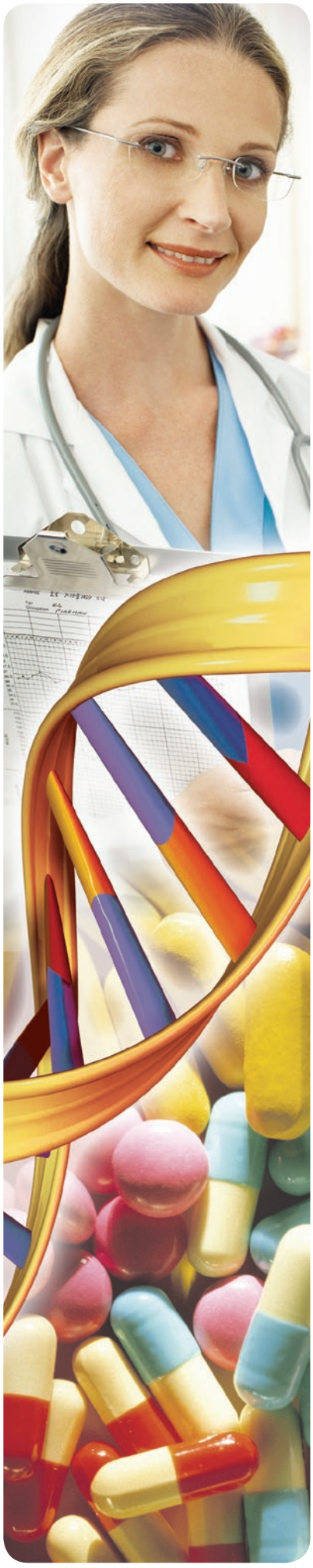

U.S. Food and Drug Administration
Protecting and Promoting Public Health

DRUG SAFETY NEWSLETTER

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IN THIS ISSUE

THE NEWSLETTER'S MISSION

This publication provides postmarketing information to healthcare professionals to enhance communication of new drug safety information, raise awareness of reported adverse events, and stimulate additional adverse event reporting. For more information, visit the FDA Drug Safety Newsletter Fact Sheet at *www.fda.gov/cder/dsn/factsheet.htm*

REPORTING ADVERSE EVENTS

FDA encourages the reporting of all suspected adverse reactions to all drugs, all suspected drug interactions, and all suspected reactions resulting in death, life-threatening outcomes, hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defects.

Report serious adverse events to FDA's MedWatch reporting system by completing a form online at *www.fda.gov/medwatch/report.htm*, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

EDITOR'S NOTE

In each issue of the DSN, we highlight safety issues related to a diverse group of FDA-approved drug products based on our assessment of the importance and timeliness of these topics to patient care and the seriousness of the adverse events. We also provide a list of recent advisories on drug safety, with related links, that have been posted on FDA's Web site.

In this issue, an article on TNF-alpha antagonists summarizes our postmarketing reviews of cases of rare but serious skin reactions (erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis) associated with infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira). This novel class of drugs is approved for and increasingly used to treat inflammatory and autoimmune diseases including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis.

The second article describes the occurrence of sudden sensorineural hearing loss associated with the use of phophodiesterase type 5 inhibitors, sildenafil citrate (Viagra), vardenafil hydrochloride (Levitra) and tadalafil (Cialis) approved for treatment of erectile dysfunction. Sildenafil citrate marketed as Revatio is also approved for treatment of pulmonary arterial hypertension.

The exenatide (Byetta) article describes cases of acute pancreatitis, a serious and potentially life-threatening adverse event. Exenatide is the first product in a new class of drugs known as incretin mimetics and is approved for the treatment of type 2 diabetes mellitus.

Also in this issue, we offer an overview of reported adverse events of interest associated with use of the new molecular entity, duloxetine (Cymbalta), a serotonin and norepinephrine reuptake inhibitor. Duloxetine is used to treat major depression, diabetic peripheral neuropathic pain, and generalized anxiety disorder in the United States.

Finally, we present our first feature article on pharmacogenomics as it relates to the potential clinical implications of this emerging science on the future of drug safety. Our evolving understanding of the pharmacogenomic variability of individual responses to drugs increases the potential to target therapies to those patients likely to get the greatest benefit as well as avoid treatment in those patients at greatest risk of adverse events.

In 2007, FDA has made available free, electronic access to a variety of clinically useful information resources for healthcare professionals at the point of care including:

- an RSS (Really Simple Syndication) feed via FDA's MedWatch Web site (*www.fda.gov/medwatch* or *www.fda.gov/oc/rss*)
- audio podcasting (*www.fda.gov/cder/drug/podcast/default.htm*), and
- the Drug Safety Newsletter (DSN).

We hope that healthcare providers find this newsletter a valuable complement to their clinical practices and an aid in the decision-making process for their patients.

Renan A. Bonnel, PharmD, MPH
Senior Scientific Editor

POSTMARKETING REVIEWS

EXENATIDE (marketed as BYETTA)

Acute Pancreatitis

FDA has been monitoring cases of acute pancreatitis in its postmarketing review of adverse event reports associated with the use of exenatide. Spontaneous adverse event reports of acute pancreatitis were described in the *Adverse Reactions* section of product labeling. Further postmarketing review of exenatide identified additional cases of acute pancreatitis associated with use of the drug. The product labeling has been updated to include information about acute pancreatitis in the *Precautions* section of the label, and information for healthcare professionals has been posted on FDA's Web site.[1] This article, based on the

review of 30 reports of acute pancreatitis, describes the postmarketing data that prompted the revision to product labeling and provides recommendations to healthcare professionals regarding this serious adverse event.

Exenatide, the first-in-class incretin mimetic, is a glucagon-like peptide-1 (GLP-1) analogue that stimulates insulin release from pancreatic beta-cells in a glucose-dependent manner, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.[1] Exenatide was approved by FDA on April 28, 2005, and is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control.[1] Exenatide is administered by subcutaneous (SC) injection, initially as a 5 micrograms (mcg) dose before the morning and evening meals, which can be increased to 10 mcg twice daily injections after 1 month of therapy. Commonly reported side effects of exenatide include nausea, vomiting, diarrhea, indigestion, and upper abdominal discomfort.

Exenatide was originally identified in the saliva of the poisonous Gila monster lizard. Pancreatitis has been reported with envenomation with Gila monster saliva due to overstimulation of the pancreas.[2]

From April 28, 2005, to December 31, 2006, FDA received 30 domestic reports of acute pancreatitis in patients who received exenatide treatment. Nineteen (63%) patients were female. The median age of patients described in the case reports was 60 years (range: 43-72 years).

The daily dose of exenatide was reported in 25 (83%) cases and ranged from 10-20 mcg. The median time to onset of symptoms of acute pancreatitis from the start of exenatide therapy was 34 days (range: 4-300 days). A dose-response relationship was observed in six patients who reported the onset or worsening of symptoms associated with acute pancreatitis soon after the dose of exenatide was increased from 5 mcg twice daily to 10 mcg twice daily.

Serum amylase, reported in 17 (57%) cases, ranged from 40-1,845 IU/L (normal range: 30-170 IU/L). The median serum amylase value was 384 IU/L. Serum lipase, reported in 25 (83%) cases, ranged from 62-16,970 (normal range: 7-60 IU/L). The median serum lipase value was 545 IU/L. The diagnosis of acute pancreatitis was confirmed by CT scan or ultrasound in 11 (37%) cases.

