

New FDA Law Stimulates Availability of Drug Safety Information

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Recent FDA Generic Approvals: Risperidone, Oxcarbazepine, Zaleplon.
Tentative approvals: Topiramate Escitalopram, Lamotrigine

In September 2007, Congress approved the "FDA Amendments Act of 2007" (FDAAA) which provides the FDA more latitude to inform the public about drug safety and impose stipulations for the drug manufacturers when their drug product may pose a safety risk. Part of this new law authorizes the FDA to require drug companies to submit and implement a REMS (Risk Evaluation and Mitigation Strategy) along with requiring them to provide Medication Guides to patients by pharmacists. There are currently over 60 drugs requiring a Medication Guide and since September 2007, 25 drugs require a REMS. "These safety plans allow patients to have continued access to certain medicines for which there are safety concerns that can be managed through appropriate use", said a spokesperson for the FDA. Since this new law in September 2007, the FDA has issued several warnings. These warnings are not new to medications, but the increased availability of information on the internet, media publicity and the recent increased fervor and authority of the FDA to communicate and regulate safety warnings more promptly, have brought these to a heightened exposure. The following are from recent FDA releases and safety alerts:

Fluoroquinolones – Risk for Tendon Rupture Products include: Cipro, Levaquin, Avelox, Noroxin, Floxin, Factive and generics

The FDA is requiring the addition of a boxed warning to the prescribing information about the increased risk of developing tendonitis and tendon rupture in patients taking fluoroquinolones. The risk is further increased in patients over 60 yrs, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy. Patients should stop taking the drug at the first sign of tendon pain, swelling, or inflammation and avoid exercise and use of the affected area until resolved.

Varenicline (Chantix®)— More Neuropsychiatric, Mood, Drowsiness Warnings

The FDA has been releasing communication to prescribers about risk and warnings from Chantix use since October 2007. They have required Pfizer to implement a REMS and Medication Guide as of April 2008. A third FDA public health advisory was sent out on May 16, 2008 which highlighted the following related safety information: mood changes, worsening of pre-existing psychiatric illness, vivid, unusual dreams, and other behavioral changes. In May 2008, The Institute for Safe Medication Practices (ISMP) issued a 14 page report indicating the FDA has received 28 reports of road-traffic accidents, 68 cases of blurred vision and 86 cases of seizures from mid-2006, when Chantix first became available in the U.S. through Dec 2007. As a result the ISMP wants the FDA and Pfizer to warn physicians and patients about more than the neuropsychiatric side effects. Meanwhile, the Federal Aviation Administration (FAA) announced that pilots and air traffic controllers are now banned from using Chantix.

www.fda.gov/cder/drug/advisory/varenicline.htm

Desmopressin Acetate--- Hyponatremia and Seizures Products include: DDAVP, DDVP, Minirin®, and Stimat®

Children treated with desmopressin intranasal formulations for primary nocturnal enuresis (PNE) are particularly susceptible to severe hyponatremia and seizures. The intranasal formulations are no longer indicated for the

treatment of PNE and should not be used in any hyponatremic patients or patients with a history of hyponatremia. The desmopressin tablets may be used for PNE but should be interrupted during episodes of fluid and/or electrolyte imbalance, such as fever, recurrent vomiting or diarrhea, vigorous exercise or other conditions of increased water consumption. Fluid intake should be restricted from 1 hour before to 8 hours after administration of desmopressin tablets. All desmopressin formulations should be used cautiously in patients taking drugs such as anticholinergic drugs (tricyclic antidepressants, oxybutynin, tolterodine, trospium,), or drugs which cause the patient to drink more fluids.

www.fda.gov/cder/drug/infopage/desmopressin/default.htm

Bisphosphonates-- Risk of severe musculoskeletal Pain Products: Actonel®, Fosamax®, Didrone®, Aredia®, Boniva®, Skelid®, Reclast®, Zometa®

FDA informed healthcare professionals and patients of the possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking bisphosphonates. The severe musculoskeletal pain may occur within days, months, or years after starting a bisphosphonate. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete resolution. The risk factors for and incidence of severe musculoskeletal pain associated with bisphosphonates are unknown.

www.fda.gov/cder/drug/infopage/bisphosphonates/default.htm

Exenatide- (Byetta®)—Pancreatitis Reports

FDA has reviewed 30 post marketing reports of acute pancreatitis in patients taking Byetta (exenatide), a drug used to treat adults with type 2 diabetes. An association between Byetta and acute pancreatitis is suspected in some of these cases. Healthcare professionals should be alert to the signs and symptoms of acute pancreatitis and instruct patients taking Byetta to seek prompt medical care if they experience unexplained, persistent, severe abdominal pain which may or may not be accompanied by vomiting. If pancreatitis is suspected, Byetta should be discontinued. If pancreatitis is confirmed, Byetta should not be restarted unless an alternative etiology is identified.

www.fda.gov/cder/drug/infopage/exenatide/default.htm

Mycophenolate mofetil (CellCept®) and Mycophenolate sodium (Myfortic®)—Life threatening PML Reports

