IM placebo injections were administered. The same time course of stabilization and spontaneous withdrawal were repeated for the 2nd opioid. To objectively measure withdrawal-associated hyperalgesia (WAH), volunteers underwent quantitative sensory testing (QST) 10 times: day 9 of active study drug administration and during early, middle and late withdrawal from each opioid (days 2, 4, 8, and 15 of placebo administration). QST measurements were Z-transformed and combined to create detection, pain threshold, suprathreshold, and overall hyperalgesia indices for each session. Repeated measures 2-factor ANOVA using drug condition, day, and condition-by-day interaction revealed significant time course differences for WAH between opioids ($F= 4.56$, $p=0.01$ for condition-by-day interaction). Further analyses revealed a similar significant time course difference for suprathreshold index ($F=3.93$, $p=0.01$), but not sensory detection ($F= 2.31$, $p=0.09$) or pain threshold ($F=1.16$, $p=0.36$) indices. As predicted, Tukey's post-hoc comparisons demonstrated significantly ($p<0.05$) greater hyperalgesia during early withdrawal (day 2 of placebo administration) from morphine as compared to buprenorphine; buprenorphine WAH did not peak until day 8 of placebo administration. Buprenorphine WAH appears to be milder and peaks approximately 1 week after morphine, suggesting buprenorphine may be optimal for patients with low tolerance for spontaneous withdrawal.

(391) A single-dose pharmacokinetic study of fentanyl sublingual spray in cancer patients with and without oral mucositis

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Fentanyl sublingual spray provides safe, effective, and rapid analgesia for opioid-tolerant patients with breakthrough cancer pain. Mucositis, a common complication after chemotherapy and radiation, may alter drug absorption. In this open-label study, the pharmacokinetic, tolerability, and safety profile of a single 100 mcg dose of fentanyl sublingual spray was evaluated in cancer patients with or without mucositis. Eighteen adult, opioid-tolerant patients (9 with Grade 1 or 2 mucositis; 9 without mucositis) were treated and analyzed for safety. No statistically significant differences occurred between groups for maximum plasma concentration (Cmax), time to maximum concentration (Tmax), and area under the concentration-time curve from time 0 to last observation (Auc0-last). Mean Cmax (SD, 90% CI) was 0.67 ng/mL (0.60, 0.23-0.70) in patients with mucositis and 0.26 ng/mL (0.15, 0.13-0.42) in patients without mucositis. Mean Tmax (SD, 90% CI) was 0.53 h (0.57, 0.19-0.87) for patients with mucositis and 0.56 h (0.59, 0.20-0.92) for patients without mucositis. Mean AUC0-last (SD, 90% CI) was 3.11 hr*ng/mL (4.80, 1.16-2.70) and 0.91 hr*ng/mL (0.13, 0.58-1.41) among patients with and without mucositis, respectively. The higher absolute mean values in the mucositis group were due to the inclusion of a patient (Grade 2) found to be in protocol violation after data analyses. Two of 9 patients (22%) in the mucositis group reported a mild burning sensation in the oral mucosa; no other adverse events were reported and mucositis did not worsen in any patient. The absorption and distribution pharmacokinetic profile of fentanyl sublingual spray was not affected by the presence of mucositis, but variances in absolute mean values may warrant judicious use in this population. Development of this abstract funded by INSYS Therapeutics.