DRUG SAFETY NEWSLETTER

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).
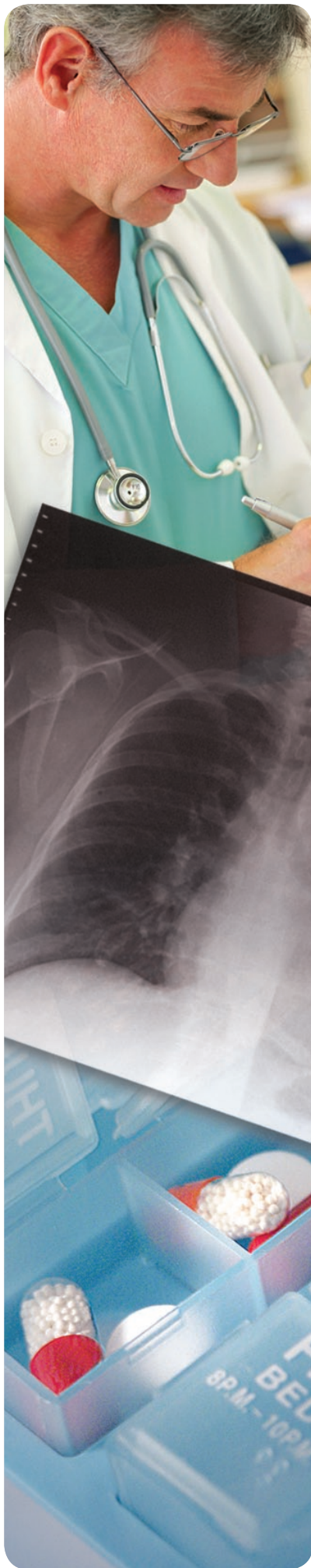
Welcome to the summer issue of the *Drug Safety Newsletter*. Our feature article focuses on medication errors and the steps healthcare professionals can take to prevent this common source of serious drug-related adverse events. We also describe the steps FDA takes to help reduce drug prescribing, dispensing and administration errors. In this issue, we discuss a drug-drug and a drug-device interaction, two types of medication errors that can be readily prevented.

On the topic of drug-drug interactions, we discuss an increased risk of rhabdomyolysis associated with the concurrent use of amiodarone (Cordarone and the generic drug Pacerone) and all marketed simvastatin products (Zocor, Vytorin, and Simcor) at doses of simvastatin greater than 20 mg per day. This drug-drug interaction is listed in the product labeling of both medicines.

Second, the risk of a potentially serious, sometimes fatal, drug-device interaction involving icodextrin (Extraneal), a peritoneal dialysis solution, and certain test strips used by some portable blood glucose monitors is reviewed. Falsely elevated glucose readings may be given to diabetic patients while undergoing peritoneal dialysis with this solution. This drug-device interaction was identified prior to marketing of icodextrin, and several safety measures, including patient/healthcare professional education, have been undertaken by the manufacturer. Nevertheless, FDA continues to receive reports of this adverse event.

In this issue, we also report on eosinophilic lung disease and pneumonitis in association with mefloquine (Lariam). This drug is currently approved and widely used for the treatment and prevention of malaria. This medication has been available for the past two decades. Serious pulmonary toxicity is rare, and in many cases, may not be immediately associated with mefloquine use.

Finally, we describe serious skin reactions, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), following the use of lenalidomide (Revlimid). This drug is indicated for the treatment of multiple myeloma and myelodysplastic syndromes.

We hope you find this issue of the *Drug Safety Newsletter* a useful source of information. We appreciate your feedback on the Newsletter. Please continue to share your thoughts with us via *www.fda.gov/cder/comment.htm*.

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Senior Scientific Editor

MEFLOQUINE HYDROCHLORIDE (MARKETED AS LARIAM AND GENERICS)

Pneumonitis

A postmarket safety review of mefloquine, an antimalarial agent, identified cases of pneumonitis or eosinophilic pneumonia associated with use of this drug. This review was prompted by the manufacturer's request to revise the *Adverse Reactions-Postmarketing* section of the label to include pneumonitis of possible allergic etiology. The product labeling has been updated to reflect this new safety information.

Mefloquine hydrochloride was approved by FDA in 1989. It is widely used as an oral treatment for mild-to-moderate malaria caused by mefloquine-susceptible strains of *Plasmodium falciparum* (both chloroquine-sus-ceptible and resistant strains) or by *Plasmodium vivax*. This drug is also approved as a prophylactic treatment for *P. falciparum* and *P. vivax* malaria infections, including chloroquine-resistant strains of *P. falciparum*.[1]

Mefloquine is usually well-tolerated, although it may cause mild nausea, vomiting, dizziness, insomnia, and nightmares. Rare, severe neuropsychiatric reactions may also occur, including depression, anxiety, psychosis, hallucinations, and seizures.[1] There have been five reported cases of mefloquine-associated eosinophilic pneumonia or pneumonitis in the medical literature.[2-6]

From May 1989 (the date of original approval) to January 2008, FDA has received 13 reports (U.S.-3, non-U.S.-10) of pneumonitis associated with mefloquine therapy. Of the 13 case reports, five are reported in the medical literature. This article summarizes FDA's analysis of these 13 AERS cases.

REPORTED CASES OF PNEUMONITIS

The 13 cases of pneumonitis reported to AERS involved patients ranging in age from 4-68 years (median age of 53 years). Sixty-nine percent of the patients (9/13) were female. Five patients received mefloquine for treatment of malaria. Six patients were given mefloquine as prophylaxis for malaria. In two cases, information on the underlying condition for which mefloquine therapy was begun was unknown. The median time-to-onset from first administration of mefloquine to respiratory symptoms was 2 days (range 1-84 days). All patients in this case series were hospitalized with various respiratory diagnoses, including pneumonitis, diffuse interstitial pneumopathy, and dyspnea/lung infiltration. Radiographic imaging indicated bilateral lung infiltrates in seven patients. In two cases, fluid from bronchoalveolar lavage (BAL) showed elevated eosinophils and neutrophils. In one patient, lung biopsy revealed an autoimmune interstitial alveolitis. A four-year-old female died after developing pneumonitis. This patient developed symptoms (pulmonary fibrosis and interstitial pneumonitis) after several prophylactic doses of mefloquine. No prior medical history was reported for this patient. Seventy-seven percent of patients (10/13) fully recovered when mefloquine was discontinued. Thirty-eight percent of patients (5/13) improved with systemic corticosteroid therapy. One patient was rechallenged with mefloquine and developed severe pneumonitis. In a number of cases, the recognition of the relationship between the pneumonitis and the use of mefloquine was delayed.

Two representative case reports implicating mefloquine in the development of pneumonitis are described in Box 1. These cases were selected based on the close temporal relationship of the adverse event to the taking of drug, the seriousness of the event, and a positive rechallenge with mefloquine.

In the first case, a case also reported in the medical literature,[3] pneumonitis developed one day after initiating mefloquine. Respiratory symptoms reappeared upon rechallenge with the drug. Symptoms gradually waned over a three-week period, most likely attributable to the length of the drug's elimination half-life of two to four weeks.[1] The second case describes the development of pulmonary fibrosis and interstitial pneumonitis in a 4-year-old female after she received several prophylactic doses of mefloquine. This patient had no prior medical history of pulmonary disease, and in the absence of other infectious processes, mefloquine was implicated as the causative agent.