The FDA is investigating a potential association between the use of Cellcept and Myfortic, medications used to prevent organ rejection, and development of progressive multifocal leukoencephalopathy (PML), a life-threatening disease. PML is a rare disorder that affects the CNS and it usually occurs in patients with suppressed immune systems due to disease or medication.

www.fda.gov/cder/drug/early_comm/mycophenolate.htm

Erythropoiesis Stimulating Agents (ESAs):—Increased Mortality Products: Aranesp® (darbepoetin alfa), Epogen® (epoetin alfa), and Procrit® (epoetin alfa)

Amgen and FDA notified healthcare professionals of changes to the prescribing information which added: ESAs shortened overall survival and/or time to tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of ≥ 12 g/dL.

www.fda.gov/cder/drug/early_comm/ESA.htm

Modafinil (Provigil®)—Increased Psychiatric and Life Threatening Allergic Reactions

Mania, delusions, hallucinations and suicidal ideation have been reported during post marketing studies with modafinil. Most of these have occurred in patients with a previous psychiatric history, so caution is being advised for the use of modafinil in patients with a history of psychosis, depression, or mania. There have been reports of rashes, including one possible case of Stevens-Johnson Syndrome and one case of apparent multi-organ hypersensitivity reaction. Most cases of rash occurred within 1 to 5 weeks after starting therapy.

www.fda.gov/medwatch/safety/2007/safety07.htm#Provigil

Darunavir (Prezista®)— Reports of Hepatotoxicity

FDA and Tibotec Therapeutics notified healthcare professionals of changes to the WARNINGS section of the prescribing information for Prezista (darunavir) tablets regarding the risk of hepatotoxicity. In clinical trials and post marketing experience, drug induced hepatitis has been reported in patients receiving combination therapy with Prezista/ritonavir. Appropriate laboratory testing should be conducted prior to initiating therapy with Prezista/ritonavir and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pretreatment elevations of transaminases, especially during the first several months of Prezista/ritonavir treatment.

www.fda.gov/cder/drug/infopage/darunavir/default.htm

Fentanyl Patch--Deaths from incorrect use

Deaths and adverse events with Fentanyl patches have been documented. Fentanyl patches should only be used in opioid-tolerant patients already taking around the clock narcotic pain medicine and with chronic conditions that are not well controlled with other pain medicines. They should not be used for acute pain, pain following surgery, headaches, occasional or mild pain. Fentanyl patches should never be cut. Heat sources (heating pads, electric blankets, saunas or heated waterbeds, sunbathing, hot baths, heavy exercise) should be avoided when wearing a patch as heat will release more drug from the patch. Concomitant use of cytochrome P450 3A4 isoenzyme (CYP 3A4) inhibitors (ie. Ketoconazole, erythromycin, nefazodone, diltiazem, and grapefruit juice) can increase plasma concentrations and the risk for respiratory depression. Patches are developed to release the drug over 72 hours, thus changing the patch earlier than every 3 days is strongly discouraged.

www.fda.gov/medwatch/safety

Fentora® buccal tablets (Fentanyl)— Fatal overdoses when dosing Fentora Like Actiq

Fentora is to be used in opioid tolerant patients already taking around the clock narcotic pain medicine. It should not be used to treat any type of short term pain (headache, postoperative pain, pain due to injury, acute pain). Fentora is not the same as, or comparable to other fentanyl products and cannot be substituted on a mcg/mcg basis for Actiq®. Fentora® delivers more fentanyl than Actiq®, increasing the possibility of a fatal overdose.

www.fda.gov/medwatch/safety

Spiriva® (tiotropium) and Foradil® (formoterol) for inhalation— Do NOT Swallow Capsules

FDA and the American Association of Poison Control Center's (AAPCC) National Poison Data System have received many reports of patients swallowing Spiriva and Foradil capsules rather than placing the capsules in the inhalation devices. Both products are to be used in the HandiHaler (Spiriva) and Aerolizer (Foradil) devices to deliver the medicine to the lungs. Both products will not treat a patient's breathing condition if the contents of a capsule are swallowed rather than inhaled. Healthcare professionals should discuss with patients how to correctly use the Spiriva HandiHaler or Foradil Aerolizer.

www.fda.gov/cder/drug/advisory/tiopropium_formoterol.htm

Testosterone topical products—Do NOT Apply to Genitals

Testosterone transdermal products, Androderm®, and topical gels, AndroGel® and Testim® are not to be applied to the scrotum or genitals. Androderm® patch can be applied to the back, abdomen, upper arms or thighs. AndroGel® can be applied to shoulders, upper arms or abdomen. Testim®gel/jelly is to be applied to shoulders or upper arms only. [Drug Facts and Comparisons 2008 Edition. Wolters Kluwer Health; St. Louis, Missouri.](#)

Tussionex® Suspension (Long acting hydrocodone cough product)— Dosing is every 12 hours only!

Reports indicate that healthcare professionals have prescribed Tussionex for patients younger than the approved age group of 6 years and older, and more frequently than the labeled dosing interval of every 12 hours. Patients have administered the incorrect dose due to misinterpretation of the dosing directions, and have used inappropriate devices to measure the suspension. Overdose of Tussionex in older children, adolescents, and adults has also been associated with life-threatening and fatal respiratory depression.

www.fda.gov/cder/drug/advisory/hydrocodone.htm