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Limited Quantities of Generic Oxycodone May Become Available Late 2008

According to an agreement between Purdue Pharma L.P. and Mallinckrodt Inc., limited amounts of generic oxycodone extended-release tablets may become available in late 2008. The agreement comes after months of litigation revolving around the enforceability of Purdue Pharma's patent of exclusivity involving the popular opioid pain reliever, OxyContin®. Under the new agreement, Mallinckrodt has agreed to honor the enforceability of Purdue's patent for OxyContin and was granted a royalty-bearing license allowing for the sale of limited quantities of oxycodone 10 mg, 20 mg, 40 mg, and 80 mg extended-release tablets through 2009. In early 2008, United States District Courts for the state of New York deemed that

allegations indicating that Purdue's patent for exclusivity were unenforceable were invalid. According to the District Courts of New York, "There is no evidence of deceptive intent with respect to Purdue's failure to disclose prior controlled-release formulations or its failure to disclose affiliations, both of which were made in good faith." Information regarding the official release date is not currently available; however, it is anticipated that these quantities will be of a limited nature.

Reference: *Purdue Pharma L.P. Announces Resolution of OxyContin Patent Lawsuit with Mallinckrodt Inc.*
<http://www.purduepharma.com/pressroom/news/20080902.htm> <Accessed September 18, 2008>

features

FDA Panel Recommends Against Expanded Label for Fentora®

Subsequent to the submission of a supplemental New Drug Application in late 2007 and the development of the Joint Advisory Commission by the U.S. Food and Drug Administration (FDA), Cephalon® has announced that its plans to broaden the indication for Fentora buccal tablets remain unapproved secondary to continued concerns regarding the risk potential with expanded Fentora utilization. During Cephalon's initial meeting with the FDA early this year, the drug manufacturer presented its Risk Management Action Plan (RiskMAP) as mandated by the Food and Drug Administration in early 2005. With the intention to prospectively minimize risk by targeting select areas such as the point of prescribing, point of dispensing, and product disposal, the plan was developed in an effort to expand Fentora's indication to non-cancer related pain in opioid-tolerant patients. In its communiqué with Cephalon, the FDA indicated

that it wished to receive evidence of the implementation and efficacy of the program as well as routine safety updates; further studies supporting the safety and efficacy of Fentora were not requested. "The FDA request for revisions to the Fentora risk management program was expected and over the last four months we have been working diligently to prepare for implementation of the program as soon as possible," commented Dr. Lesley Russell, Chief Medical Officer at Cephalon. Secondary to recent FDA regulation updates, Cephalon is anticipating receiving further guidance on maximizing the effectiveness of the RiskMAP program. "We anticipate that the subsequent letter from the agency will provide useful guidance to finalize the time for and implementation of ongoing enhancements to the risk management."

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features

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In early October 2008, Cephalon agreed to pay \$444 million to end investigations by state and federal investigators into allegations that the company promoted the use of Fentora for unapproved indications. According to the settlement, Cephalon was also required to release the names of all physicians who acted as speakers and/or consultants for the pharmaceutical manufacturer as mandated by a corporate integrity agreement from the Department of Health and Human Services. The Physician Payments Sunshine Act is currently being reviewed by Congress and may one day require all pharmaceutical manufacturers to disclose physician payment information.

Reference: *Cephalon, Inc. (CEPH) Says Expanded Fentora Label Not Approved*. http://www.biospace.com/news_story.aspx?StoryID=109620&full=1. <Accessed September 18, 2008>

Under Sweeping Settlement, Cephalon Will Disclose Doctor Payments. <http://blogs.wsj.com/health/2008/09/29/under-sweeping-settlement-cephalon-will-disclose-doctor-payments/> <Accessed October 28, 2008>



NDA Submitted for Tapentadol— a New Centrally Acting Analgesic

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. and Grunenthal GmbH have announced that a New Drug Application (NDA) is currently being reviewed by the U.S. Food and Drug Administration (FDA) for tapentadol, the newest member to the centrally acting analgesic drug class in more than a decade. Tapentadol exerts its analgesic effect via a dual mechanism of action, preventing the re-uptake of norepinephrine and partially stimulating mu-receptors in the central nervous system. Available data from phase II and III trials have indicated that tapentadol offers significant analgesia over placebo; however, clinical trials have yet to be conducted comparing the efficacy of this agent in relation to other opioid analgesics. Ultram® (tramadol), the first agent to join this class of analgesics, has been approved in the United States since 1995.