These cases, including a positive rechallenge in one individual, suggest an association between pneumonitis and mefloquine use. Serious cases of pulmonary toxicity occurred when mefloquine was used prophylactically, as well as during the course of treating malaria. One-third of the patients improved following treatment with corticosteroids. Most patients fully recovered upon discontinuing the drug. Antibiotics proved to be an ineffective treatment in many cases, suggesting an immune-mediated, rather than infectious, etiology.

BOX 1

Case 1

Three weeks prior to traveling to Kenya, a 60-year-old woman began prophylactic treatment for malaria with mefloquine (250 mg weekly). On the day following the first dose of mefloquine, she developed a high fever and chills. Empiric antibiotic treatment was started. Four days after her symptoms appeared, she was admitted to the hospital with a fever (101 °F), shortness of breath, cyanosis, myalgia, a nonproductive cough, and headaches. A work-up for the etiology of the infection, including tests for tuberculosis and HIV, was negative. Laboratory blood tests showed a leukocytosis [white blood cell count: 19.9 x103/mm3 (normal 4.3-10 x10^3/mm^3) with 71% neutrophils, 18% lymphocytes and no eosinophils], an elevated C-reactive protein [CRP: 194 mg/dl (normal <3mg/dl)] and an elevated lactate dehydrogenase. A chest X-ray showed bilateral interstitial infiltrates. The patient improved slowly without additional treatment and was discharged after a few weeks with a diagnosis of diffuse interstitial pneumonia of unknown etiology. Four months later, the woman self-started mefloquine prophylaxis (250 mg weekly) ahead of another scheduled trip to Kenya. On the day following the first dose, she once again became severely ill with high fever, and respiratory distress (positive rechallenge). The symptoms were so severe that she was admitted to intensive care unit. Laboratory tests showed results similar to those obtained during her previous hospitalization (leukocytosis, a raised CRP, and elevated LDH). Specifically, there was severe hypoxemia (PaO$_2$: 45mm Hg, pCO$_2$: 32 mm Hg, pH: 7.44) as evidenced by an arterial blood gas analysis. High resolution computed tomography (HRCT) indicated diffuse pulmonary infiltration with ground-glass attenuation. Evaluations for an infectious etiology remained negative. The patient responded well clinically and radiologically to treatment with corticosteroids.

Concomitant medications included aspirin (for atherosclerosis), bisoprolol fumarate (for hypertension), and ciprofibratum (for hyperlipidemia). She had no history of smoking, allergies or pulmonary disease. There was no exposure to animals.

Case 2

A 4-year-old female patient died from pulmonary fibrosis and interstitial pneumonitis after prophylactic treatment with mefloquine. In 2006, prior to

traveling, she was started on mefloquine 75 mg per week, an age appropriate dose for the prevention of malaria. The patient had previously taken mefloquine (unknown date). Before the trip, the child was tired and had weight loss. During the trip, she experienced rash and fever (102.2 °F) at night, but was afebrile during the day. She was given an antibiotic for a suspected infection, although subsequent tests revealed no evidence of an infection. Tests revealed no evidence of an infection. On her return, she was hospitalized with suspected inflammatory disease, but no specific diagnosis was given. She was continued on the mefloquine and received corticosteroids which led to her improvement. After 45 days, however, her general state of health worsened. She started to cough and developed interstitial pneumonitis. Mefloquine was discontinued. A chest radiograph showed bilateral infiltration confluent in the lung. Compared to a previous film, the degree of infiltration had progressed. She was intubated and ventilated due to her rapidly progressive lung failure. A pulmonary biopsy showed autoimmune interstitial alveolitis. She was treated with high dose corticosteroids, plasmaphoresis, and immunoglobulins. After five weeks of extracorporeal membrane oxygenation (ECMO) treatment, the patient died suddenly. An autopsy revealed alveolitis and pulmonary fibrosis.

Mefloquine-induced pneumonitis is an infrequently reported, but serious, adverse event. FDA will continue to monitor AERS for reports of serious pulmonary toxicity in association with mefloquine.

FDA encourages physicians to:
• Be vigilant if travelers taking mefloquine as prophylaxis or for the treatment of malaria present with symptoms of lung disease or pneumonitis
• Be aware of this infrequent, but serious, adverse event when prescribing mefloquine to avoid delay in diagnosis or treatment
• Report cases of serious pulmonary toxicity in patients taking mefloquine to FDA's MedWatch program at *www.fda.gov/medwatch* FDA

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LENALIDOMIDE (MARKETED AS REVLIMID)

Serious skin reactions

A postmarket safety review of lenalidomide identified cases of serious skin reactions, including reports of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme (EM), associated with its use. Lenalidomide, an analogue of thalidomide, is an immunomodulatory agent with anti-angiogenic and antineoplastic properties

In December 2005, lenalidomide 5 mg and 10 mg capsules were approved to treat patients with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.[1] The risk classification of MDS is part of an international scoring system for evaluating the prognosis of MDS. This scoring system allows physicians to identify candidates for drug therapy.[2] In June 2006, lenalidomide 15 mg and 25 mg capsules were approved for use in combination with dexamethasone for the treatment of multiple myeloma in patients who had received at least one prior therapy for their myeloma. Lenalidomide is considered a teratogenic agent and, in order to prevent pregnancy exposures, is only available under a special restricted distribution program (RevAssist®). Currently, lenalidomide's product labeling does not include information regarding SJS or TEN.[1]

From the date of its original approval in December 2005 through January 23, 2008, FDA received 14 reports

(U.S.-13, non-U.S.-1) of serious skin reactions (i.e., SJS, TEN, and EM) associated with lenalidomide therapy. No additional cases were identified from the literature. This article summarizes FDA's analysis of these cases from the AERS database.

REPORTED CASES OF SERIOUS SKIN REACTIONS

The 14 cases in this report are referred to as SJS/TEN, given the clinical information provided was insufficient to differentiate cases of SJS from TEN. Upon review, three of the 14 reports in this analysis, initially coded in AERS as EM, were re-designated as SJS/TEN as they presented with two or more signs of SJS/TEN (e.g., grade 3 blisters, generalized rash with or without eye and mucosal involvement, and erythema with erosion and crusting of the skin) based on the Common Terminology Criteria for Adverse Events v3.0 (CTCAE; see *http://ctep.cancer.gov/reporting/ctc.html*). All of these cases required medical intervention.

All dermatological events occurred while patients were taking lenalidomide, with a median time-to-onset of 25 days (range: 3 to 112 days; n=12). Ten patients (71%) were female. The median age of these patients was 70.5 years (range: 46-94 years; n=12). The daily dose reported in 14 cases ranged from 5- 25 mg.