In 21 of the 30 cases (70%), the patients were hospitalized. There were no fatalities and no cases describing a hemorrhagic or necrotizing pancreatitis event. However, five patients developed serious complications, including dehydration and renal failure associated with dehydration (2), suspected ileus (2), ascites (1), and phlegmon (1) (these events are not mutually exclusive). Twenty-two

BOX 1

Case 1

A 69-year-old obese man with a 15-year history of type 2 diabetes was started on exenatide 5 mcg SC twice a day due to poorly controlled blood glucose (HbA1c 10.5%). With the initiation of exenatide treatment, pioglitazone and metformin were stopped. Following the first exenatide injection, the patient developed midepigastric abdominal pain radiating to the back. The pain intensified over the next few days and he was admitted to the hospital. Admission laboratory results were significant for an elevated serum amylase of 384 IU/L, serum lipase of 346 IU/L, low serum sodium of 130 mg/dL, blood glucose of 309 mg/dL, and white blood cell count of 11,000 cells/mm ^{3}. His serum creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), triglycerides, serum calcium, and hemoglobin were within normal limits. CT scan of the abdomen revealed no evidence of cholelithiasis, and the presumptive diagnosis of acute pancreatitis was made. The patient was treated with intravenous fluids, pain medication, pantoprazole, and insulin. The patient's abdominal pain resolved, his serum lipase normalized, and he fully recovered.

The patient's medical history was significant for diabetic neuropathy, retinopathy, hypertension, hyperlipidemia, coronary artery disease, gastroesoghageal reflux disease, colonic polyposis, depression, benign prostatic hypertrophy, convulsions, anxiety, stress, hypothyroidism, and rheumatoid arthritis. There was no previous history of pancreatitis, gallstones, or alcohol use. Concomitant medications included pioglitazone, metformin, Humulin NPH, rapid-acting insulin analogue, paroxetine, primidone, metoprolol, gabapentin, lovastatin, irbesartan, clopidogrel, infliximab, ezetimibe, and esomeprazole.

Case 2

A 51-year-old woman with a history of type 2 diabetes was started on exenatide 5 mcg SC twice a day. The patient experienced nausea, vomiting, and loss of appetite after starting the 5 mcg dose. One month later, the dose was increased to 10 mcg twice a day. Her symptoms increased, and she subsequently developed

... box continued on page 14

patients improved after exenatide therapy was discontinued, and 15 reports described the event as resolved at the time of the report.

Twenty-seven cases (90%) reported one or more possible contributory factors, including concomitant use of medications that list pancreatitis among reported adverse events in product labeling, or confounding conditions such as obesity, gallstones, severe hypertriglyceridemia, and alcohol use. Twenty-two cases reported a positive dechallenge once the drug was discontinued; three of these cases reported recurrence of various symptoms (e.g., nausea and vomiting, abdominal pain) at re-initiation of exenatide. These findings suggested a strong temporal association between exenatide and acute pancreatitis.

Two cases reported to AERS that suggest a role for exenatide in the development of acute pancreatitis are summarized in Box 1. The first case is described in the medical literature.[3] These cases were selected based on the temporal relationship between initiation of exenatide treatment or dose escalation and onset of symptoms associated with acute pancreatitis and the level of detail provided by the case reporter.

Subsequent to this review of 30 cases, additional cases of acute pancreatitis in association with exenatide use have been reported to FDA, including one case with serious complications resulting in pancreatic pseudocyst and sepsis leading to death. The cause of death was reported as metabolic acidosis from ischemic stomach, liver, and small intestines due to peripheral vascular disease.

FDA will continue to monitor AERS for reports of acute pancreatitis in association with the use of exenatide and carefully evaluate the data. Healthcare professionals are asked to report any suspected serious adverse reactions in association with exenatide therapy to the FDA MedWatch program.

... box continued from page 13

diarrhea and upper abdominal discomfort on the 10 mcg dose. Exenatide was discontinued. She was admitted to the hospital with a diagnosis of pancreatitis. She was treated with antibiotics, a liquid diet, and intravenous fluid. Diagnostic testing revealed a normal chest x-ray, normal sonogram of the gallbladder and kidneys, and an enlarged pancreas without a mass on abdominal ultrasound and CT scan. Admission laboratory results were significant for elevated serum amylase of 1,373 IU/L and serum lipase of 1,490 IU/L. During hospitalization, serum amylase and lipase decreased to 185 IU/L and 100 IU/L, respectively, and serum AST was 38 IU/L.

Nausea, vomiting, and diarrhea returned after the patient restarted exenatide therapy. At the time of the report, the pancreatitis was described as resolving, but the events of "nausea, vomiting, decreased appetite, and diarrhea were ongoing."

Her medical history included depression, hyperlipidemia, urinary tract infections, and thalassemia diagnosed in childhood. The patient denied any history of pancreatitis. Her relevant concomitant medications included metformin/rosiglitazone, glimepiride, nateglinide, fenofibrate, and atorvastatin.

FDA ENCOURAGES:

- Healthcare professionals to be aware of the potential for acute pancreatitis with exenatide and be alert to the signs and symptoms of acute pancreatitis. Symptoms include persistent, severe abdominal pain that can radiate to the back and may be accompanied by nausea and vomiting. Acute pancreatitis is typically confirmed by the presence of elevated levels of serum amylase and/or lipase and characteristic findings by radiological imaging.

- Physicians to discontinue exenatide if pancreatitis is suspected. If pancreatitis is confirmed, exenatide should not be restarted unless an alternative etiology for the pancreatitis is identified.

- Exenatide-treated patients to promptly seek medical care if they experience unexplained severe abdominal pain with or without nausea and vomiting. FDA

RELEVANT WEB SITES:

www.fda.gov/cder/drug/infopage/exenatide/default.htm
www.fda.gov/cder/drug/InfoSheets/HCP/exenatideHCP.htm
www.fda.gov/medwatch/safety/2007/safety07.htm#Byetta

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2. Sherman M. Therapeutic Venoms. US Pharm. 2005; 12: 33-36.
3. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. Diabetes Care. 2006; 29 (2):471.

PHOSPHODIESTERASE TYPE 5 (PDE5) INHIBITORS

Sildenafil citrate (marketed as VIAGRA and REVATIO), vardenafil hydrochloride (marketed as LEVITRA), and tadalafil (marketed as CIALIS)

Sudden Hearing Loss

A published case report of sudden sensorineural hearing loss (SSHL) in a male patient taking sildenafil citrate (Viagra) for the treatment of erectile dysfunction (ED) prompted FDA to search the Adverse Event Reporting System (AERS) for postmarketing reports of hearing impairment associated with use of PDE5 inhibitors.[1] There were 29 unique cases that described hearing loss, with or without associated vestibular symptoms, that met the definition of SSHL (see Box 1, page 16) and reported a strong or reasonably plausible temporal relationship to use of a PDE5 inhibitor (sildenafil citrate (Viagra, Revatio), vardenafil hydrochloride (Levitra), and tadalafil (Cialis)). The labeling for this class of drugs was revised to reflect this information in the *Adverse Reactions* section and provide guidance for patients who experience sudden hearing loss in the *Precautions, Information for Patients* section of the labeling. This article describes the postmarketing data that prompted the revisions to product labeling and provides indication-specific recommendations to healthcare professionals and patients regarding this adverse event.

Phosphodiesterase type 5 degrades cyclic guanosine monophosphate (cGMP). Inhibition of PDE5 results in increased cGMP which causes smooth muscle relaxation. Smooth muscle relaxation in the vascular beds of the corpus cavernosum and pulmonary arteries is responsible for the PDE5 inhibitor effects seen in erectile dysfunction (ED) and pulmonary arterial hypertension (PAH), respectively. Sildenafil, vardenafil, and tadalafil were approved for treatment of ED in 1998, 2003, and 2003, respectively; sildenafil (as Revatio) was approved for treatment of PAH in 2005. For ED, the recommended dose of tadalafil and vardenafil is 5 mg-20 mg and the recommended dose of sildenafil is 25 mg-100mg. These drugs are taken on an as-needed basis for ED, and the dose should not exceed once a day. The recommended dose of sildenafil for PAH is 20 mg, three times a day (60 mg/day). Sildenafil use by patients with PAH is both continuous and may be at a higher dose than for men taking sildenafil intermittently for ED.