Reference: *New Data From Phase 3 Study Suggests Tapentadol Immediate Release Effective For Acute Pain From Common Foot Surgery*. <http://www.reuters.com/article/pressRelease/idUS232336+09-May-2008+PRN20080509>. <Accessed May 19, 2008>



Chronic Pain Shown to Disrupt Cognitive and Behavioral Function

Researchers from Northwestern University's Feinberg School of Medicine in Chicago have discovered that chronic back pain sufferers may exhibit altered cognitive and behavioral brain function as a direct result of persistent pain levels. Participants with chronic pain were shown to possess a decreased "default mode network," which typically acts to maintain a resting level for the brain; chronic pain participants exhibited an increase in cortical function translating into increased emotional involvement and alterations in behavior. "If you are a chronic pain patient, you have pain 24 hours a day, seven days a week, every minute of your life. That permanent perception of pain in your brain makes these areas in your brain continuously active. This continuous dysfunction in the equilibrium of the brain can change the wiring forever and could hurt the brain," explains Dante Chialvo, associate research professor of physiology at Northwestern University. Chialvo further explains, "These changes may make it harder for you to make a decision or be in a good mood to get up in the morning. It could be that pain produces depression and the other reported abnormalities, because it disturbs the balance of the brain as a whole."

Reference: Baliki et al. *Beyond Feeling: Chronic Pain Hurts the Brain, Disrupting the Default-Mode Network Dynamics*. <http://www.jneurosci.org/cgi/content/abstract/28/6/1398> *The Journal of Neuroscience*. February 6, 2008;28(6):1398-1403



FDA Views New OxyContin Formulation as Questionable

Purdue Pharma's efforts to market a more abuse-resistant form of its popular long-acting opioid pain reliever, OxyContin, were thwarted earlier this year by the Food and Drug Administration as criticisms arose revolving around Purdue's failure to show the effectiveness of its abuse deterrent system in the "real world." Critics argued that the new OxyContin formulation would be no match for someone with a basic knowledge of chemistry. Purdue Pharma's plan was to produce the abuse resistant form of the opioid analgesic for lower doses while selling the 60 mg and 80 mg version in their original formulation. The Food and Drug Administration argued that this would serve to confuse the medical community and potentially encourage abusers to concentrate on attaining the old formulation of the drug. Purdue Pharma vowed

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it would continue to "...work with the FDA on our New Drug Application (NDA) for a new formulation of OxyContin (oxycodone HCL controlled-release) tablets."

Reference: *FDA Panel Nixes 'Abuse Proof' OxyContin*. <http://www.rxlist.com/script/main/art.asp?articlekey=89304>. <Accessed September 18, 2008>



Extended-Release Vicodin CR™ Achieves Efficacy Endpoints in Phase III Trial

Abbott Laboratories has announced that its investigational extended-release formulation of the popular opioid analgesic, Vicodin, has shown positive primary efficacy endpoints in a recent Phase III clinical trial. Available since the early 1980s, hydrocodone/acetaminophen products, such as Vicodin, have risen to become the most prescribed short-acting opioid analgesic in the United States workers' compensation market. Although extended-release formulations of products containing hydrocodone are available for the treatment of cough and congestion (i.e., Tussionex®), none is FDA approved for the treatment of pain. Unlike regular-release Vicodin, Abbott indicates that Vicodin CR is formulated to be taken every 12 hours; thereby, providing more consistent pain relief. Eugene Sun, M.D., vice president of Abbott's Global Pharma-ceutical Development team comments, "Immediate-release hydrocodone with acetaminophen has four- to six-hour dosing and is the most prescribed medication in pain care today. These new extended-release data are encouraging because they showed that 12-hour dosing provided pain relief in patients with moderate to severe chronic low-back pain."