These patients presented with a rash to the arms and/or legs, or to the whole body. Some patients presented with large bullous or vesicular eruptions. In addition, some cases noted the development of pruritis, erythema, burning, facial edema, pain, eruptions in the mouth, around the eyes, or over the abdomen, sore throat, difficulty swallowing, and/or fever. One patient who had a history of a drug allergy to thalidomide (i.e., a rash) experienced what was described as a "Stevens-Johnson type rash" after three days of lenalidomide therapy, suggesting the possibility of a cross-sensitivity between these two drugs.

Thirteen patients received lenalidomide for the approved indications of multiple myeloma (10) and myelodysplastic syndrome (3). One patient was treated with lenalidomide for myelofibrosis, an unapproved indication. Some patients also received treatment with systemic corticosteroids.

Six patients who developed SJS/TEN required hospital-

BOX 2

What are Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme (EM)?

SJS and TEN are two related, and potentially life-threatening, acute skin disorders that may result from drug exposure. SJS and TEN are characterized by varying degrees of blistering with detachment of the epidermis. For SJS, 10-30% of the body surface area is affected. For TEN, greater than 30% of the body surface area is affected.[3] The mortality resulting from these reactions is reported to be between 1-3% for SJS and 10-70% for TEN.[4] In industrialized countries, the estimated annual incidence of these adverse events is reported to be 1-2 cases/one million people/year.[5]

The prodromal phase of SJS/TEN may begin with symptoms of fever, malaise, headache, cough, and rhinorrhea. These initial symptoms may last for 1-3 days before the appearance of flat atypical or purpuric macular lesions. These lesions may then progress to blistering, erosions, and epidermal detachment. The mucosal membranes of the mouth, eye, and genital areas are affected in most patients. Respiratory and gastrointestinal tract lesions may also be present.

Skin lesions may be tender and mucosal mucosal lesions may be painful. Early lesions show scattered necrotic keratinocytes in the epidermis. Late lesions show confluent "full-thickness" epidermal necrosis and may eventually form subepidermal bullae.[6]

SJS/TEN are most often caused by drugs (e.g., anti-infective sulfonamides, non-steroidal anti-inflammatory drugs, anticonvulsants, and allopurinol). Vaccinations, exposure to chemicals and fumigants, and infection with mycoplasma pneumonia are also associated with SJS.[6] The greatest risk for developing SJS or TEN is during the first two months of drug therapy.[7] Drug causality is usually suspected if the time between the initiation of drug therapy and the onset of SJS and TEN is 4–28 days.[6]

There are no definitive treatments for SJS and TEN. Supportive care and treatment of specific symptoms are critical. SJS- and TEN-associated mortality may be reduced by early identification and immediate discontinuation of the suspect drug.[6] Patients often do better if the discontinued drug has a short half-life (< 24 hours). Corticosteroids, intravenous immunoglobulins, plasmapheresis, cyclophosphamide, cyclosporine, and thalidomide[†] have been used in the treatment of TEN.[7]

Erythema multiforme (EM), in contrast to SJS and TEN, is most often caused by the herpes simplex virus. It is a recurrent condition characterized by a limited number of typical or raised target lesions. Blisters may also develop with EM. There is limited oral mucosa involvement. The condition has low morbidity and no mortality.[4,6]

Footnote

[†] The study assessing the safety and efficacy of thalidomide in treating TEN was terminated due to a higher mortality with thalidomide compared with the placebo group.[7] Thalidomide itself is labeled for SJS/TEN and hypersensitivity reactions.

ization. Nine of the 14 patients improved or recovered, six of whom also received systemic corticosteroid treatment. There were no rechallenge cases.

There were three deaths reported. Of these cases, one patient died 12 days following hospitalization. Although the cause of death was not provided, there was a diagnosis of SJS at the time of death. The second patient with SJS died eight days following hospitalization. The cause of death was cited as progression of multiple myeloma. The third patient developed TEN following the 4th cycle of lenalidomide (each cycle was 21 days). The patient was hospitalized and the rash resolved five days later. Thirty days following hospitalization, the patient died from progression of multiple myeloma.

Eight patients (57%) reported prior or concurrent therapy with medications that have also been associated with SJS/TEN (i.e., fluoxetine, omeprazole, lansoprazole, esomeprazole, nabumetone, moxifloxacin, escitalopram, sertraline, alprazolam, allopurinol, alendronate, simvastatin, oxcabazepine, and lisinopril). These agents were not listed as co-suspect causes of SJS/TEN. For many of these drugs, however, the date of initiation of treatment was unknown.

Two cases suggesting a role for lenalidomide in the development of serious skin reactions are summarized below (see Box 3). These cases were selected based on a temporal relationship between the adverse event and exposure to drug, the seriousness of the event, and, in one case, a potential cross-sensitivity with thalidomide.

The first case presented describes a patient with a confirmed diagnosis of SJS. The time from the initiation of lenalidomide to the onset of SJS/TEN event was 13 days. This time frame is consistent with the time of onset generally observed for drug-induced SJS/TEN (4-28 days).[6] In this case, the patient died from a cause(s) not reported. However, the rash and SJS had not resolved at the time of death.

The second case describes a patient with a history of a thalidomide-induced rash. Three days after receiving lenalidomide, this patient developed a maculopapular rash, urticaria and bullous or vesicular eruptions (SJS-like symptoms). This case suggests a potential cross-sensitivity between lenalidomide and thalidomide.

Although some patients in this case series may have received previous or concurrent medications labeled for SJS/TEN (see above), in all cases, the skin reactions manifested while patients were taking lenalidomide. Some of these patients recovered or improved after discontinuation of lenalidomide. Lenalidomide is an analogue of thalidomide, a drug which is known to cause SJS/TEN, strengthening the probable association between lenalidomide and SJS/TEN in one case. In all cases, the events were serious, required hospitalization and/or medical interventions.

This case series suggests that serious dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, may occur with lenalidomide therapy.

Case 1

A 59-year-old female received lenalidomide 25 mg daily for 21 days for multiple myeloma stage III cancer with bone metastasis and renal failure. The patient received dialysis two weeks prior to starting lenolidomide. Twelve days after the first dose of lenalidomide, the patient developed a small rash on her chest. This rash lasted for approximately one week before it eventually resolved while on lenolidomide (no intervention was reported). During the week following cessation of lenolidomide, the rash returned, worse than before, affecting the whole body, including the face. With the reappearance of the rash, the patient was hospitalized. A diagnosis of SJS was confirmed. Twelve days later, the patient died. Her SJS had not resolved by the time of her death. The cause of death was not provided. Concomitant medications included dexamethasone, eszopiclone, escitalopram, loperamide, a multivitamin, transdermal fentanyl, and hydromorphone.

Case 2

A 67-year-old female received lenalidomide 5 mg orally for three days for treatment of myelofibrosis. Her relevant medical history included a drug allergy to thalidomide (rash).[††] After 3 days of lenalidomide treatment, the patient experienced pruritis, burning, localized maculopapular rash with urticaria, and bullous or vesicular eruptions (Stevens-Johnson type rash). A skin biopsy was not performed. The rash was treated with systemic corticosteroids and resolved. Concomitant medications— some of which had begun more than nine months earlier— included allopurinol, atenolol, folic acid, alendronate, furosemide, glipizide, potassium chloride, levothyroxine sodium, calcium plus Vitamin D, simvastatin, spironolactone, epoetin alfa, docusate sodium, hydroxyurea, metformin, prednisone, and lansoprazole. None of these medications were suspected to be the causative agent in the development of SJS/TEN.