REPORTED CASES OF SSHL

There have been 113 cases of hearing loss in patients using PDE5 inhibitors reported to FDA and drug product sponsors through September 20, 2007. Of the 113 reports, 84 cases were excluded from the case series. The reasons for exclusion include: significant uncertainty about the temporal association between PDE5 inhibitor use and hearing loss; hearing loss that did not meet the definition of SSHL; hearing loss that pre-dated drug use; a report that was too vague for attribution; and gradual hearing loss over several years, among others.

There were 29 unique cases (U.S.-14, non-U.S-15) in FDA's AERS database that contained a narrative supporting a strong or reasonably plausible temporal association between sildenafil, vardenafil, or tadalafil use and sudden hearing loss, both with and without accompanying vestibular symptoms (tinnitus, vertigo, or dizziness). Sudden hearing loss also was reported in a few patients in clinical trials for each of these drugs. The mechanism by which PDE5 inhibitors may be associated with SSHL remains uncertain. In many cases, medical conditions and other factors may have contributed to the adverse event. The discussion below is focused on analysis of these 29 cases.

The products involved in these 29 cases were sildenafil (15 ED and 4 PAH patients), vardenafil (5), and tadalafil (5). In one instance, more than one PDE5 inhibitor was used by a patient in proximity to the onset of SSHL and drug attribution was based on patients "usual" drug or drug listed first in the AERS report.

For the 25 cases reporting use for the ED indication, the age ranged from 38 to 85 years. Nine individuals reported co-existing medical conditions such as hypertension, heart disease, and diabetes mellitus that are risk factors for hearing loss. Three cases described a history of hearing loss (and, in one case, Meniere's disease). Many reports did not contain information regarding concomitant diseases, smoking history, or concomitant drug use.

Four patients (three females and one male) treated with

sildenafil for PAH reported sudden hearing loss. The time to onset of sudden hearing loss ranged from less than 3 weeks to 11 months after beginning sildenafil therapy. In all 4 cases, the sudden hearing loss was described as unilateral and ongoing at the time of the report. Sildenafil therapy continued for three of the reported cases and was discontinued in one case.

Unlike the 25 patients being treated for ED, the four PAH patients received sildenafil 2-3 times per day and also all were receiving other chronic medications at the time of the sudden hearing loss. Although the history of chronic, daily exposure to sildenafil for many weeks or months prior to the onset of SSHL in the PAH cases differs from the pattern observed in the 25 ED cases described above, the SSHL did occur while on sildenafil therapy. Therefore, a possible association between sildenafil exposure and hearing loss in PAH cases could not be ruled out.

There were no predictable warning signs for sudden hearing loss in the reported cases. In some cases, sudden hearing loss was accompanied by ringing in the ears and dizziness. The available information in these 29 cases was not sufficient to determine if any patient-specific risk factors were more likely to be associated with SSHL. There was limited medical follow-up information for these post-marketing case reports, making it difficult to determine whether these reports were directly related to the use of a PDE5 inhibitor, an underlying medical condition, or other risk factors for hearing loss, a combination of these factors, or other factors.

The key demographics and patient characteristics of SSHL cases are as follows:

- 27 patients reported the onset of SSHL within 24 hours of PDE5 use (sildenafil (15 ED, 4 PAH), vardenafil (4), tadalafil (4))
- The age range of patients using PDE5 inhibitors for ED was 38 to 85 years (mean- 61 years; median- 63 years); for PAH was 36 to 63 years (mean- 47 years; median- 44 years)
- 13 (45%) reported either generalized vascular disease (hypertension, diabetes, atherosclerosis), or other underlying contributory factors (tobacco use, history of hearing loss)
- The hearing loss was unilateral in 17 cases, bilateral in 4 cases, and not reported in 8 cases
- The hearing loss occurred with the first dose in 10 cases, with subsequent doses in 4 cases, and was not reported related to dosing in 15 cases
- Fifteen (52%) patients had concomitant tinnitus, vestibular symptoms, or both
- Nine patients (31%) reported that sudden hearing loss was temporary, in 16 cases the event was ongoing, and in 4 cases the outcome was not reported
- Twenty (70%) patients reported either pharmacologic interventions (such as systemic corticosteroid, antiviral, antiemetic therapy), and/or discontinuation of the drug
- Two patients with ED reported a positive re-challenge

BOX 1

What is SSHL?

According to the National Institute on Deafness and Other Communication Disorders (NIDCD)[2], sudden sensorineural hearing loss (SSHL), more commonly known as "sudden deafness", is a rapid loss of hearing that can occur all at once or evolve over a period of up to 3 days. It should be considered a medical emergency and persons experiencing SSHL should seek medical care immediately.

Hearing loss is unilateral in 90% of SSHL cases and may be associated with tinnitus or vestibular symptoms (e.g., disequilibrium, nausea). Spontaneous partial or full recovery of hearing is possible, although 15% of patients develop worsening hearing over time.

NIDCD estimates that approximately 4,000 cases of SSHL occur in the United States annually (an incidence of roughly 1-2 cases per 100,000 per year); others have reported that the incidence may be as high as 5-20 cases per 100,000 persons annually.[3] There are more than 100 possible causes of sudden deafness including vascular insult and drug-related ototoxicity; the cause is identified in only 10-15% of cases.

Hearing loss is very commonly reported in an aging population, especially in patients with risk factors for erectile dysfunction. However, sudden hearing loss is an uncommon event at any age. It is not known whether age was a factor in the cases of sudden hearing loss reported in temporal relation to use of the PDE5 inhibitors.

BOX 2

Case 1

A 50-year-old male reported bilateral hearing loss and ringing-type tinnitus, right greater than left, after taking an unknown dose of sildenafil (Viagra) for erectile dysfunction. He had no prior history of hearing loss; his medical history included arteriosclerotic vascular disease and hypercholesterolemia. He did not have his hearing evaluated and it is unclear if the hearing loss resolved. Approximately three months later, he noted hearing loss with increased tinnitus in the right ear within one hour of taking sildenafil. Audiogram showed a mild, bilateral, symmetric, high tone sensorineural hearing loss (SSHL) and a low tone SSHL on the right. A head MRI was normal. Two months later, he indicated that his hearing loss persisted unchanged and that

... box continued on page 17

Three cases that illustrate the temporal relationship between PDE5 inhibitor use and onset of SSHL are summarized in Box 2.

CURRENT STATUS

There appears to be a strong or reasonably plausible temporal relationship between PDE5 inhibitor exposure and SSHL in these 29 cases. In many cases, however, medical conditions and other factors may have contributed to the adverse event. FDA encourages:

- Physicians who prescribe Viagra, Levitra, or Cialis, for ED should advise their patients to immediately stop taking the drug if they experience any sudden decrease or loss of hearing and seek prompt medical attention
- Physicians should advise their patients with PAH who experience a sudden decrease or loss of hearing while taking Revatio to seek prompt medical attention. Patients should NOT stop taking the drug without consulting their physician about other treatment options

Healthcare professionals and patients should be watchful for sudden hearing loss associated with the use of sildenafil, vardenafil, and tadalafil and report cases to FDA's MedWatch.

RELEVANT WEB SITES

www.fda.gov/bbs/topics/NEWS/2007/NEW01730.html
www.fda.gov/cder/drug/InfoSheets/HCP/ED_HCP.htm

Sildenafil citrate (Viagra) product labeling.
www.fda.gov/cder/foi/label/2007/020895s027lbl.pdf

Vardenafil hydrochloride (Levitra) product labeling.
www.fda.gov/cder/foi/label/2007/021400s010lbl.pdf

Tadalafil (Cialis) product labeling.
www.fda.gov/cder/foi/label/2007/021368s012lbl.pdf

Sildenafil citrate (Revatio) product labeling.
www.fda.gov/cder/foi/label/2007/021845s004lbl.pdf

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3. Byl FM. Sudden hearing loss: eight years' experience and suggested prognostic table. Laryngoscope. 1984; 94: 647-661.

