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## Propoxyphene Withdrawn from U.S. Market

In late 2010, the Food and Drug Administration (FDA) indicated that it was requesting a voluntary recall of all propoxyphene-containing products from the market, citing clinical trial results that indicated an increased risk of negative cardiovascular outcomes with the use of propoxyphene, even at normal therapeutic doses. Propoxyphene is a synthetic opioid pain reliever similar to methadone and FDA approved for the treatment of mild to moderate pain.

First approved in 1957, propoxyphene has experienced a bumpy road along its approval lifetime. Since the late 1970s, the FDA has received two petitions regarding the removal of propoxyphene products and the possible reclassification of the analgesic to a Schedule II narcotic agent. More recently, in early 2009, an FDA advisory committee was called into action to evaluate the safety and efficacy of propoxyphene as an overall opioid analgesic. Despite a 14 to 12 vote against the continued use of propoxyphene, the FDA decided to continue the analgesic's approval; however, the administration mandated that the drug contain a black-box warning regarding the possibility of fatal overdose situations.

Since that time, clinical trial data from Xanodyne® Pharmaceuticals, Inc. has indicated that the use of propoxyphene products across the entire dosing spectrum may place patients at risk for harmful cardiac changes, ultimately leading to possible death. Concerned about these findings, the FDA notified Xanodyne and other propoxyphene

manufacturers on November 19, 2010 that it was requesting a voluntary recall of all propoxyphene products from the market. The FDA has recommended that prescribers immediately cease prescribing the analgesic to all patients, consider alternate agents, and contact patients who may currently be utilizing propoxyphene products. Similarly, patients were asked to contact their prescriber about alternative agents.

While the removal of propoxyphene products represents the loss of a potential analgesic option for pain patients, most healthcare professionals agree that the availability of alternative agents means that patients will continue to receive appropriate pain management. An analysis of PMSI's transactional data indicates that injured workers were generally converted to tramadol (Ultram®), tramadol-acetaminophen (Ultracet®), codeine-acetaminophen (Tylenol® with codeine), and hydrocodone-acetaminophen products (e.g., Vicodin®, Lortab®, etc.) following the FDA's voluntary withdrawal

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**Click here to see PMSI's Drug Advisory about Propoxyphene Products**



announcement. This decrease in propoxyphene utilization was not matched by an equal increase in the products named above, likely indicating that the use of propoxyphene occurred on a one-time fill basis or that continued narcotic therapy was not required. Interestingly, a general decrease in

the use of propoxyphene products in favor of other products has been occurring since before the FDA's notice.

Reference: *Propoxyphene: Withdrawal - Risk of Cardiac Toxicity*. FDA MedWatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm234389.htm> <Accessed January 11, 2011>

# Features

## FDA Mandates Maximum Acetaminophen Content in Combination Analgesics

On January 13, 2011, the FDA announced that it would ask manufacturers of prescription acetaminophen products to limit the amount of acetaminophen in combination analgesic products to 325mg per dosage unit. Acetaminophen is widely and effectively used in both prescription and over-the-counter (OTC) products to reduce pain and fever. Prescription products that contain acetaminophen include hydrocodone-acetaminophen (e.g., Vicodin, Lortab) and oxycodone-acetaminophen (e.g., Percocet®).

The FDA continues to receive reports of severe liver injury associated with the use of acetaminophen-containing products. Patients that take more than the prescribed dose, take more than one acetaminophen-containing product at a time, or drink alcohol while taking acetaminophen are at greatest risk. Severe liver injury can lead to liver failure, liver transplant, and death. The FDA believes this action will reduce the risk of severe liver injury from acetaminophen overdosing. The total number of dosage units and frequency at which they may be prescribed will not be affected by this action. OTC

acetaminophen products (e.g., Tylenol) are also not affected by this action.

A boxed warning highlighting the potential for severe liver injury and a warning highlighting the potential for allergic reactions are also being added to the label of all prescription products that contain acetaminophen. Information about the potential for liver injury is already required on the label for OTC acetaminophen products. The FDA does not feel this regulatory action will affect patient healthcare. All prescription products containing acetaminophen also contain an additional pain medicine and there is no data indicating that more than 325 mg of acetaminophen per dosage unit provides more pain relief. The elimination of higher-dose prescription combination acetaminophen products will be phased in over three years and should not create a shortage of pain medication.

