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FDA Emphasizes Importance of Appropriate Medication Disposal, Particularly Opioids

Due to the acute nature of many industrial injuries, many patients are oftentimes left with an arsenal of prescription medications that they no longer require and a sense of confusion regarding their disposal. Although the U.S. Food and Drug Administration (FDA) recommends that patients mix most medications with an unpalatable substance (e.g. coffee grounds, cat litter) before disposing of them in their trash, the agency recommends a more fool-proof method for disposal of medications with high-abuse potential.

As part of its effort to reduce the inappropriate use of high-risk medications, the FDA requires drug manufacturers to propose appropriate disposal methods when a New Drug Application (NDA) is received for a new drug product. Besides reducing the accessibility of potentially life-threatening medications to those for whom the medication was not intended, recommendations for disposal also help to quell environmental concerns regarding the presence of drug concentrations in public waterways. So, how exactly should high-risk medications be discarded once a patient no longer needs them?

Following Federal Guidelines set forth by the Office of National Drug Control Policy, the FDA has formulated a list of high-risk medications that should be disposed of by flushing down the toilet or sink in order to prevent unintentional or inappropriate use. Although the majority of medications should not be discarded in this fashion, the FDA has determined

that the potential risk of inappropriate encounters with these high-risk medications is severe enough to warrant this method of disposal (list provided on page 2).

Those with questions about the appropriate disposal of prescription medications should contact their local pharmacy for instructions regarding the disposal of prescription medications or they can visit the FDA website at www.fda.gov for more detailed instructions regarding high-risk medications.

At PMSI we are committed to continually educate on the appropriate use of prescription medications as well as instruct our clients and patients about appropriate disposal methods. Rest assured that PMSI will continue to highlight important FDA updates regarding this and other crucial medication topics.



High-Abuse Potential Medications That Should be Flushed

Medication	Active Ingredient	Medication	Active Ingredient
Actiq®	Fentanyl Citrate	Avinza®	Morphine Sulfate
Daytrana®	Methylphenidate	Demerol®	Meperidine
Diastat®	Diazepam	Dilaudid®	Hydromorphone Hydrochloride
Dolophine®	Methadone Hydrochloride	Duragesic®	Fentanyl
Embeda™	Morphine Sulfate; Naltrexone Hydrochloride	Fentora®	Fentanyl Citrate
Kadian®	Morphine Sulfate	MS Contin®	Morphine Sulfate
Onsolis™	Fentanyl Citrate	Opana®	Oxymorphone Hydrochloride
Opana ER®	Oxymorphone Hydrochloride	Oramorph SR®	Morphine Sulfate
OxyContin®	Oxycodone Hydrochloride	Percocet®	Oxycodone Hydrochloride; Acetaminophen
Percodan®	Oxycodone Hydrochloride; Aspirin	Xyrem®	Sodium Oxybate

References: Disposal by Flushing of Certain Unused Medicines: What You Should Know. FDA. <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm> <Accessed January 6, 2010>

Medication Disposal: Questions and Answers. FDA. <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186188.htm> <Accessed January 6, 2010>

features

FDA Approves Morphine Oral Solution after 2009 Removal of Unapproved Medications

In March 2009, the FDA sent warning letters directing companies to stop making and distributing specific narcotic products in certain dosage forms that had not been subject to the FDA approval process, including morphine sulfate oral solutions. While morphine sulfate oral solutions had been manufactured, distributed, and used by patients for a number of years, the FDA asserted that the safety of these unapproved drugs was unknown.

In January 2010, the FDA approved morphine sulfate oral solution 20 mg/ml as the only FDA-approved oral liquid dosage formulation of morphine for the treatment of moderate to severe, acute and chronic pain in opioid-tolerant patients. Although morphine sulfate oral

products have been commercially available in the U.S. for years, there were no FDA-approved products on the market until now.

Currently, Roxane Laboratories is the sole FDA-approved manufacturer of morphine sulfate oral solution products. Interestingly, prior to this approval, Roxane Laboratories did possess an FDA approved morphine sulfate solution in the 10 mg/5 ml and 20 mg/5 ml concentrations, but not in the 20 mg/ml concentration.

There are still a variety of opioid analgesics from different manufacturers that remain unapproved (e.g. hydromorphone tablets by Roxane and Roxicodone tablets by Xanodyne Pharmaceuticals). It is anticipated that these manufacturers will submit New Drug Applications in order to get their products officially approved. Since the FDA's unapproved drug initiative began, chronic pain patients have

continued on page 3

continued to have access to alternate opioid analgesics for the management of moderate to severe pain; thereby, minimizing the risk of under-treated pain in the chronic pain population.

References: Questions and Answers for Consumers About FDA's Actions Involving Unapproved Narcotics Containing Morphine Sulfate, Hydromorphone, or Oxycodone. Food and Drug Administration. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm165587.htm> <Accessed February 1, 2010>

FDA Approves Morphine Sulfate Oral Solution for Relief of Acute and Chronic Pain. Food and Drug Administration. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm198667.htm> <Accessed February 1, 2010>

Consumer Advocate Recommends Removal of Fibromyalgia Drug from Market

Public Citizen, a consumer advocacy group, recently urged the FDA to pull the drug Savella® (milnacipran) off the U.S. market secondary to allegations that the drug lacks effectiveness and can lead to dangerously high blood pressure. The group built their case by stating that European regulators had rejected the approval of the agent last summer due to a lack of effectiveness and the presence of significant side effects, as well as less than desired clinical trial results.

Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) similar to Cymbalta® (duloxetine) and Effexor® (venlafaxine) and was FDA approved for fibromyalgia syndrome on January 14, 2009. Currently, it is the only drug FDA approved for fibromyalgia that possesses no other approved indications, and one of three FDA approved drugs for the condition. The other approved medications include Cymbalta and the anticonvulsant Lyrica® (pregabalin). SNRIs including Savella are associated with adverse cardiovascular effects such as increased heart rate and blood pressure.

According to the American College of Rheumatology, fibromyalgia affects 2 – 4% of the population, predominantly women, and is defined by chronic widespread muscular pain and tenderness. Although the FDA has been formally petitioned by Public Citizen regarding this matter, the agency is not bound to follow their recommendation.

Reference: Group Urges Recall of Drug for Fibromyalgia. Therapeutics Daily. <http://www.therapeuticsdaily.com/news/article.cfm?contentvalue=1953987&contenttype=sentryarticle&channelID=29> <Accessed February 2, 2010>

Fibromyalgia. American College of Rheumatology. http://www.rheumatology.org/public/factsheets/diseases_and_conditions/fibromyalgia.asp <Accessed February 2, 2010>

Savella Package Insert. 2010 Forest Laboratories. <http://www.savella.com/savella-information-hcp.aspx> <Accessed February 2, 2010>

NicOx Files NDA for Possible New Sub-class of NSAIDs for Pain Relief

The French pharmaceutical company NicOx recently announced that the FDA accepted the company's New Drug Application (NDA) for its novel drug, naproxcinod.

According to NicOx, naproxcinod is the first in a new class of anti-inflammatory agents known as CINODs or cyclooxygenase-inhibiting nitric oxide donors. If approved, this medication will likely be indicated for relieving the signs and symptoms of osteoarthritis; although, it is possible that it may be used for other painful conditions in an off-label manner.

The American College of Rheumatology states that osteoarthritis is the most common form of arthritis in the United States, affecting nearly 27 million Americans or approximately 12% of the adult population. According to the manufacturer, this new class of anti-inflammatory drugs is designed to provide comparable analgesic and anti-inflammatory properties as currently approved non-steroidal anti-inflammatory drugs (NSAIDs); however, naproxcinod is expected to offer a superior side effect profile compared to traditional anti-inflammatory agents on the market.

As designed, CINODs will function similarly to currently available NSAIDs with the exception of the additional release of nitric oxide into the vasculature and gastrointestinal tract. The systemic role of nitric oxide is thought to provide reduced gastrointestinal toxicity and prevent an increase in blood pressure as experienced with current NSAIDs.

Medications to treat symptoms of pain and inflammation are some of the most common drugs used by patients within the PMSI population. It is possible that the introduction of this new class of anti-inflammatory analgesic agent could alter the market share of current NSAID therapies in the workers' compensation market due to its anticipated limited gastrointestinal effects.

References: NicOx announces FDA accepts naproxcinod NDA for filing. NicOx Press Release. November 18, 2009. http://www.nicox.com/upload/PR_NDA_filingaccept_181109_EN.pdf <Accessed February 4, 2010>

Osteoarthritis. National Institute of Arthritis and Musculoskeletal and Skin Diseases. http://www.niams.nih.gov/Health_Info/Osteoarthritis/#2 <Accessed February 4, 2010>

Wallace, John et al. Cyclooxygenase-inhibiting nitric oxide donors for osteoarthritis. Trends in Pharmacological Sciences. 2009.30;3:112-117



New Approvals

Pennsaid® (diclofenac sodium topical solution, 1.5% w/w)

Approved: November 4, 2009

Nuvo's new drug application for **Pennsaid** topical solution has been approved by the FDA as of late 2009. Similar to other topical diclofenac preparations, **Pennsaid** is intended for application at the site of pain and discomfort. According to the FDA, **Pennsaid** is currently only indicated for the relief of the signs and symptoms of osteoarthritis of the knee(s); however, it is anticipated that prescribers will utilize this agent for other painful conditions in an off-label manner. **Pennsaid** should be available in early to mid 2010.

Qutenza® (capsaicin 8%, topical patch)

Approved: November 16, 2009

As of late 2009, **Qutenza** becomes the first concentrated, synthetic capsaicin topical product available only through a doctor's prescription. Approved for the treatment of post-herpetic neuralgia (neuropathic pain following Shingles), **Qutenza** must be applied by a healthcare professional no sooner than

every three months due to significant pain associated with its administration. The anticipated launch date for this product has yet to be determined but it is expected to become available in the first half of 2010.