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he was still bothered by sound distortion and hearing asymmetry. Physical examination showed normal ear canals and tympanic membranes and follow-up audiometry was unchanged. It is unknown whether sildenafil was used subsequently.

Case 2

A 58 year-old male physician recently begun on tadalafil (Cialis) awoke with sudden right hearing loss approximately 6 hours after taking a 20 mg tablet. He experienced aural fullness and increasing tinnitus as well as imbalance, nausea, diaphoresis, and vertigo. He had no prior history of ear problems; his medical history included type II diabetes mellitus of 4 years duration, reactive airway disease, gastroesophageal reflux, benign prostatic hyperplasia, and progressive erectile dysfunction over 2 years.

An otolaryngic evaluation with audiometry showed a severe, flat, right-sided SSHL with a 0% speech discrimination score at 100 decibel hearing level. Hearing in the left ear was normal. A vestibular assessment showed normal electronystagmography, no positional nystagmus, and negative Dix-Hallpike maneuvers bilaterally. Bithermal caloric studies showed a 25% right-sided weakness. A brain MRI scan was negative.

He was treated with a 10-day course of prednisone as well as a course of antiviral medication and meclizine. He had episodic vertigo which gradually improved over 2 weeks, but his hearing loss and tinnitus persisted. Serial audiograms showed a persistent sensorineural hearing loss with no speech discrimination ability. The hearing loss was ongoing at the time of the report to the AERS database.

Case 3

A 59-year-old male experienced sudden bilateral SSHL shortly after taking a double dose (dose not reported) of vardenafil (Levitra) for erectile dysfunction. The patient has been taking vardenafil for many years, but awakened with hearing loss after the additional dosage. The patient had formal audiometric assessment and MRI with contrast of internal auditory canals; however, the results of the tests were not reported. The patient had no history of tobacco or alcohol use. Concomitant medications were not reported. The sudden hearing loss resolved after vardenafil was discontinued.

TUMOR NECROSIS FACTOR ALPHA (TNF-α) ANTAGONISTS

Infliximab (marketed as REMICADE), etanercept (marketed as ENBREL), and adalimumab (marketed as HUMIRA)

Serious Skin Reactions

Safety reviews of tumor necrosis factor-alpha (TNF-α) antagonists, infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira) identified rare cases of serious skin reactions, including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), associated with the use of these biological products. The product labeling for infliximab has been updated to describe postmarketing reports of serious skin reactions.[1] FDA is continuing to analyze what, if any, revisions to product labeling are needed for etanercept and adalimumab. Healthcare professionals and patients should be watchful for skin reactions associated with the use of infliximab, etanercept, and adalimumab and report cases to FDA's MedWatch.

Infliximab, etanercept, and adalimumab are biological products that work to block TNF-α, an inflammatory cytokine, but via different mechanisms. Infliximab and adalimumab are monoclonal antibodies that bind TNF-α while etanercept is a dimeric fusion protein consisting of a portion of the human TNF receptor linked to the Fc portion of human IgG1. TNF-α antagonists have been approved to reduce the signs and symptoms of rheumatoid arthritis (Remicade, Enbrel, Humira), psoriatic arthritis (Remicade, Enbrel, Humira), ankylosing spondylitis (Remicade, Enbrel, Humira), polyarticular juvenile idiopathic arthritis (Enbrel and Humira only), ulcerative colitis (Remicade only), and Crohn's disease (Humira and Remicade only) and treat adult patients with chronic plaque psoriasis of certain severity (Enbrel, Remicade, Humira).[1,2,3] Infliximab is administered as an infusion; etanercept and adalimumab are given subcutaneously. Table 1 (page 21) presents a summary of the demographics and characteristics of postmarketing cases reported to AERS that describe serious skin reactions associated with the use of infliximab, etanercept, or adalimumab.

The presenting signs and symptoms of the serious skin reactions were mainly rash and skin lesions on the trunk, legs, arms, shoulder, back, hands, and face. Oral mucositis or ulceration, genital ulceration, and/or fever were reported in some SJS cases. One patient experienced an allergic type reaction; she initially experienced hives and swollen lips, eyes, and face, then developed erythema multiforme lesions on her back and subsequently became

BOX 1

Case 1

A 36-year-old woman with rheumatoid arthritis began **infliximab** therapy. Her concomitant medications included clomipramine and amitriptyline. Two infusions of infliximab were administered two weeks apart. A day after the second infusion, she developed small cutaneous lesions of eczema-like appearance on the trunk and all limbs, and she was treated with an antihistamine. A third infusion was given about a month later, and she developed severe generalized erythroderma associated with Stevens-Johnson syndrome, which was confirmed by a dermatologist. She had mucositis and fissures localized on her hands and feet. A cutaneous biopsy suggested allergic erythroderma, and the immunofluorescence testing was negative. Infliximab was discontinued and other medications were continued. She was treated with systemic corticosteroids, antihistamine, and cutaneous care. Her condition improved over the course of several weeks. The final diagnosis was erythroderma due to infliximab with Stevens-Johnson syndrome.

Case 2

A 32-year-old female patient with rheumatoid arthritis was started on **etanercept** 25 mg twice a week. She also was taking prednisolone 7.5 mg daily. Her past medical history included toxic epidermal necrosis after approximately ten days of leflunomide therapy. The etanercept was started approximately ten months after leflunomide.

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hypoxic. A few cases of TEN described the skin reactions as skin desquamation and progressive pruritis over the whole body; generalized whole body skin peeling; a severe, scaly, pigmented necrotizing rash over the body; and erythema with blepharoconjunctivitis, angioedema, and throat tightness.

Three cases that illustrate the temporal relationship between TNF-α antagonist therapy and onset of serious skin reactions are summarized below (see Box 1).

INFLIXIMAB (REMICADE)

From the date of approval in August 1998 to August 2006, FDA received 21 (domestic-7, foreign-14) reports of cases in adult patients of severe cutaneous adverse reactions associated with infliximab, including EM (15 cases), SJS (5 cases), and TEN (1 case). Of these 21 cases, 16 were postmarketing reports and five were study/registry cases. Two cases of SJS and three cases of EM in this case series were also reported in the medical literature.[4,5,6]

The majority of the cases (76%) were female. Most cases (62%) received infliximab for the treatment of rheumatoid arthritis. The median time to onset between the first infusion and onset of the adverse reaction was 28 days. The patients received one to six infusions before the event (median 2 infusions). In one case, cutaneous, eczema-like lesions developed after the second infusion, and SJS developed following the third infusion (the clinical diagnosis of SJS was confirmed by a dermatologist).

Although fifteen cases (71%) reported one or more concomitant medications that have been associated with EM, SJS, and/or TEN, in only five of these cases were the concomitant medications (sulfasalazine, mercaptopurine, and leflunomide) reported as co-suspect medications. There was limited information on the start/stop dates of concomitant medications.

Twelve patients required hospitalization due to their cutaneous reactions. One patient who was hospitalized due to TEN subsequently died of multi-organ system failure 20 days after the first infusion. Fifteen cases reported positive dechallenge; two cases reported positive rechallenge (recurrence of similar cutaneous lesions with reintroduction of infliximab); one case reported negative rechallenge with no recurrence of the event with reintroduction of infliximab infusion approximately five months later. Despite confounding factors, such as concomitant medications which have been associated with skin reactions, several cases reported to AERS described a plausible temporal relationship, positive dechallenge, and/or positive rechallenge supporting an association between infliximab and serious cutaneous skin reactions.