[Click here to see PMSI's Drug Advisory about Acetaminophen Combination Products](#)

Reference: *FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure*. FDA MedWatch. <http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm> <Accessed January 13, 2011>

## Upcoming Complimentary Webinars



### Anti-emetics, Laxatives and Anti-ulcer Agents

March 22

2:00 – 2:30 PM EST

[Click here to register](#)

### Antihistamines and Stimulants

April 26

2:00 – 2:30 PM EST

[Click here to register](#)

### Therapeutic Drug Information Series

Strengthen your knowledge with PMSI's monthly educational series about Therapeutic Drug Classes. Armed with a better understanding of drug classes and their use in workers' compensation, you will be able to make more informed decisions in the drug approval process.

Topics will include:

- Common medications
- Typical use
- Indications
- Side effects
- Monitoring parameters

Note: These informational webinars are not eligible for Continuing Education Credits.

## The Therapeutic Potential for Topical Opioids

The use of topical agents, specifically for analgesia, is not a new concept. Topical medications have traditionally included nonsteroidal anti-inflammatory drugs (NSAIDs), capsaicin, local anesthetics (i.e., lidocaine), and rubefacients or counterirritants (i.e., menthol and camphor). Even though the use of topical opioids may be a safe and effective option for acute and chronic pain patients, their use has been minimal to date. Just recently the Cochrane Collaboration has planned a first-ever systemic review of the literature on topical analgesics that will include topical, peripheral-acting opioids.

Limited human trials, mostly published as case reports, indicate that topical opioids offer a therapeutic benefit for acute and chronic pain conditions. Although compounding pharmacies often formulate topical mixtures that contain prescribed opioids, topical formulations of opioids are an “off-label” indication in the U.S. and there are currently no FDA-approved preparations commercially available.

According to the researcher, not all opioids provide topical pain relief. Some opioids, such as hydrocodone, codeine, and

tramadol, require activation by the liver to convert them to active compounds and are inert on the skin surface. Fentanyl is a poor topical opioid due to its high solubility and ability to rapidly dissolve through the skin and into the bloodstream, making it very effective systemically. Many examples in the literature of effective applications of topical opioids include formulations containing morphine, hydromorphone, and oxycodone, which are all relatively insoluble and act directly on opioid receptors at the site of pain without requiring further metabolism.

While more extensive research is required, the topical use of opioids has the potential to be a safe and effective therapeutic option for patients with acute and chronic pain conditions.

References: *Is There a Role for Topical Opioids in Pain Care?* <http://updates.pain-topics.org/2011/01/is-there-role-for-topical-opioids-in.html>. <Accessed January 19, 2011>

Tennant Forest., MD, DrPH. Taking Advantage of the Peripheral Opioid Receptor. *Practical Pain Management*. 2010A; 10(3):28-30 [abstract].



## Duration of Therapy Assessed in Patients Utilizing Antidepressants for Anxiety Disorders

It is often difficult for clinicians to gauge how long they can expect a medication to be effective in treating their patients. Much of the challenge is due to the design of clinical trials presently utilized by drug manufacturers to gain approval from the FDA for their products. Unfortunately, most trials are only conducted for a fraction of the time that medications will actually be utilized in clinical practice. With most medications, the reality is that agents will be used much longer than what the manufacturer reports in the literature to support efficacy and safety. A recent clinical trial reported that only 6.7% of patients experienced relapse of anxiety symptoms when utilizing the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine extended-release capsules to treat generalized anxiety disorder (GAD) for 12 months. However, 20% of the placebo-only patients experienced relapse, and 32.3% of patients who utilized venlafaxine extended-release capsules, but were then switched to placebo, reported relapse symptoms in this study.

Clinical intervention programs that utilize medication reviews have become a popular tool to address the appropriateness of pharmacologic therapy. A comprehensive review typically contains an assessment of duration of therapy and discusses how long a patient could possibly be on a particular agent, based on evidence-based studies and guidelines. Although individual cases may vary, this study suggests that patients who utilize a serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant, such as venlafaxine extended-release capsules, may experience superior outcomes for the treatment of generalized anxiety disorder (GAD), when treated for 12 months, compared to patients who are not treated for the same amount of time. This data may be helpful when assessing anxiety that is associated with workers' compensation patients.