Footnote

[††] Rash, SJS, and TEN are included in thalidomide product labeling.[8]

FDA encourages physicians to:
- Be aware of the possibility of rare serious skin reactions when prescribing lenalidomide
- Discontinue lenalidomide treatment if a skin rash occurs and only resume lenalidomide therapy after appropriate clinical evaluation
- Discontinue and not resume lenalidomide treatment if the rash is exfoliative, purpuric, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected

Healthcare professionals and patients should be watchful for skin reactions when using lenalidomide and report any suspected cases to FDA's MedWatch program (*www.fda.gov/medwatch/*). FDA

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INTERACTION BETWEEN AMIODARONE (MARKETED AS CORDARONE AND PACERONE) AND SIMVASTATIN (MARKETED AS ZOCOR AND GENERICS) OR SIMVASTATIN-COMBINATION PRODUCTS (MARKETED AS VYTORIN AND SIMCOR):

Amiodarone potentiates the risk for simvastatin-associated rhabdomyolysis

FDA continues to receive reports of rhabdomyolysis in patients given amiodarone in combination with higher doses of simvastatin. Amiodarone is an antiarrhythmic drug indicated to treat certain types of recurrent ventricular arrhythmias. Simvastatin is a 3-hydroxy-methylglutaryl-coenzyme A reductase inhibitor (statin) used to lower cholesterol levels. As with all statins, the risk of rhabdomyolysis is dose-related and increased by high plasma levels of statin. Patients who take amiodarone with simvastatin doses greater than 20 mg daily have an increased risk of rhabdomyolysis. The precise mechanism for this drug interaction is unknown, but stems, in part, from amiodarone's inhibition of the cytochrome P450 3A4 (CYP3A4) enzyme, the same enzyme that metabolizes simvastatin (see Illustration 1, next page). This interaction may result in an increase in the levels of simvastatin in the plasma, potentiating the risk of rhabdomyolysis. Labeling for all of the amiodarone (Cordarone and the generic drug Pacerone)[1] and simvastatin-containing products [Zocor[2], ezetimibe/simvastatin (Vytorin[3]) and niacin/simvastatin (Simcor[4])] describe this potential risk.

Rhabdomyolysis, a severe form of myopathy, involves injury to and breakdown of skeletal muscles, which in some cases leads to renal failure and death.[5] There are multiple etiologies for rhabdomyolysis, including, but not limited to, exposure to certain drugs, including statins.[6,7] Healthcare professionals should be aware of the increased risk of rhabdomyolysis when amiodarone is taken concomitantly with doses of simvastatin that exceed 20 mg

daily. Prescribers should avoid doses of simvastatin greater than 20 mg per day in patients taking amiodarone (the maximum recommended simvastatin dose is 80 mg daily).

Both the simvastatin and amiodarone labels were changed in 2002 to reflect the increase in risk for myopathy when amiodarone is taken concurrently with simvastatin.[1-4] The simvastatin label (*Warnings, Precautions and Dosage and Administration sections*) specifically indicates that the dose of simvastatin should not exceed 20 mg daily in patients concomitantly receiving amiodarone, and that the combined use of simvastatin and amiodarone at simvastatin doses higher than 20 mg daily should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The amiodarone label (*Precaution* section) notes that there is an increased risk for myopathy/rhabdomyolysis when amiodarone is taken in combination with HMG-CoA reductase inhibitors that are CYP 3A4 substrates, such as simvastatin.

Since this labeling change was made, FDA has received 52 additional U.S. reports of rhabdomyolysis associated with the concurrent use of amiodarone and simvastatin. This article summarizes FDA's analysis of these 52 cases from FDA's Adverse Event Reporting System (AERS) database dating from January 1, 2003 to January 1, 2008.

ILLUSTRATION 1

Amiodarone-Simvastatin Interaction
Postulated Mechanism

This illustration depicts a postulated mechanism for the amiodarone-simvastatin interaction, including the subsequent impact of this interaction on skeletal muscle and the kidney. In the first column, amiodarone inhibits the enzyme CYP3A4, limiting simvastatin metabolism (depicted by dashed arrow). By limiting the metabolism of simvastatin, there is an increase in levels of circulating simvastatin in the blood. In the second column, high circulating simvastatin levels may result in myotoxicity in the skeletal muscles (rhabdomyolysis). The rapid breakdown of muscle protein produces excessive levels of myoglobin in the blood. In the third column, myoglobin, now at high circulating levels, reaches the kidneys where it can obstruct renal tubules and lead to acute renal failure. *Amiodarone's direct inhibition of CYP3A4 has been characterized as weak, suggesting that other factors may also contribute to how these two drugs interact.

REPORTED CASES OF RHABDOMYOLYSIS

The 52 cases of rhabdomyolysis reported to AERS involved patients ranging in age from 50 to 88 years (median age was 73). Thirty-seven patients (71%) were male and 10 were female (19%). The sex was not reported for the remaining five patients (10%). In half of the reported rhabdomyolysis cases (26/52), amiodarone was being taken in combination with 80 mg simvastatin. Thirteen patients (25%) were taking amiodarone in combination with 40 mg simvastatin, while four patients (8%) were taking amiodarone with 20 mg simvastatin. One patient (2%) developed rhabdomyolysis when taking amiodarone with 5 mg simvastatin. Eight patients (15%) were taking an unknown dose of simvastatin in combination with amiodarone.
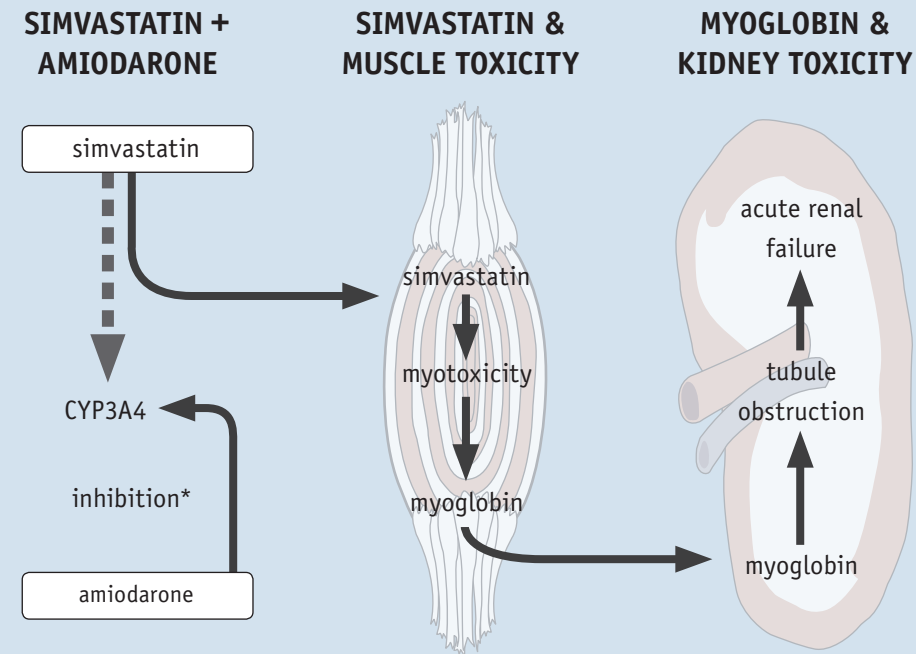
Regarding other concomitant medications, 37 patients (71%) were taking medications in addition to amiodarone and simvastatin. These drugs included diuretics (20), beta-blockers (18), angiotensin-converting enzyme inhibitors (16) and insulin (11). Among the concurrent medications taken by these patients, all except for niacin and levofloxacin are either substrates for and/or inhibitors of CYP3A4. These medications included gemfibrozil (9), angiotensin II receptor blockers (3), clarithromycin or levofloxacin (2), protease inhibitors (2), niacin (2), fenofibrate (1), atorvastatin (1), and risperidone (1). The labels of several of these products reflect the risk of rhabdomyolysis when they are used as monotherapy or when administered concurrently with simvastatin.