ETANERCEPT (ENBREL)

From the date of approval in November 1998 to November 2006, FDA received 22 (domestic-10, foreign-12) reports of cases of severe cutaneous adverse reactions associated with etanercept, including EM, SJS, and TEN, involving an adolescent and adult patients. Of these cases, 17 were postmarketing, and five were study/registry cases. There were reports of 13 cases of EM, four cases of TEN, four cases of SJS, and one case of SJS/TEN. Two of the thirteen cases reported that biopsy results were consistent with the diagnosis of EM. One case of EM and one case of SJS/TEN also were described in the literature.[7] Fourteen (64%) patients were female. Most patients used etanercept for the treatment of rheumatoid arthritis.

Time to onset since last etanercept dose was provided for two cases and was reported as five days and nine days. The total number of etanercept doses was provided in six of the postmarketing cases and ranged from one to four doses; one registry case reported receiving 17 doses of etanercept before the skin reaction occurred. Four cases reported etanercept as the only medication that the patient was receiving.

Fifteen cases (68%) reported the use of concomitant medications associated with EM, SJS, and/or TEN. Five of these cases reported a co-suspect medication (isoniazid, indapamide, ciprofloxacin, terbinafine, or ethinyl estradiol/levonorgestrel) in addition to etanercept. Although there was limited information on the start/stop dates of the concomitant medications that have also been associated with serious skin reactions, most cases reported a temporal relationship with the use of etanercept.

Eleven patients required hospitalization due to their skin reaction. Eleven cases reported positive dechal-

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A vesicular erythematous rash started after the second etanercept injection, which worsened and spread to affect the trunk and arms and legs after the fourth injection. The rash was described as much more aggressive than the leflunomide reaction. The etanercept was discontinued. A skin biopsy showed areas of central necrosis, perivascular inflammation, and an inflammatory infiltrate at the dermoepidermal junction with necrosis of the basal keratinocytes. Clinical presentation and histology of the rash were consistent with erythema multiforme. The patient recovered after several months of treatment with moderate doses of prednisolone therapy.

Case 3

A 49-year-old male patient received **adalimumab** for rheumatoid arthritis in 2004. One month after beginning adalimumab therapy, after the second injection, the patient experienced red skin lesions on his arms and body. A dermatologist diagnosed EM based on a skin biopsy (site unspecified). Adalimumab therapy was discontinued, and the patient recovered. Concomitant medications included methadone, prednisone, multivitamins, and iron; however, no information was given on the start/stop dates of these other medications.

lenge; three cases reported positive rechallenge; and three cases reported negative rechallenge. There was one death reported of a patient who had been on etanercept therapy for approximately six months to treat rheumatoid arthritis and who was also treated with four concomitant medications associated with serious skin reactions. The patient was diagnosed with leukemia and EM one month after etanercept was discontinued. The patient refused treatment for leukemia and died approximately one month after the diagnosis of EM, with the cause of death reported as leukemia.

ADALIMUMAB (HUMIRA)

From the date of approval in December 2002 to November 2006, FDA received 7 (domestic-4, foreign-3) reports of cases of severe skin reactions. There were four cases of EM, two cases of SJS, and one case reporting both EM and SJS. An additional case of EM associated with adalimumab use was described in the literature.[7] Most patients (85%) were female, and five patients (71%) received adalimumab to treat rheumatoid arthritis. The median time to onset of skin reactions since starting adalimumab was 60 days. In three cases, the skin reaction occurred within the first two months of therapy (after one to two doses of adalimumab). One case reported biopsy results consistent with the diagnosis of EM.

Two cases listed adalimumab as the only medication the patient was receiving. Two cases reported the use of methotrexate as a concomitant medication associated with EM, SJS, and TEN, but none of the seven AERS cases reported suspect medications other than adalimumab. One patient required hospitalization. There were no reported deaths. Four of the seven cases reported recovery after discontinuation of adalimumab, and there were no reports of adalimumab rechallenge.

DISCUSSION

As protein products, all three TNF-α antagonists are potentially immunogenic and could precipitate immune-mediated serious skin reactions such as EM, SJS, and/or TEN.[6,7,8]

Evaluating the association between TNF-α antagonists and serious skin reactions can be challenging due to confounding factors, such as co-administration of one or more medications associated with EM, SJS, and/or TEN. Despite the lack of information regarding the beginning and ending dates of treatment with concomitant or co-suspect medications, several postmarketing reports described a temporal relationship between the first dose or most recent dose of the TNF-α antagonist and the time to onset of the skin reaction. These data accompanied by reports of positive dechallenge and/or positive rechallenge support an association between infliximab, etanercept, and adalimumab and serious skin reactions. FDA continues to monitor serious skin reactions in association with TNF-α antagonists.

Practitioners who prescribe TNF-α antagonists should be aware of the possibility of rare adverse skin reactions during treatment, ranging from mild to severe in nature. The development of any severe skin reaction while receiving TNF-α antagonist therapy may require a work-up to determine the appropriate diagnosis and treatment and consideration of an alternative therapy. FDA

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3. Adalimumab (Humira) product labeling *www.fda.gov/cder/foi/label/2007/125057s108lbl.pdf*
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REMINDER: HOW TO REPORT ADVERSE REACTIONS

Report serious adverse events to FDA's MedWatch reporting system by completing a form online at www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

Table 1. Summary of demographics and clinical characteristics of serious skin reaction cases following use of infliximab, etanercept, and adalimumab

Biological Product			
	Infliximab (Aug 1998-Aug 2006)* n=21 reports†	**Etanercept** (Nov 1998-Nov 2006)* n=22 reports†	**Adalimumab** (Dec 2002-Nov 2006)* n=7 reports†
Sex			
Male	5	7	1
Female	16	14	6
Unknown	-	1	-
Age (years)			
Median	54	53	51
Range	27-70 *(data provided for 20 patients)*	16-84	23-61
Indication			
	RA-13	RA-15	RA-5
	CD-4	PA-3	CD-1
	UC-3	AS-1	Unknown-1
	Other§-1	Other§-2	
		Unknown-1	
Skin reactions			
EM	15	13	4
SJS	5	4	2
TEN	1	4	-
SJS/TEN	-	1	-
EM/SJS	-	-	1
Patient using one or more concomitant medications associated with EM, SJS, and/or TEN			
	15 (71%) carbamazepine, celecoxib, diltiazem, furosemide/ hydrochlorothiazide, leflunomide, methotrexate, mercaptopurine, meloxicam, naproxen, rofecoxib, sulfasalazine, sertraline	15 (68%) aspirin, amoxicillin, celecoxib, ciprofloxacin, diclofenac, etoricoxib‡, ethinyl estradiol/ levonorgestrel, flurbiprofen, hydroxychloroquine, indapamide, isoniazid, lamotrigine, methotrexate, meloxicam, naproxen, rofecoxib, sulfasalazine, terbinafine, venlafaxine, warfarin	2 (29%) methotrexate
Time to onset since first dose			
Median (days)	28	50	60
Range	4 days-18 months *(data provided for 11 patients)*	5 days-52 months	6 days-3 years
Number of doses (dosing regimens differ by product and indication)			
	Median - 2 infusions	One dose-2	One dose-1
	Range 1-6 infusions *(data provided for 17 patients)*	Two doses-1	Two doses-1
	Unknown-4	Four doses-3	Unknown-5
		Seventeen doses-1	
		Unknown-15	

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	Infliximab (Aug 1998-Aug 2006)* n=21 reports†	**Etanercept** (Nov 1998-Nov 2006)* n=22 reports†	**Adalimumab** (Dec 2002-Nov 2006)* n=7 reports†
Outcome *(more than one outcome may be reported for some cases)*			
Death	1	1	0
Hospitalization	12	9	1
Disability	1	1	-
Life-threatening	-	-	1
Other (medically significant)	8	-	5
Unknown	-	11	1
Positive dechallenge	15	11	4
Positive rechallenge	2	3	-
Negative rechallenge	1	3	-

FOOTNOTES

RA = rheumatoid arthritis, CD = Crohn's disease, UC = ulcerative colitis, PA = psoriatic arthritis, AS = ankylosing spondylitis, EM = erythema multiforme, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis

* From U.S. approval date (month/year) until AERS search date (month/year)

§ Two cases reported use of etanercept for systemic lupus erythematosus or graft-versus-host disease (GVHD), respectively, which are unapproved indications. One case reported use of infliximab for polyarthritis, an unapproved indication.