Reference: Rickels K, et al. *Time to relapse after 6 and 12 months' treatment of generalized anxiety disorder with venlafaxine extended release*. *Archives of General Psychiatry*. Volume 67, No. 12, December 2010. <http://archpsyc.ama-assn.org/cgi/content/full/67/12/1209>. <Accessed January 28, 2011>

## New Generic Launches

### **Xyzal® (Levocetirizine)**

*Launched: November 29, 2010*

Approved for the treatment of allergic rhinitis and urticaria, **Xyzal** is now available as a generic equivalent in a 5 mg tablet formulation. Although an oral solution is currently also available, this formulation is still only available as a brand-name product.

## New Generic Approvals

### **Ambien CR® (Zolpidem CR, 12.5 mg)**

*Approved: December 6, 2010*

Following the generic launch of the 6.25 mg dosage strength, the FDA recently approved the generic formulation for 12.5 mg **Ambien CR**. Similar to the brand-name product, extended-release zolpidem is currently approved for the treatment of insomnia characterized by difficulties falling asleep or waking up during the night.

### **Fentora® (Fentanyl citrate)**

*Approved: January 10, 2011*

Watson® Pharmaceuticals, Inc. recently announced that it had received FDA approval to market its generic version of **Fentora**. Similar to Actiq®, Fentora is currently FDA indicated only for the treatment of breakthrough pain in cancer patients who are taking and are tolerant of opioid analgesics. Although Actiq and Fentora share identical FDA indications, these products are not interchangeable and cannot be substituted on a mcg per mcg basis.

## New Drug Approvals

### **Abstral® (Fentanyl citrate)**

*Approved: January 10, 2011*

The FDA recently announced the approval of **Abstral**, the next fentanyl citrate product to join the cancer-related opioid analgesic market. Similar to other rapid-acting fentanyl citrate

products, Abstral is approved only for the treatment of breakthrough pain in cancer patients already tolerant of opioid pain relievers. Due to similarities to existing fentanyl citrate products, it appears that this agent may not offer any significant clinical advantages.

### **Viibryd™ (Vilazodone)**

*Approved: January 21, 2011*

PGxHealth recently announced that the FDA approved **Viibryd** for the treatment of major depressive disorder in adults. Viibryd works by inhibiting the reuptake of serotonin and by acting as a partial serotonin agonist. Given that some patients may develop industrially related depression as a result of chronic, unresolved pain, it is possible that Viibryd may be a potential therapeutic option in these patients.



# FDA

## MedWatch Reports

Highlighting Important Safety Issues from the FDA

## Albuterol Sulfate Inhalation Solution Recalled

*Posted: January 3, 2011*—The Ritedose Corporation is conducting a voluntary recall of 0.083% Albuterol Sulfate Inhalation Solution, 3 mL in 25, 30, and 60 unit dose vials. This product is being recalled because the 2.5 mg/3 mL single use vials are embossed with the wrong concentration of 0.5 mg/3 mL and therefore, represents a potential significant health hazard. Only the unit dose vials are incorrectly embossed as containing 0.5 mg/3 mL. The correct

concentration of 2.5 mg/3 mL is labeled on the primary foil overwrap pouches and shelf cartons. Administration of this defective product could result in a range of potential health effects that spans from temporary and medically reversible to life threatening and death.

The following lot numbers manufactured by The Ritedose Corporation under NDC: 0591-3797-83, 0591-3797-30, and 0591-3797-60 are included in the recall: 0N81, 0N82, 0N83, 0N84, 0NE7, 0NE8, 0NE9, 0NF0, 0P12, 0P13,

0P46, 0P47, 0PF0, and 0S15. No other albuterol formulations or products are included in this recall. Consumers should immediately return the affected product to the location where it was obtained (i.g., doctor's office, pharmacy, etc.). Wholesalers and retailers should return the product to

the address stated in the firm's press release at the following link, <http://www.fda.gov/Safety/Recalls/ucm238528.htm>.