The mean time interval between the initiation of amiodarone therapy in conjunction with simvastatin (or simvastatin therapy in conjunction with amiodarone) and the onset of rhabdomyolysis was five months (median-2 months). Specifically, 42% of the cases (22) indicated that symptoms of rhabdomyolysis emerged within 2 months of the initiation of concurrent amiodarone-simvastatin

therapy. Forty percent of the cases (21) did not report the time interval between the onset of rhabdomyolysis and the initiation of amiodarone-simvastatin therapy.

Ninety-two percent of rhabdomyolysis cases (48) required hospitalization. Twenty-eight percent of the reported cases (15) were considered life-threatening. Ten percent of patients (5) who developed rhabdomyolysis were noted to have become disabled. One death was reported (2%).

Three representative case reports of amiodarone-simvastatin associated rhabdomyolysis are described in Box 4. These cases were selected based on their representation of the demographics and circumstances usually reported with amiodarone/simvastatin-associated rhabdomyolysis. In addition to being reported to AERS, Case 3 has also been published in the scientific literature.[8]

The concomitant use of amiodarone with simvastatin reduces the dose threshold for simvastatin-associated rhabdomyolysis. The cessation of symptoms (and lowering of laboratory values indicative of rhabdomyolysis) after discontinuation of one or both of these drugs indicates that muscle breakdown can be halted and reversed if identified early. Healthcare professionals should be aware that amiodarone may potentiate the risk for simvastatin-associated rhabdomyolysis. Simvastatin doses greater than 20 mg day daily should be avoided in patients taking or initiating amiodarone therapy. Prescribers should consider using another statin for patients on amiodarone or initiating amiodarone therapy and who require simvastatin doses greater that 20 mg daily to meet their lipid goals. FDA

RELEVANT WEBSITE
Patient information sheet on amiodarone: *www.fda.gov/cder/drug/InfoSheets/patient/amiodaronePT.htm*

REFERENCES
1. Amiodarone (Cordarone) product labeling.
   www.fda.gov/cder/foi/label/2004/18972s030lbl.pdf
2. Simvastatin (Zocor) product labeling.
   www.fda.gov/cder/foi/label/2008/019766s076lbl.pdf
3. Ezetimibe/Simvastatin (Vytorin) product labeling.
   www.fda.gov/cder/foi/label/2008/021687s022lbl.pdf
4. Niacin extended-release/Simvastatin (Simcor) product labeling.
   www.fda.gov/cder/foi/label/2008/022078lbl.pdf
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   Intern Emerg Med. 2007;2:210-18.
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9. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. N Engl J Med. 2004; 351(15):1548-63.

BOX 4

Case 1
A 74-year-old male was hospitalized with ventricular tachycardia. While hospitalized, the patient underwent coronary artery bypass graft surgery and was subsequently started on ezetimibe/simvastatin (10/40 mg daily). At the time of discharge, the patient was also prescribed amiodarone 200 mg (to be taken twice daily), aspirin, ramipril, and metoprolol. Three weeks following his discharge from the hospital, the patient complained of extreme muscle weakness. His creatinine level was "highly elevated". A diagnosis of rhabdomyolysis was made. Ezetimibe/simvastatin was discontinued and the patient recovered.

Case 2
A 50-year-old male was hospitalized for coronary artery bypass graft surgery. During his hospitalization, the patient developed atrial fibrillation and was started on amiodarone 400 mg (taken three times daily). The next day, the patient was also started on ezetimibe/simvastatin 10/80 mg daily. Six days following the initiation of simvastatin, the patient experienced progressive leg weakness with a creatine kinase (CK) of 117,400 units/L (for males, normal reference range: 60 to 400 units/L) and a serum creatinine (SCr) of 3.5 mg/dL (normal reference range: <1.5 mg/dL).[9] The patient was transferred to the intensive care unit and ezetimibe/simvastatin was discontinued. Three days after the discontinuation of simvastatin, the patient's CK and SCr levels had decreased to 26,700 units/L and 2 mg/dL, respectively.

Case 3
In 2004, a 72-year-old white male was hospitalized complaining of aches and weakness in his thighs. He also noted that his urine was dark for the week prior to his admission. He had a history of diabetes mellitus, hyperlipidemia, hypertension, azotemia, and coronary artery disease. In the summer of 2004, the patient had bypass surgery. Immediately following his bypass surgery, the patient was started on 200 mg amiodarone (taken once daily). One month later, simvastatin (80 mg/day) was prescribed. Other concomitant medications included metformin, enalapril, glimepiride, hydrochlorothiazide and aspirin.

Laboratory testing at the time of the most recent hospital admission indicated a CK level of 19,620 units/L (for males, reference range: 60 to 400 units/L)[9] and a SCr of 2.6 mg/dL (normal reference range: <1.5 mg/dL).[9] Rhabdomyolysis was suspected and simvastatin was immediately discontinued. Amiodarone was also discontinued four days after discontinuation of simvastatin. Within one day of stopping simvastatin, CK and SCr levels began to fall. Thirteen days after admission to the hospital, CK was 323 units/L and SCr was 1.7 mg/dL.

ICODEXTRIN (MARKETED AS EXTRANEAL) AND POINT-OF-CARE GLUCOSE MONITORING

A Dangerous Drug-Device Interaction

FDA continues to receive reports of adverse events, including fatalities, related to a drug-device interaction associated with the use of icodextrin (Extraneal), a peritoneal dialysis solution, and certain point-of-care glucose monitoring devices that do not use a glucose-specific test strip. Icodextrin is broken down into maltose *in vivo*. Some test strips used with portable glucose meters cannot differentiate between maltose, glucose and other sugars as they use methods that are not glucose-specific. The test strips associated with this drug-device interaction use glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase (GDO) as reagents. Examples of meters currently using these types of test strips include the Accu-Chek (manufactured by Roche) and FreeStyle (manufactured by Abbott) models. We urge healthcare providers and patients to refer to test strip package inserts or to consult the glucose monitoring device and test strip manufacturer(s) to confirm the glucose methodology in any system that is to be used for monitoring patients receiving icodextrin.† A list of toll free numbers for glucose monitor and test strip manufacturers is available at the Baxter Renal Clinical Help Line (1-888-RENAL-HELP).