† The total number of reports in each column represents both spontaneous AERS reports as well as study/registry cases in FDA's AERS database. The number of cases reported to FDA's AERS database cannot be used to calculate incidence rates, to estimate drug risk for a particular product, or to compare risks between products. Furthermore, the postmarketing reviews that described these data used slightly different inclusion criteria for these case series.

‡ Etoricoxib is not an approved drug product in the United States.

NEW MOLECULAR ENTITY (NME) EVALUATION—3 YEARS LATER

DULOXETINE (marketed as CYMBALTA)

Duloxetine hydrochloride (Cymbalta) is a serotonin and norepinephrine reuptake inhibitor (SNRI) for oral administration initially approved in August 2004 to treat major depressive disorder. Subsequently, FDA approved duloxetine for the treatment of diabetic peripheral neuropathic pain (September 2004) and generalized anxiety disorder (February 2007) in adult patients.

Duloxetine was the first product reviewed as part of FDA's ongoing pilot evaluation of a new systematic method of reviewing the safety of New Molecular Entities (NMEs) after approval (*www.fda.gov/cder/drug/postmarketing_safety/default.htm*). The purpose of the pilot is to determine the value of this systematic method of review, and to determine how, when, and for which products the reviews would be most useful.

The NME evaluation consists of a comprehensive review of safety data, including a review of adverse event reports in FDA's Adverse Event Reporting System (AERS) database, a data mining analysis of AERS data, a review of sponsor-submitted periodic safety reports, a literature review, a medication error analysis, an analysis of product use, and a review of postmarketing clinical trial and epidemiologic study findings. The results for duloxetine are summarized below.

Between August 2004 and December 2006, more than 3 million patients received a prescription for duloxetine.[1] The most common diagnoses in office-based practice settings for which duloxetine was prescribed during this period were psychiatric disorders (72%) and pain/neurop-

athy (17%).[2] Diagnoses related to bladder incontinence and female stress incontinence represented less than 1% of diagnoses[2] for which duloxetine was prescribed and are unapproved indications.

Approximately 50% of use was among patients aged 41-60 years. Pediatric patients (ages 0-16 years) accounted for less than 1% of total dispensed prescriptions.[1,3]

Initial review of the safety data identified a number of adverse events requiring further evaluation and more detailed review. These events included reports of bleeding, blindness, drug interactions, falls, loss of consciousness, hyponatremia, urinary hesitancy/retention, medication errors, and liver toxicity. The cases of blindness were subsequently determined to be related to underlying disease or other causes, rather than to drug use. The underlying cause of loss of consciousness already appeared to be appropriately reflected in current labeling. The potential risk of liver toxicity had been previously identified in clinical trials and prior analyses of postmarketing information, and is reflected in current labeling. Analysis of additional reports of liver injury is ongoing and labeling will be modified as needed.

The remaining adverse events identified in this review—bleeding, hyponatremia, falls, urinary retention/hesitancy, as well as medication errors—are discussed below.

Bleeding Disorders: There were 170 unique postmarketing AERS cases describing bleeding associated with duloxetine therapy. While most bleeding was in the gastrointestinal (GI) tract, bleeding also was reported in the vascular system (such as cerebral hemorrhage), renal/urinary system, reproductive system (such as vaginal bleeding), respiratory system, ears, and eyes. Bleeding ranged in severity from bruising to fatal GI hemorrhage. There were 6 cases of bleeding with death as an outcome; 4 of the deaths were considered unlikely to be related to duloxetine, but in the remaining 2 cases a role of duloxetine could not be excluded. There were an additional 33 hospitalizations attributed to a bleeding event. In 12 of these cases, the patients were taking concomitant medications that may have increased the risk of bleeding, including warfarin, aspirin, or other NSAIDs (such as ibuprofen). The 170 cases also included 1 case of platelet dysfunction, 9 cases of thrombocytopenia, and 5 cases of increased prothrombin time/international normalized ratio (PT/INR). Serotonin plays an important role in the coagulation process and abnormal bleeding is an expected effect of drugs that interfere with serotonin reuptake. All of the selective serotonin reuptake inhibitors (SSRIs) and the other SNRI (venlafaxine) have labeling describing the potential for abnormal bleeding; this information has been added to the labeling for duloxetine as a result of the NME evaluation.

Hyponatremia and Falls: Eleven unique postmarketing cases of hyponatremia were identified during evaluation of reports related to fall and loss of consciousness. The patients had serum sodium levels in the range of 100-120 mmol/L. Although hyponatremia is already described in the duloxetine labeling, FDA concluded that labeling would be more informative if it better described symptoms that suggest low serum sodium levels. Labeling therefore was supplemented to describe clinical manifestations of hyponatremia, including headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls, as well as hallucination, syncope, seizure, coma, respiratory arrest, and death in more severe and/or acute cases.

Urinary Retention/Hesitancy: There were 78 unique postmarketing cases of urinary retention/hesitancy associated with duloxetine use. Twenty-six of the 78 cases reported serious outcomes in 16 females and 10 males, with 8 of the females and 4 of the males described as having had a positive dechallenge. These 26 cases included 9 hospitalizations with catheterization, 8 hospitalizations without catheterization, and 9 catheterizations without hospitalization. Seven of the hospitalized patients had a primary or secondary diagnosis of urinary retention/hesitation. The existing product labeling had previously described the possibility of urinary hesitation with duloxetine. It has been supplemented to inform healthcare providers of the potential for the serious outcomes (catheterization and/or hospitalization).

Medication Errors: 177 cases of medication errors were reviewed and classified by the following error types: wrong strength, administration errors associated with opening the capsules, and wrong drug. For each of these error types, reviewers identified contributing factors associated with the container label, carton, and insert labeling.

FDA RECOMMENDATIONS

As a result of this NME review, the following changes have been made to duloxetine labeling or to the product container label.

- Information on the risk of hyponatremia, already described in the duloxetine labeling prior to this review, has been updated to provide more information about the clinical manifestations of hyponatremia. Changes have been made to the hyponatremia section of labeling, as well as to the overdosage section of labeling.
- Information on the risk of bleeding has been added to the *Warnings/Precautions* and *Patient Information* sections and language has been added on concomitant use of duloxetine with warfarin and other drugs that affect hemostasis. The revised labeling states that concurrent use of an NSAID, aspirin, warfarin, or any other drug that affects hemostasis may potentiate the risk of bleeding. In addition, it states that patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued.
- The information in labeling regarding urinary hesitancy/

retention has been updated (cautionary information in the *Warnings/Precautions* section).
- Changes have been made to the product container labels and labeling to prevent future medication errors, including warning against opening the capsules, which can affect the enteric coating.

FDA will continue to monitor the potential for liver toxicity with duloxetine, but has concluded that this risk is appropriately reflected in the current labeling. FDA is currently reviewing cases of drug interactions associated with duloxetine use. Healthcare professionals are requested to report any suspected serious adverse reactions in association with duloxetine therapy.