The efficacy of Vicodin CR was demonstrated in an Abbott-sponsored clinical trial comparing the efficacy of the novel extended-release formulation to placebo. Although hydrocodone/acetaminophen is fairly effective as a short-acting analgesic in the treatment of moderate pain it is uncertain if the introduction of an extended-release formulation will offer any significant clinical advantage over already available long-acting agents. Clinical trials comparing the efficacy of Vicodin CR to other long-acting opioid analgesics (i.e., OxyContin) have not been conducted; a comparison that could paint a clearer picture of the true clinical significance of this new product.

Reference: *New Abbott Study of Investigational Vicodin CR Meets Primary Efficacy Endpoints in Phase III Trial*. http://www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0610.htm. <Accessed September 18, 2008>

FDA update

Generic Drug Arrivals

Lamictal® (lamotrigine)

Launched: July 22, 2008

Lamotrigine tablets are now available as the generic equivalent of **Lamictal**, an anticonvulsant agent utilized in the treatment of various conditions such as bipolar disorder and partial seizures. Lamotrigine has also been used off-label in the treatment of neuropathic pain.

Prilosec® (omeprazole)

Launched: July 25, 2008

As previously anticipated, omeprazole 40 mg recently has become generically available and joins the already available 10 mg and 20 mg generic version of the hugely popular proton pump inhibitor, **Prilosec**.

Risperdal® (risperidone)

Launched: July 1, 2008

Risperdal is now available as the generic equivalent, risperidone, an atypical antipsychotic agent used in the treatment of various psychiatric conditions such as bipolar disorder and schizophrenia.

Marinol® (dronabinol)

Launched: June 30, 2008

Marinol has recently become generically available as dronabinol, a cannabinoid agent FDA approved in the treatment of anorexia and chemotherapy-induced nausea/vomiting. Clinical trials are studying the efficacy of various cannabinoids in the treatment of neuropathic pain.

Depakote® (Divalproex)

Launched: July 29, 2008

Depakote is now available as the generic equivalent, divalproex, an anticonvulsant agent FDA approved for the treatment of various conditions including migraine prophylaxis, bipolar disorder, and partial seizures.

New Indications

Cymbalta® (duloxetine)

Approved: June 2008

As of June 2008, **Cymbalta**, a hugely popular antidepressant agent, joins **Lyrica**® as one of only two FDA-approved therapies for the treatment of fibromyalgia. Already approved for the treatment of depression, anxiety, and diabetic neuropathy, **Cymbalta** is currently being studied as a treatment option for osteoarthritis knee pain; although, an FDA indication for this condition is currently not in place for this agent.

New Launches

Stavzor® (valproic acid)

Launched: August 2008

Approved in July 2008, **Stavzor** is now available for the treatment of seizure disorders, bipolar depression, and migraine prophylaxis. Although the introduction of this agent provides for a smaller capsule, which some patients may find easier to swallow, this agent does not reflect a novel treatment strategy; therefore, the clinical significance of **Stavzor** is yet to be seen.

New Drug Approvals

Aloxi® (palonosetron)

Anticipated Launch: late 2008

Approved in August 2008, **Aloxi** is the newest member to join the serotonin receptor antagonist class of anti-emetic therapy. **Aloxi** is currently approved for the prevention of nausea/vomiting following chemotherapy treatment and postoperative nausea/vomiting (PONV). It is uncertain if this agent will be used in an off-label manner for the treatment of opioid-induced nausea/vomiting.

clinical literature digest studies

STUDY #1: Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness

Constipation is a common adverse gastrointestinal effect associated with opioid therapy. One survey of patients taking opioid analgesics for pain of non-cancer origin found that approximately 40% of patients experienced constipation associated with opioid therapy (< 3 complete bowel movements per week) compared with 7.6% of patients in a control group. Moreover, of the subjects who required laxative therapy, only 46% of opioid-treated patients reported achieving the desired laxative effect > 50% of the time. The mechanism of opioid-induced constipation is mediated primarily by stimulation of opioid receptors in the gastrointestinal tract. Treatments that selectively antagonize peripheral opioid receptors are more advantageous in contrast to both centrally and peripherally acting opioid antagonists.