Exalgo (hydromorphone)

Approved: March 2, 2010

Expected to have been approved last year, the makers of **Exalgo** suffered a brief hiccup in the FDA approval process in November 2009 as FDA officials expressed concerns over the drug's abuse potential indicating that it could be easily crushed. However, the FDA has formally approved the New Drug Application for **Exalgo** as of early March 2010. Once released on the market later this year, **Exalgo** will be the only long-acting formulation of hydromorphone available.

New Generic Launches

Actiq® (fentanyl citrate)

Approved: October 30, 2009

An AB rated generic version of the popular short-acting opioid analgesic, **Actiq**, has become available as of late 2009. Although a non-rated generic

To learn more about what makes up a REMS program, read the December 2009 edition of PMSInfo.

version of **Actiq** has been commercially available since late 2006, an AB rated version has not been available until now. Similar to brand name **Actiq**, the newly rated generic is only indicated for the treatment of cancer-related breakthrough pain in patients already utilizing around-the-clock opioid pain relievers.

Anticipated Drug Approvals

Abstral® and Rapinyl™ (fentanyl citrate, sublingual)

Anticipated Approval date: June 2010

With an anticipated approval date in the second quarter of 2010 **Abstral** and **Rapinyl** are expected to become the third and fourth additions to the sublingual line of fentanyl citrate products, joining **Actiq** and **Fentora** in the treatment of cancer-related pain. Although **Abstral** and **Rapinyl** will only have FDA indications for cancer-related pain, it is expected that they may have a large impact in the market share of **Actiq** and **Fentora** in non-cancer pain management.

FDA

MedWatch Reports: Highlighting Important Safety Issues from the FDA

McNeil Expands Tylenol Recall from Late 2009

Posted: January 15, 2010—McNeil Consumer Healthcare and the FDA notified healthcare professionals in early 2010 of an expansion to the December 2009 recall of certain Tylenol® products that were identified as causing stomach pain, nausea and vomiting. McNeil has

now applied broader criteria to identify and remove all product lots that may have the potential to be affected, even if they have not been the subject of consumer complaints. Consumers who purchased certain Tylenol products from the lots included in this recall should stop using the product and contact McNeil at www.mcneilproductrecall.com for

instructions on a refund or replacement. The affected product names and lot numbers for the recalled products can be found in the firm's Press Release at the following web address: www.fda.gov/downloads/Safety/Recalls/UCM197813.pdf. Any adverse reactions may also be reported to the FDA's MedWatch Program by fax at 1-800-FDA-0178, by mail at

MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or on the MedWatch website at www.fda.gov/medwatch.

Reference: McNeil Consumer Healthcare Announces Voluntary Recall of Certain Over-The-Counter (OTC) Products in the Americas, UAE, and Fiji. FDA Medwatch. <http://www.fda.gov/Safety/Recalls/ucm197746.htm> <Accessed January 28, 2010>

Diclofenac Products May Cause Unwanted Liver Effects

Posted: December 4, 2009—Endo, Novartis and the FDA recently notified healthcare professionals of revisions to the Hepatic Effects section of the prescribing information to add new warnings and precautions about the potential for elevation in liver function tests during treatment with all products containing diclofenac sodium. In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation. Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac. The optimum times for making the first and subsequent transaminase measurement are not known. Based on clinical trial data and postmarketing experiences, transaminase levels should be monitored within 4 to 8 weeks after initiating treatment with diclofenac.

Reference: Voltaren Gel (diclofenac sodium topical gel) 1% - Hepatic Effects Labeling Changes. FDA Medwatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm193047.htm> <Accessed December 8, 2009>

Valproate Sodium May Cause Unwanted Birth Defects

Posted: December 3, 2009—The FDA notified healthcare professionals and patients about the increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular malformations, in babies exposed to valproate sodium and related products (valproic acid and divalproex sodium) during pregnancy. Healthcare practitioners should inform women of childbearing potential about these risks, and consider alternative therapies, especially if using valproate to treat migraines or other conditions not usually considered life-threatening.

Women of childbearing potential should only use valproate if it is essential to manage their medical condition. Those who are not actively planning a pregnancy should use effective contraception, as birth defect risks are particularly high during the first trimester, before many women know they are pregnant. A valproate Medication Guide, provided with each outpatient prescription, will explain the benefits and risks of valproate and encourage patients to discuss options with their healthcare professional. Pregnant women using valproate or other AEDs should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (1-888-233-2334; www.aedpregnancyregistry.org).

Reference: Valproate Sodium and related products (valproic acid and divalproex sodium): Risks of Birth Defects. FDA Medwatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm192788.htm> <Accessed December 5, 2009>

Desipramine Package Insert Updated with New Safety Information

Posted: December 2, 2009—Sanofi-Aventis and FDA notified healthcare professionals of changes to the warnings and overdose sections of the Prescribing Information for Norpramin® (desipramine hydrochloride), indicated for the treatment of depression. The new safety information states that extreme caution should be used when this drug is given to patients who have a family history of sudden death, cardiac dysrhythmias, and cardiac conduction disturbances; and that seizures precede cardiac dysrhythmias and death in some patients.

Reference: Norpramine (desipramine hydrochloride) – Dear Healthcare Professional Letter. FDA Medwatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm192655.htm> <Accessed: December 8, 2009>



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