RELEVANT WEB SITES:

Duloxetine (Cymbalta) product labeling.
www.fda.gov/cder/foi/label/2007/021427s015s017lbl.pdf
www.fda.gov/cder/drug/advisory/SSRI_SS200607.htm
www.fda.govcder/drug/InfoSheets/patient/duloxetinePT.htm
www.fda.gov/cder/drug/InfoSheets/HCP/duloxetineHCP.htm

FOOTNOTES

1. Verispan, LLC: Total Patient Tracker, Aug04-Dec06, Extracted Feb07.
2. Verispan, LLC: Physician Drug and Diagnosis Audit, Aug04-Dec06, Extracted Feb07.
3. Verispan, LLC: Vector One®: National, Aug04-Dec06, Extracted Feb07, Mar07

FEATURE ARTICLE

PHARMACOGENOMICS AND ITS ROLE IN DRUG SAFETY

"Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease … "

- Sir William Osler (1849-1919)

Pharmacogenomics is the science of determining how genetic variability influences physiological responses to drugs, from absorption and metabolism to pharmacologic action and therapeutic effect.[1] With increasing knowledge of the molecular basis for a drug's action has come the recognition of the importance of an individual's genetic makeup in influencing how he or she may respond to a drug.

This understanding of the genetic variations in drug response opens the door to "personalized medicine" by (1) identifying patients who are more prone to experience adverse events from a drug and (2) identifying patients who are more likely to benefit from a particular therapy. This information has the potential to guide the selection of a drug for a particular patient and to tailor the drug dose to achieve the optimal therapeutic effect. In addition, knowledge of the genetic makeup of infectious agents is being used to guide treatment. For example, the identification of the specific drug resistance mutations in a patient's human immunodeficiency virus (HIV) is used to select the therapy most suitable or best "targeted" for that patient. In these ways, pharmacogenomics has the potential to assist physicians in adapting drug treatments to the characteristics of individual patients, ultimately leading to safer and more effective prescribing and dosing.

Pharmacogenomics determines how genetic variability influences response to a drug.

Potential applications in the clinic:
- Tailor dosing to decrease risk of adverse events.
- Identify patients for targeted therapy.
- Detect viral drug resistance.

To view a table of drugs with pharmacogenomics information provided in product labeling go to:

www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

IMPROVING DOSING AND DECREASING ADVERSE EVENTS

Genetic variants in drug metabolizing enzymes can have a significant effect on the way a person responds to a drug. They can speed up or slow down enzymatic activity, or even inactivate an enzyme. In some patients, known as rapid metabolizers, drugs are metabolized too

quickly. As a result, the average dose of the drug may be broken down too quickly to be effective, and a higher dose may be needed. Conversely, where the metabolite of the drug is active, as in the case of codeine (see below), rapid metabolism may lead to excessive accumulation of the active metabolite, which may result in toxic levels. In slow metabolizers, a drug administered at the recommended dose can accumulate due to such slow metabolism, potentially reaching toxic levels in the patient's system and leading to adverse reactions. Such patients may require a smaller dose. In conjunction with other factors, pharmacogenomics offers the potential to enable doctors to identify the patients who are rapid or slow metabolizers of certain drugs and to adjust dosing accordingly to achieve both effective and safe treatment.

Rapid metabolizers may break down a drug too quickly and require higher doses.

Slow metabolizers may build up toxic levels of the drug and require smaller doses.

CLINICAL APPLICATIONS OF PHARMACOGENOMICS

Warfarin (Coumadin and generics), an anticoagulant, is a recent example of the clinical use of pharmacogenomics to improve dosing. Warfarin has a narrow therapeutic window and a wide range of inter-individual variability in response, requiring careful clinical dose adjustment for each patient. Genetic variants in the warfarin target, the vitamin K epoxide reductase (VKORC1), as well as the warfarin metabolizing enzyme, cytochrome P450 2C9 (CYP2C9), influence the variation in patient response. Patients with certain variants of these genes eliminate warfarin more slowly and typically require lower warfarin doses. In those individuals, a traditional warfarin dose would more likely lead to an elevated International Normalized Ratio (INR), a longer time to achieve a stable warfarin dose, and a higher risk of serious bleeding events during the induction or dose-titration period of warfarin therapy.[3] (FDA News: *www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html*)

Another recent example involves ultrarapid metabolizers of codeine, who have multiple copies of the gene for cytochrome P450 2D6 (CYP2D6), the enzyme that converts codeine into morphine, its active metabolite. Nursing mothers who are taking codeine and are ultra-rapid metabolizers could have high levels of morphine in their breast milk, increasing the risk of morphine overdose in their nursing infant.[4] Although most nursing mothers can take codeine safely after childbirth, healthcare practitioners should prescribe the lowest dose for the shortest period of time to relieve pain and nursing infants should be carefully monitored when breastfeeding women receive this drug. (FDA Information to Healthcare Professionals: *www.fda.gov/cder/drug/InfoSheets/HCP/codeineHCP.htm*)

Pharmacogenomic studies have recently identified a genetic marker in patients, the human leukocyte antigen (HLA) allele HLA-B*1502, which is associated with dangerous, sometimes fatal, skin reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) following treatment with the antiepileptic drug carbamazepine (Carbatrol: *www.fda.gov/cder/foi/label/2007/020712s029lbl.pdf*, Equetro: *www.fda.gov/cder/foi/label/2006/021710s003lbl.pdf*, Tegretol: *www.fda.gov/cder/foi/label/2007/016608s098lbl.pdf*, and generics).[5] Since the HLA-B*1502 allele is found almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians, healthcare practitioners should screen patients with ancestry in at-risk populations for the HLA-B*1502 allele prior to initiating treatment with carbamazepine.[6,7,8,9] Patients who test positive for HLA-B*1502 should not be treated with carbamazepine unless the expected benefit clearly outweighs the increased risk of SJS/TEN. In weighing these risks and benefits, it is important to recognize that other antiepileptic drugs are associated with these serious skin reactions as well. (FDA Information for Healthcare Professionals Sheet: *www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm*)

Tests to identify the three genetic polymorphisms for warfarin, codeine, and carbamazepine described above are commercially available.

A table describing the valid genomic biomarkers that are currently part of FDA-approved drug labels can be found at *www.fda.gov/cder/genomics/genomic_biomarkers_table.htm*.[2] The table provides a list of these markers, links to pharmacogenomic data that support their validity, and recommendations for the clinical use of some of these biomarkers.

Targeted therapies are directed at tumor cells with particular protein characteristics that differ from normal cells.

PHARMACOGENOMICS LEADS TO MORE EFFECTIVE TARGETED THERAPIES

The incorporation of genomics in the preclinical and clinical research of anticancer drugs has resulted in significant progress in the development of new drugs. Discovering targeted therapies that are specifically directed at tumor cells with particular protein characteristics that differ from those of normal cells has been a primary focus of innovation in cancer treatment. Targeting drugs specifically to tumor cells can decrease the toxic effects of anticancer drugs on normal cells. For some targeted therapies, diagnostic genetic tests that can help identify the tumors that are likely to respond to those particular treatments have been co-developed with the drug. Examples of these drugs and their targets include:

- Imatinib (Gleevec) for bcr-abl tyrosine kinase in several tumor types
- Cetuximab (Erbitux) for epidermal growth factor receptor (EGFR) in head and neck cancer and colorectal cancer
- Trastuzumab (Herceptin) for variants in the Her2 receptor in breast cancer

PHARMACOGENOMICS CAN DETECT DRUG RESISTANCE IN VIRUSES

HIV genomes are constantly and rapidly evolving. Changes in targeted viral proteins may cause the HIV virus to become resistant to anti-viral drugs or vaccines. HIV patients often have to try different drug combinations when the virus becomes resistant to drugs they are taking. An FDA-approved kit, the TRUGENE HIV-1 (*www.fda.gov/Cber/510ksumm/K000038S.pdf*) Genotyping Kit, is now commercially available to detect several drug-resistance gene variants in the protease and reverse-transcriptase regions of the HIV virus. These two regions are targets of anti-retroviral treatments. If drug resistance is found to be present, the physician can alter the treatment regimen accordingly.