The purpose of this study was to evaluate the safety and efficacy of subcutaneous methylnaltrexone for treating opioid-induced constipation in patients with advanced illness. The study consisted of two phases; a 2-week, double-blind, randomized, placebo-controlled phase and a subsequent 3-month, open-label extension phase. Phase-I compared methylnaltrexone 0.15mg/kg and 0.3mg/kg to placebo. Rescue-free laxation within 4 hours after receiving the first dose of methylnaltrexone was significantly greater than placebo (48% to 15%). Half of all patients in the methylnaltrexone group had a response within 30 minutes, and among all patients, the median time to laxation after the first dose was also significantly less in the methylnaltrexone group compared to the placebo group (6.3 hours to 48 hours). Patients that required dose escalations also demonstrated significantly greater laxation within 4 hours in the methylnaltrexone group compared to placebo.

Participants enrolled in Phase II were given at least one dose of methylnaltrexone during the extension phase (3 months). The rates of rescue-free laxation during the double-blind phase and the open-label extension were comparable, and the median time to laxation for each individual dose were all less than 45 minutes, which was comparable to the double-blind group. During the extension phase, the most common adverse events were abdominal pain, progression of

malignant neoplasm, nausea, and vomiting. There were no significant changes in mean pain scores or evidence of withdrawal symptoms associated with methylnaltrexone use in this study. Methylnaltrexone is currently FDA approved for opiate agonist-induced constipation in patients with advanced illness who are receiving palliative care when response to laxative therapy has been insufficient. It is listed under the brand name Relistor (12mg/0.6ml solution for injection).

Thomas et al. "Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness." *New England Journal of Medicine*. 2008 May 29;358(22):2332-43.

STUDY #2: The Relation of Post-Traumatic Stress Symptoms to Depression and Pain in Patients With Accident-Related Chronic Pain

Claimants within the workers' compensation arena may often have multiple injuries and medical conditions. The complexity of treating these types of injuries has led to much discussion and some studies regarding the correlation between conditions that claimants may experience, and how one symptom may contribute to the severity of symptoms of another condition. The intricacies of multiple medical conditions impact and influence treatment approach and claimant outcome(s). Poor treatment response may be the result of not focusing therapy toward the primary culprit that is the source of the claimant's state of dysphoria. Post-traumatic stress disorder (PTSD) occurs when an individual is exposed to an extremely traumatic, usually life-threatening stressor. The traumatic event is outside the individual's normal realm of experience and overwhelms the individual's usual psychological defenses. In post-traumatic stress disorder, the memory of the trauma is repeatedly experienced in ways that are nearly as distressing as the original trauma. The objective of this study was to examine the contribution of post-traumatic stress disorder to pain experience, functional disability, and frequency of depressive symptoms through the use of structural equation modeling.

The patient population consisted of patients that were referred to a university hospital pain rehabilitation program and who reported that their pain began after a traumatic experience. Questionnaires were mailed to the patients to fill out and return to the clinic during their first visit. The questionnaires

were used to measure the correlation between pain, disability, post-traumatic stress disorder, depression, and anxiety. Three different models were explored to examine the relationship between post traumatic stress (PTSD) symptoms to depression and pain. The first model proposed that pain influences disability, which in turn predicts depression. In this model, PTSD symptoms were hypothesized to have a simultaneous influence on levels of depression and disability. The second model examined the separate influence of depression and disability on pain, with symptoms of PTSD hypothesized to independently predict levels of depression. The third model examined the severity of depressive symptoms in relation to both pain and disability, PTSD was examined in association with depressive symptoms.

Analysis of the data indicated that model three demonstrated a significant fit for the data compared to the other models. This study highlights the position that post-traumatic stress symptoms have a direct influence on depression, whereas depression symptoms have a direct influence on pain intensity. In addition, depression possesses an indirect effect on pain intensity by its influence on disability. This study suggests that poor treatment response in claimants who have an injury that involves post-traumatic stress disorder, depression, and pain may be the result of unresolved or untreated post-traumatic stress disorder symptoms.