Due to the presence of maltose in the blood of a patient receiving Extraneal therapy, the use of test strips that are not glucose-specific provides falsely elevated glucose readings. Falsely elevated blood glucose readings may lead to inappropriate insulin administration, which has caused hypoglycemia, coma, and death. Additionally, cases of true hypoglycemia can go untreated if masked by falsely elevated glucose readings.

As indicated in the *Warning* section of Extraneal's label, blood glucose measurement in patients receiving Extraneal must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose released from Extraneal. Glucose-specific methods (i.e., methods that are not affected by this interaction) include those that use glucose oxidase, glucose hexokinase, glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), or flavin adenine dinucleotide glucose dehydrogenase (FAD-GDH) based reagents.

This drug-device interaction was identified prior to approval of icodextrin and it is described in product labeling. Several safety measures, including patient/healthcare professional education, have been undertaken by the manufacturer. Because FDA continues to receive reports of this adverse event, we are highlighting this drug-device interaction in additional FDA communications to the public. For a complete discussion on this drug-device interaction, including detailed case reports, see the recent FDA communiqué in the Institute for Safe Medication Practices' (ISMP) publication *Medication Safety Alert (www.ismp. org/newsletters/acutecare/articles/20080619.asp)*. FDA

RELEVANT LINKS AND RELATED INFORMATION
FDA Patient Safety News (Avoiding Glucose Monitoring Errors in Patients Receiving Other Sugars):
www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript. cfm?show=55#2
www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript. cfm?show=48#4

FDA Center for Biologics Evaluation and Research (Fatal Iatrogenic Hypoglycemia: Falsely Elevated Blood Glucose Readings with a Point-of-Care Meter Due to a Maltose-Containing Intravenous Immune Globulin Product):
www.fda.gov/cber/safety/glucfalse.htm

ISMP Medication Safety Alert (Be aware of false glucose results with point-of-care testing):
www.ismp.org/newsletters/acutecare/articles/20050908.asp

FOOTNOTES
† A comprehensive list of FDA-cleared GDH-PQQ and GDO blood glucose monitoring systems is not provided because any such list may become outdated or inadvertently exclude systems distributed under multiple trade names. Note, some product lines include test strips that use more than one type of enzyme methodology. Further, manufacturers of GDH-PQQ systems currently on the market may subsequently change to non-GDH-PQQ methodology. Thus, patients and healthcare providers should consult the test strip package insert or contact the glucose monitoring device and test strip manufacturer(s) for information on the type of methodology used.

MEDICATION ERRORS

Medication errors are "any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patient, or consumer" (see *www.nccmerp.org/aboutMedErrors.html*). These errors may be related to professional practice, the product itself, and/or the procedures and systems related to distribution, dispensing and administration of drugs. For instance, drugs may be given names, shapes, or colors similar to other medications. As illustrated below, similarities in product packaging may result in confusion among healthcare professionals charged with dispensing drugs or among patients taking drugs at home (see Illustration 2).
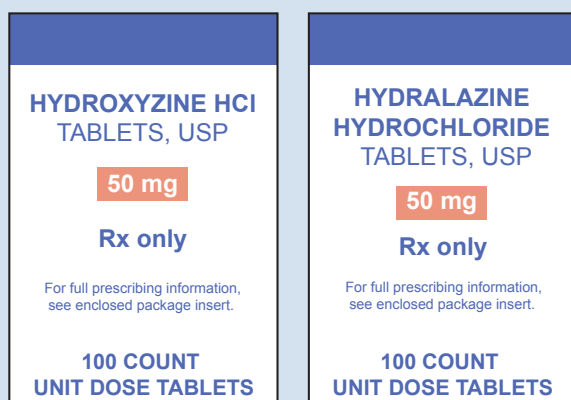
Although medication errors can and do occur—FDA has received over 95,000 reports of medication errors since the year 2000—it is difficult to assess how frequently such errors occur in medical and pharmacy practice. Medication errors such as those involving the wrong drug, an extra or wrong dose, omission of a drug, administering a drug by the wrong route or at an incorrect time are commonly reported to the FDA. Many of these errors can be prevented simply by communicating more effectively. However, some types of errors may require additional interventions such as a change in the product name, labeling and/or packaging to help minimize the likelihood of further confusion. Continued training and vigilance is essential in helping healthcare professionals and FDA reduce the likelihood of an error being made. Reporting medication errors to FDA via MedWatch, or to FDA's partners in this effort, the Institute for Safe Medical Practices (ISMP) and the U.S. Pharmacopeia via their MedMarx program, helps FDA identify factors leading to errors that can be corrected, lessening the likelihood of their recurrence (see *www.fda.gov/cder/drug/MedErrors/default.htm*).

## CHALLENGES TO PREVENTING MEDICATION ERRORS

There are numerous challenges to preventing medication errors. It is common practice, depending on the healthcare setting, to have many individuals involved in the prescribing, dispensing and administration of a medication (e.g., physicians, nurses, pharmacists, and the patient) with the potential for an error to occur at any step in the process.

ILLUSTRATION 2

HYDROXYZINE HCl
TABLETS, USP

50 mg

Rx only

For full prescribing information,
see enclosed package insert.

**100 COUNT
UNIT DOSE TABLETS**

**HYDRALAZINE
HYDROCHLORIDE**
TABLETS, USP

50 mg

Rx only

For full prescribing information,
see enclosed package insert.

**100 COUNT
UNIT DOSE TABLETS**

This illustration is is an example of similar looking packaging from the same manufacturer for two unrelated drugs. On the left are 50 mg tablets of hydroxyzine HCL, a sedating antihistamine. On the right are 50 mg tablets of hydralazine HCL, an antihypertensive drug. The packaging of these products may lead to a serious medication error.

ILLUSTRATION 3
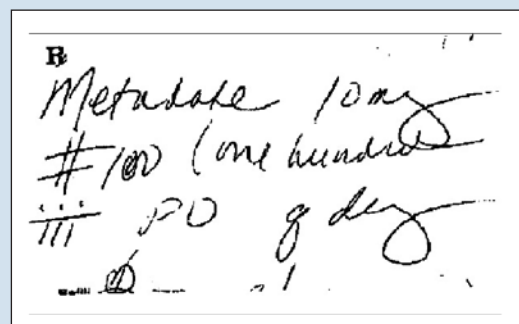
This illustration is an example of a hand-written prescription for Metadate ER 10 mg tablets. Metadate is a drug used in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Due to the similarity in name, poor penmanship and the omission of the modifier "ER", the pharmacy filling the prescription incorrectly dispensed methadone 10 mg tablets. Methadone is a morphine-based product used as a heroin substitution therapy and analgesic. Methadone is not used for the treatment of ADHD.

Healthcare professionals should be aware of the sources and types of medication errors so that they may better identify and avoid potential problems before they occur.