Reference: *Albuterol Sulfate Inhalation Solution 0.083%, 3 mL Unit Dose Vials: Recall - Mislabeled Unit Dose Vials*. FDA MedWatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm238624.htm> <Accessed January 19, 2011>

### Accidental Overdose with Morphine Sulfate Oral Solution Products

*Posted: January 10, 2011*—Roxane Laboratories and the FDA notified healthcare professionals of serious adverse events and deaths resulting from accidental overdose of morphine sulfate oral solutions, especially when using the high potency 100 mg/5 mL product. In most of these cases, morphine sulfate oral solutions ordered in milligrams (mg) were mistakenly interchanged for milliliters (mL) of the product. The approval of this product is part of the FDA's unapproved drugs initiative. Prior to the recent approval, Roxane marketed a morphine sulfate oral solution with the strength expressed as 20 mg/mL, using a container label and carton labeling that had brown lettering on a white background. The newly approved product labeling and packaging feature revisions are intended to reduce the risk of medication errors. In an effort to help reduce the potential for this mistake to be made in the future, the FDA is mandating the following changes to the product's label:

- A warning stating "ONLY FOR USE IN PATIENTS WHO ARE OPIOID TOLERANT" will be displayed in a box to highlight that the morphine sulfate oral solution 100 mg per 5 mL (20 mg/mL) is indicated for use in opioid-tolerant patients only. The 100 mg per 5 mL concentration of morphine sulfate may cause fatal respiratory depression when administered to patients not previously exposed to opioids.
- The strength will be presented as 100 mg per 5 mL followed by a less prominently displayed concentration of (20 mg/mL). The intent of this designation is to help differentiate this product from the 20 mg/5 mL morphine-sulfate product.

- A bright yellow background will be used on multiple sides of this product to differentiate the morphine-sulfate oral solution 100 mg per 5 mL (20 mg/mL) from other morphine-sulfate oral solutions marketed by Roxane with a white background.
- The drug name, strength and concentration will be displayed in white lettering on a red background as an additional means of differentiating this product from other concentrations of morphine-sulfate oral solutions.
- A reminder will be presented to the pharmacist to dispense the product to each patient with the enclosed Medication Guide.
- Both the 30 mL and 120 mL bottles of morphine sulfate 100 mg per 5 mL (20 mg/mL) oral solution will be packaged with a calibrated oral syringe to provide accurate dose measurements. Healthcare providers should read the instructions in the Medication Guide that describe the correct use of the oral syringe in order to help prevent medication errors from occurring.

For a complete description and photos of labeling and product package changes, please visit the following link: <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM239561.pdf>.

Reference: *Morphine Sulfate Oral Solution 100 mg per 5 mL (20 mg/mL): Medication Use Error - Reports of Accidental Overdose*. FDA MedWatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm239559.htm> <Accessed January 19, 2011>

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#### Hydrocodone-Acetaminophen Tablets Mislabeled as Phenobarbital – Recall in Effect

*Posted: February 7, 2011*—An individual bottle of Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10mg / 500mg, NDC 0603-3888-20, 60 count was found incorrectly labeled with a Phenobarbital Tablets, USP 32.4 mg, NDC 0603-5166-32, 1000 count label, printed with Lot Number T150G10B. Both products are manufactured by Qualitest Pharmaceuticals. As a result of this mix-up, patients may unintentionally take hydrocodone and acetaminophen tablets, instead of the intended dose of phenobarbital.

Unintentional administration of hydrocodone can lead to serious adverse events including respiratory depression, CNS depression, coma and death, especially in opioid-naïve patients and patients on other CNS depressants. Unintentional administration of acetaminophen may result in liver toxicity in patients on other acetaminophen-containing medications, patients with liver dysfunction, or people who consume more than three alcoholic beverages a day. Additionally, missing doses of phenobarbital could result in loss of seizure control.

This recall includes the following products:

- Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10mg / 500mg, NDC 0603-3888-20, 60 count, Lot Numbers T150G10B, T120J10E and T023M10A
- Phenobarbital Tablets, USP 32.4 mg, NDC 0603-5166-32, 1000 count, Lot Numbers T150G10B, T120J10E and T023M10A

Recalled lots were distributed between September 21, 2010 and December 29, 2010 to wholesale and retail pharmacies nationwide (including Puerto Rico). Consumers who possess the affected product should stop using it and contact Qualitest at 800.444.4011 for reimbursement. Lot numbers can be found on the side of the bottle. Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program.

Reference: *Hydrocodone Bitartrate And Acetaminophen Tablets, Phenobarbital Tablets by Qualitest: Recall - Incorrect Package Labeling*. FDA MedWatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm242527.htm> <Accessed February 7, 2011>



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