Roth R.S., Geisser M.E., Bates R. "The Relation of Post-Traumatic Stress Symptoms to Depression and Pain in Patients with Accident-Related Chronic Pain." *Journal of Pain*. <http://www.jpain.org/article/PIIS152659000800391X/abstract> 2008 Jul;9(7):588-96

STUDY #3: Oxycodone Plus Ultra-Low Dose Naltrexone Attenuates Neuropathic Pain and Associated mu-Opioid Receptor-Gs Coupling

Neuropathic pain is caused by direct damage to or dysfunction of nerves. Management of this condition may include tricyclic antidepressants (e.g., amitriptyline), serotonin-norepinephrine reuptake inhibitors (e.g., Cymbalta®), and anticonvulsants (e.g., gabapentin). Patients that are unresponsive to first-line treatment may often require the addition of opioid therapy to relieve painful symptoms associated with neuropathic pain. Although opioids, such as oxycodone have shown to be effective in treating pain associated with nerve injury, there are unwanted

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side effects, which may include constipation, sedation and respiratory depression. In addition, chronic use of opioids may lead to tolerance and hyperalgesia. Increased sensitivity to pain associated with chronic opioid therapy has been proposed to involve opioid enhanced mu-opioid receptor-Gs coupling. Naltrexone is an opioid receptor antagonist; it is used to help maintain an opiate-free state in patients who are known abusers. This study investigated whether oxycodone plus ultra-low-doses of naltrexone could alleviate the symptoms of neuropathic pain, and whether this combination can reduce the coupling of mu-opioid receptors and Gs proteins, which is believed to play a role in the excitatory effects of chronic opioid use.

First, results indicated that surgically induced nerve pain increase mu-opioid receptor-Gs coupling alone. Second, surgically induced nerve pain and oxycodone or naltrexone alone also increased the mu-opioid receptor-Gs protein coupling. Third, in contrast to the other results, animals with surgically induced nerve pain that were treated with the combination of oxycodone and naltrexone reduced the coupling effect of mu-opioid receptors and Gs proteins. Further results indicated surgically induced nerve damaged animals treated with naltrexone alone did not demonstrate any significant response to pain sensitivity after intrathecal administration. The greatest response to thermal hypersensitivity for the oxycodone-only group was on day two with an approximate 60% reversal rate; however, this group showed a rapid development of analgesic tolerance shortly after day two. In contrast, animals treated with oxycodone and naltrexone demonstrated an approximate 75% reversal rate of thermal hypersensitivity, and more than 50% of these test animals did not show an increased sensitivity to pain (hyperalgesia). The results were comparable when test medication was given by the oral route; oxycodone and naltrexone groups demonstrated a superior reversal rate to thermal hypersensitivity, compared to either oxycodone or naltrexone alone.

This study suggests that in neuropathic pain, the coupling of mu-opioid receptors and Gs protein may contribute to the excitatory neurotransmission effect observed in these animals. In addition, the combination of oxycodone and naltrexone may be a promising approach to manage neuropathic pain.

Largent-Milnes T.M., Guo W., Wang H.Y., Burns L.H., Vanderah T.W. "Oxycodone Plus Ultra-Low-Dose Naltrexone Attenuates Neuropathic Pain and Associated Mu-Opioid Receptor-Gs Coupling." *Journal of Pain*. 2008 Aug;9(8):700-13



FDA MedWatch Report

Morphine 60 mg and 30 mg extended-release tablets

Posted June 10, 2008 — ETHEX Corporation notified healthcare professionals of a voluntary recall of a single lot of morphine sulfate 60 mg extended-release tablets (Lot No. 91762) due to a report of a tablet with twice the appropriate thickness. Oversized tablets may contain as much as two times the labeled level of active morphine sulfate. The lot was distributed by ETHEX Corporation under an "ETHEX" label between April 16th and April 27th of 2008. Opioids such as morphine have life-threatening consequences if overdosed. Consequences can include respiratory depression (difficulty or lack of breathing), and low blood pressure. Many patients for whom this product is prescribed are likely to be highly debilitated with reduced strength or energy as a result of illness, and may be less likely to determine that a tablet is overweight or oversized than an unimpaired individual. If consumers have any questions about the recall, they should call their physician, pharmacist, or other health care provider.

Update June 16, 2008 — Additional lots of morphine sulfate 60 mg extended-release tablets and specific lots of morphine sulfate 30 mg extended-release tablets, were recalled due to the possible presence of oversized tablets. The recalled lots were distributed by ETHEX Corporation under an "ETHEX" label between June 2006 and May 2008.

Patients who suspect that their prescriptions have been affected by lots of morphine involved in this voluntary recall should contact the pharmacy where the prescription was dispensed. Dispensing pharmacies will handle affected prescriptions on a case-by-case basis.



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