There are many steps that healthcare professionals can take to reduce the occurrence of medication errors at the point of prescribing a medication. Two major sources of errors in prescribing are poor penmanship and the use of error-prone abbreviations. For instance, healthcare professionals should be cognizant of their penmanship and use computerized prescriber order entry (CPOE, see below), if available, to lessen any confusion that may result from poorly written prescriptions (see Illustration 3).

There are certain error-prone abbreviations, symbols and dose designations that healthcare professionals should avoid. For example, the abbreviation for microgram, "μg", is often misread for milligram, "mg", when written. FDA and ISMP recommend that the abbreviation "mcg" be used in lieu of "μg". Another common source of misinterpretation and error is the use of the decimal point and a trailing zero. Writing "1.0 mg" can be read as "10 mg" if the decimal point is not clearly visible. Similarly, ".1" mg can be misinterpreted as "1 mg". FDA and ISMP recommend that no trailing zeros be used when denoting doses expressed as whole numbers and that preceding zeros be used whenever a decimal point is needed for a dose that must be administered as a fraction of a whole number. Certain abbreviations can also be misread, for example, "HCL", hydrochloride, and "KCL", potassium chloride. FDA and ISMP recommend that the complete drug name be used unless expressed as a salt of the drug. By avoiding the use of abbreviations, symbols and dose designations that are easily confused with each other, the risk of error can be greatly reduced. For a list of error-prone abbreviations, symbols and dose designations, healthcare professionals are referred to *www.ismp.org/Tools/errorprone-abbreviations.pdf.*

As noted, another way healthcare professionals can minimize the confusion over handwritten prescriptions (and their misinterpretation; see Illustration 3), and/or potential errors that may result in a drug's misuse, is through the use of technology. For example, CPOE technology is an electronic data entry system that allows healthcare professionals to communicate instructions about a patient at either the point-of-care or remotely. Although not every institution uses CPOE, data have shown that CPOE simplifies and streamlines patient care, and significantly reduces medication errors.[1] Estimates of the proportion of hospitals that have fully implemented CPOE systems range from 37% to 50%.[2] CPOE is capable of storing medical histories and can alert healthcare professionals to, among other things, drug allergies, and dangerous drug-drug or drug-device interactions.

A 2008 review of the effects of CPOE on medication errors [MEDLINE (1966 to April 2006) and EMBASE (1976 to April 2006)] indicated that most studies report significant reductions in the relative risk of medication errors when CPOE is used.[2] Specifically, 25 of the 27 studies evaluated show a relative risk reduction for medication

errors of 13% to 99%. These data strongly support the use of CPOE for the reduction of medication errors.

Another important way to avoid prescribing errors is for healthcare professionals to be up-to-date on the latest information for a product, especially for a drug that may not be commonly used. The professional product label is the best source for information on indications, proper use, and adverse events associated with a drug. The product label is updated as new information becomes available. The label provides important information that healthcare professionals should know prior to prescribing a drug. For instance, a boxed warning, when used, often contains information about serious adverse reactions (e.g., life-threatening) that should be considered when weighing the benefits of prescribing a drug. Special restrictions and distribution programs are also highlighted in boxed warnings.

Starting in 2006, the professional product label has a new look. Included at the top of the label is a highlights section. This feature makes key prescribing information about the drug readily accessible and provides an index to the rest of the information in the label.[3] Healthcare professionals should always consult the drug label prior to prescribing a drug they are unfamiliar with or when there has been an update to the prescribing information. The most recent drug labels can be readily accessed on the National Library of Medicine's DailyMed website (*http://dailymed.nlm.nih.gov/dailymed/about.cfm*).

FDA'S ROLE IN REDUCING MEDICATION ERRORS
In addition to ensuring that drug labels contain accurate, up-to-date information, FDA also takes an active role identifying factors that may contribute to the incorrect distribution, dispensing, or taking of a medication (see *www.fda.gov/cder/drug/MedErrors/default.htm*). FDA has promulgated regulations (e.g., bar codes) and developed programs aimed at mitigating medication errors. FDA has taken steps to ensure that drug packaging is compatible with emerging technologies (e.g., CPOE). Here are three examples of how FDA is working to reduce medication errors.

Drug names: FDA reviews drug names from both a promotional and safety perspective. The safety review focuses on the avoidance of error. FDA considers whether the proposed name looks and sounds like the names of drug products that are already marketed in the US and evaluates this risk using Failure Mode and Effects Analysis, a process by which potential failures in a system (e.g., drug design) and the effects of such failures (e.g., medication errors) can be assessed. When evaluating the promotional aspects of the name, FDA considers if the proposed name/label is misleading because it overstates the efficacy, minimizes the risk, broadens the indication, makes unsubstantiated superiority claims for the product, or is overly fanciful. The safety goal of this review is to reduce name and label confusion prior to the drug entering the market. Of approximately 400 drug name and labels submitted

for approval by pharmaceutical companies each year, FDA rejects one-third for reasons of, but not limited to, appropriateness, similar spelling and pronunciation of the drug name to another currently marketed product, ambiguity in a drug name and/or identifier, or being misleading.

Over-the-counter (OTC) Drug Labeling: For OTC drugs, consumers must rely on the information on the package in order to safely and properly use these medications, or to give them to children or others they are caring for. The OTC label is the primary mechanism by which all necessary safety and effectiveness information associated with the use of the OTC drug is conveyed to the consumer. In 1999, FDA redesigned and standardized the components of the OTC label so that information about the drug is readily available and can be easily read by the consumer. The label describes the purpose of the compound and any safety information and warnings associated with the drug. The label also clearly outlines how to use the drug appropriately. In addition, standardization of the OTC label reduces confusion among OTC drugs as a class.

Bar Codes: In 2004, FDA published a final rule requiring a bar code be placed on all drugs distributed and used in hospital settings. According to the rule, manufacturers, repackers, relabelers and private label distributors of drug products commonly used in hospitals must place a bar code on their product. The function of the bar code is to reduce error by increasing standardization among products so that, in conjunction with bar code scanning technology, the right patient can get the right drug at the right time. Supporting the use of bar codes are reports indicating that bar codes reduce dispensing errors and adverse drug events by 96% and 97%, respectively.[4] In 2006, the American Society of Health-System Pharmacists (ASHP; *www.ashp.org/s_ashp/index.asp*) reported that 13.2% of hospitals have adopted technology that utilizes bar code technology. This rate constitutes a 3.8% increase in bar code utilization from the previous year.[5] The bar code rule highlights FDA's commitment to patient safety by integrating new labeling components that works with new technology.

By increasing awareness about medication errors, and instituting rules that standardize the use and promotion of medications, FDA seeks to reduce the incidence of medication errors and the impact these errors have on patients, families and the healthcare system. FDA closely monitors medication error reports as they are received, and issues warnings and/or intercedes when necessary. Healthcare providers are encouraged to continue to report medication errors to MedWatch (*www.fda.gov/medwatch/*) or through FDA's partner organizations such as the ISMP (*www.ismp.org/orderforms/reporterrortoISMP.asp*). 𝖥𝖣𝖠

RELEVANT WEBSITES

FDA's medication error website
www.fda.gov/cder/drug/MedErrors/default.htm

FDA 101: Medication Errors
www.fda.gov/consumer/updates/medicationerrors031408. html

Institute for Safe Medical Practices
www.ismp.org/

U.S. Pharmacopeia MedMarx Program
www.usp.org/products/medMarx/

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2. Ford EW, McAlearney AS, Phillips MT, et al. Predicting computerized physician order entry system adoption in US hospitals: can the federal mandate be met? Int J Med Inform. 2008;77(8):539-45.