FDA'S ROLE IN PHARMACOGENOMICS AND PERSONALIZED MEDICINE

Pharmacogenomics holds the promise to individualize our healthcare and to improve drug safety and effectiveness for the population as a whole. FDA is in a unique position to promote pharmacogenomics and personalized medicine. It encourages the incorporation of pharmacogenomics in the drug development process (Genomics at FDA: *www.fda.gov/cder/genomics/*). In 2004, FDA launched the Critical Path Initiative (*www.fda.gov/oc/initiatives/criticalpath/*), a national effort to stimulate and facilitate the modernization of the sciences through which regulated products are developed, evaluated, and manufactured. The Critical Path Initiative is aimed at facilitating development of innovative tools, such as predictive genetic tests, valid biomarkers, assays, and information technology, to enable the efficient development and evaluation of safer and more effective drugs and promote the safe use of FDA-regulated products.

As part of the Critical Path Initiative, FDA is working to develop guidance for the pharmaceutical industry on co-development of drugs and diagnostic tests. FDA is also collaborating with the National Institutes of Health (NIH) and other research institutions in applied research efforts to study the genetic basis of drug-related toxicities. These research networks are working to improve the safety profiles of drugs in preclinical and clinical development as well as those, like warfarin and carbamazepine, that are already in the marketplace. Much work remains in understanding the role that genetics plays in achieving the goal of tailoring therapeutics to the individual patient.

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DRUG SAFETY COMMUNICATIONS

Drug Safety Communications posted by FDA from June 1, 2007 to December 31, 2007 (advisories are available at www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm)

Date	Product(s)	Safety Issue and Web Address
December 21, 2007	Fentanyl transdermal system (Duragesic and generics)	Update highlighting information on appropriate prescribing and use in light of continued reports of death and life-threatening adverse events related to fentanyl overdose. *www.fda.gov/cder/drug/advisory/fentanyl_2007.htm*
December 12, 2007	Carbamazepine (Carbatrol, Equetro, Tegretol, and generics)	Increased risk of serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) in patients with a particular human leukocyte antigen allele, HLA-B*1502. *www.fda.gov/cder/drug/infopage/carbamazepine/default.htm*

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Date	Product(s)	Safety Issue and Web Address
December 10, 2007	Omeprazole (Prilosec) and Esomeprazole (Nexium)	Update of safety review finding that long-term use is not likely associated with an increased risk of heart problems. *www.fda.gov/cder/drug/early_comm/omeprazole_esomepazole_update.htm*
December 4, 2007	Desmopressin acetate (DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimate Nasal Spray)	Reports of severe hyponatremia and seizures in children and removal of primary nocturnal enuresis indication for intranasal formulations. *www.fda.gov/cder/drug/InfoSheets/HCP/desmopressinHCP.htm*
November 20. 2007	Varenicline (Chantix)[1]	Ongoing safety review of reports of suicidal thoughts and aggressive and erratic behavior. *www.fda.gov/cder/drug/early_comm/varenicline.htm*
November 19, 2007	Rosiglitazone maleate (Avandia, Avandamet, and Avandaryl)	Update highlighting new labeled warning about the potential increased risk of myocardial ischemia. *www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm*
November 14, 2007	Phosphodiesterase type 5 (PDE5) inhibitors [sildenafil (Viagra and Revatio) vardenafil (Levitra),and tadalafil (Cialis)]	Potential risk of sudden hearing loss. *www.fda.gov/cder/drug/InfoSheets/HCP/ED_HCP.htm*
November 14, 2007	Cefepime (Maxipime)[1]	Ongoing safety review to further evaluate the risk of death in patients treated with cefepime. *www.fda.gov/cder/drug/early_comm/cefepime.htm*
November 8, 2007	Erythropoiesis Stimulating Agents (ESAs) [darbepoetin alfa (Aranesp), (epoetin alfa (Epogen, (Procrit)]	Update: New revisions to the product labeling to clarify the evidence for safety and effectiveness in cancer and chronic kidney failure patients. *www.fda.gov/cder/drug/infopage/RHE/default.htm*
October 25, 2007	Aprotinin (Trasylol)[1,2]	Ongoing safety review re-evaluating the overall risks and benefits in light of preliminary findings of a randomized trial in a cardiac surgery population (BART study). *www.fda.gov/cder/drug/early_comm/aprotinin.htm*
October 16, 2007	Exenatide (Byetta)	Reports of acute pancreatitis. *www.fda.gov/cder/drug/infopage/exenatide/default.htm*
October 12, 2007	Perflutren Micro-bubble Contrast Agents (Definity and Optison)	Reports of deaths and serious cardiopulmonary reactions following the administration of ultrasound micro-bubble contrast agents used in echocardiography. *www.fda.gov/cder/drug/infopage/microbubble/default.htm*
October 1, 2007	Bisphosphonates [alendronate (Fosamax, Fosamax Plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel with Calcium), tiludronate (Skelid), and zoledronic acid (Reclast, Zometa)][1]	Ongoing safety review to further evaluate the risk of atrial fibrillation in patients who take bisphosphonates. *www.fda.gov/cder/drug/early_comm/bisphosphonates.htm*
September 26, 2007	Fentanyl buccal tablets (Fentora)	Reports of serious adverse events, including death, with prescribing to non-opioid-tolerant patients, misunderstanding of dosing instructions, or inappropriate substitution for other fentanyl-containing products. *www.fda.gov/cder/drug/infopage/fentanyl_buccal/default.htm*
September 17, 2007	Haloperidol (Haldol, Haldol Decanoate, and Haldol Lactate)	Increased risk of Torsades de Pointes and QT prolongation. *www.fda.gov/cder/drug/InfoSheets/HCP/haloperidol.htm*
September 11, 2007	Ceftriaxone sodium (Rocephin)	Reports of fatal interactions in neonates treated with ceftriaxone and intravenous calcium-containing products. *www.fda.gov/cder/drug/infopage/ceftriaxone/default.htm*

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Date	Product(s)	Safety Issue and Web Address
August 17, 2007	Codeine	Report of very rare, but serious side effect (morphine overdose) in nursing infants whose mothers are taking codeine and are ultra-rapid metabolizers of codeine. *www.fda.gov/cder/drug/infopage/codeine/default.htm*
August 15, 2007	Nonprescription cough and cold drug products	Reports of serious and life-threatening adverse events associated with overdose and misuse of these products in children, especially in children under 2 years of age. *www.fda.gov /cder/drug/advisory/cough_cold.htm*
August 14, 2007	Rosiglitazone maleate (Avandia, Avandamet, and Avandaryl); Pioglitazone hydrochloride (Actos, Actoplus Met, and Duetact)	Increased risk of developing congestive heart failure or worsening of heart failure. • Rosiglitazone maleate *www.fda.gov/cder/drug/infopage/rosiglitazone/default.htm* • Pioglitazone HCl *www.fda.gov/cder/drug/infopage/pioglitazone/default.htm*
August 9, 2007 (updated December 10, 2007)	Omeprazole (Prilosec) and Esomeprazole (Nexium)[1]	Ongoing safety review of potential risk of heart attacks, heart failure, and heart-related sudden deaths based upon two small long-term clinical studies in patients with severe gastroesophageal reflux disease. *www.fda.gov/cder/drug/early_comm/omeprazole_esomeprazole.htm*
July 2, 2007	Omalizumab (Xolair)	Update highlighting revisions to product labeling and a new medication guide to address the risk of anaphylaxis. *www.fda.gov/cder/drug/infopage/omalizumab/default.htm*
June 29, 2007	Colistimethate (Coly-Mycin M and generics)	Report of death of a patient with cystic fibrosis after use of a liquid solution of colistimethate that was premixed for inhalation with a nebulizer. *www.fda.gov/cder/drug/infopage/colistimethate/default.htm*
June 15, 2007	Propofol (Diprivan and generics)	Reports of chills, fever, and body aches shortly after receiving propofol for sedation or general anesthesia. *www.fda.gov/cder/drug/infopage/propofol/default.htm*

FOOTNOTES:

1. Early Communication about an Ongoing Safety Review.
2. Withdrawn from marketing November 5, 2007.

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