3. Requirements on Content and Format of Labeling for Human Prescription drug and biological Products and Draft Guidances and Two Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products: Final Rule and Notices. Federal Register. January 24, 2006;71(15):3922-3997. (see *www.fda.gov/OHRMS/ DOCKETS/98fr/06-545.pdf*)

4. Poon EG, Cina JL, Churchill W, et al. Medication dispensing errors and potential adverse drug events before and after implementing bar code technology in the pharmacy. Ann Intern Med. 2006; 145(6):426-34.

5. Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: dispensing and administration – 2005. Am J Health Syst Pharm. 2006; 63(4):327-45.

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).

DRUG SAFETY COMMUNICATIONS

Drug Safety Communications posted by FDA from May 1, 2008 to August 31, 2008 (advisories are available at www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm)

Date	Product(s)	Safety Issue and Web Address
August 25, 2008	Natalizumab (Tysabri)	Update highlighting two new cases of progressive multifocal leukoencephalopathy (PML) in patients who received Tysabri monotherapy. *www.fda.gov/cder/drug/InfoSheets/HCP/natalizumab2008HCP.htm*
August 21, 2008	Simvastatin (Zocor and generics), Ezetimibe/Simvastatin (Vytorin) and Ezetimibe (Zetia)[1]	Ongoing safety review to further evaluate a potential increased incidence of cancer in patients treated with Vytorin (a combination of simvastatin plus ezetimibe) in light of preliminary findings of SEAS trial. *www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin_SEAS.htm*
August 18, 2008	Exenatide (Byetta)	Update highlighting new reports of hemorrhagic or necrotizing pancreatitis. *www.fda.gov/cder/drug/InfoSheets/HCP/exenatide2008HCP.htm*
August 12, 2008	Naltrexone for extended-release injectable suspension (Vivitrol)	Reports of injection site reactions including cellulitis, induration, hematoma, abscess, sterile abscess, and necrosis. *www.fda.gov/cder/drug/InfoSheets/HCP/naltrexoneHCP.htm*
August 8, 2008	Simvastatin (Zocor and generics), Ezetimibe/Simvastatin (Vytorin), Niacin extended-release/Simvastatin (Simcor), used with amoidarone (Cordarone, Pacerone)	Increased risk of rare and potentially fatal muscle injury, rhabdomyolysis, in patients treated concurrently with amiodarone and simvastatin, particularly with simvastatin doses greater than 20 mg daily. *www.fda.gov/cder/drug/InfoSheets/HCP/simvastatin_amiodaroneHCP.htm*
July 30, 2008	Erythropoiesis Stimulating Agents (ESAs) [epoetin alfa (Procrit, Epogen) and darbepoetin alfa (Aranesp)]	Update highlighting additional safety-related changes to the labeling to clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should not be initiated. *www.fda.gov/cder/drug/infopage/RHE/default.htm*
July 29, 2008	Mitoxantrone hydrochloride (Novantrone and generics)	Alert informing healthcare professionals about additional recommendations for cardiac monitoring in patients with multiple sclerosis (MS) before initiating treatment and prior to administering each dose of mitoxantrone. *www.fda.gov/cder/drug/InfoSheets/HCP/mitroxantroneHCP.htm*
July 24, 2008	Abacavir (Ziagen) and Abacavir-containing medications [abacavir/lamivudine (Epzicom), abacavir/ lamivudine/ zidovudine (Trizivar), and generics]	Alert informing healthcare professionals about an increased risk of serious hypersensitivity reactions (HSRs) in patients who test positive for the human leukocyte antigen (HLA) allele, HLA-B*5701. *www.fda.gov/cder/drug/InfoSheets/HCP/abacavirHCP.htm*
July 17, 2008	Perflutren Micro-bubble Contrast Agents (Definity and Optison)	New revisions to the *Boxed Warning, Warnings,* and *Contraindications* sections of the product labeling about the continued risk of serious cardiopulmonary reactions with specific recommendations on intensive monitoring for patients with pulmonary hypertension or unstable cardiopulmonary conditions and close observation of patients without these underlying conditions. *www.fda.gov/cder/drug/infopage/microbubble/default.htm*
July 8, 2008	Fluoroquinolone Antimicrobial Drugs [ciprofloxacin (Cipro and generic ciprofloxacin), ciprofloxacin extended release (Cipro XR and Proquin XR), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), and ofloxacin (Floxin and generic ofloxacin)]	Update highlighting a new labeled *Boxed Warning* and Medication Guide about an increased risk of developing tendinitis and tendon rupture. *www.fda.gov/cder/drug/InfoSheets/HCP/fluoroquinolonesHCP.htm*

Date	Product(s)	Safety Issue and Web Address
July 8, 2008	Fluoroquinolone Antimicrobial Drugs [ciprofloxacin (Cipro and generic ciprofloxacin), ciprofloxacin extended release (Cipro XR and Proquin XR), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), and ofloxacin (Floxin and generic ofloxacin)]	Update highlighting a new labeled *Boxed Warning* and Medication Guide about an increased risk of developing tendinitis and tendon rupture. *www.fda.gov/cder/drug/InfoSheets/HCP/fluoroquinolonesHCP.htm*
June 16, 2008	Antipsychotics [prochlorperazine (Compazine), haloperidol (Haldol), loxapine (Loxitane), thioridazine (Mellaril), trifluoperazine (Stelazine), molindone (Moban), thiothixene (Navane), perphenazine (Trilafon),pimozide (Orap),fluphenazine(Prolixin), chlorpromazine (Thorazine), aripiprazole (Abilify), clozapine (Clozaril, FazaClo), quetiapine (Seroquel), paliperidone (Invega), ziprasidone (Geodon) risperidone (Risperdal), olanzapine (Zyprexa), olanzapine and fluoxetine (Symbyax)]	Update highlighting information on increased risk of death in elderly patients treated for dementia-related psychosis with both conventional and atypical antipsychotic drugs. Antipsychotics are not approved for the treatment of dementia-related psychosis. *www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_ conventional.htm*
June 6, 2008	Becaplermin (Regranex)	Update on new revisions to product labeling indicating an increased risk of mortality secondary to malignancy in patients with diabetes mellitus. *www.fda.gov/cder/drug/early_comm/becaplermin_update_200806.htm*
June 4, 2008	Tumor Necrosis Factor (TNF) Blockers [infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), and certolizumab (Cimzia)][1]	Ongoing safety review to evaluate the potential risk of lymphoma and other cancers in children and young adults. *www.fda.gov/cder/drug/early_comm/TNF_blockers.htm*
May 30, 2008	Chlorofluorocarbon (CFC) propelled Albuterol Inhalers (Proair HFA Inhalation Aerosol, Proventil HFA Inhalation Aerosol,and Ventolin HFA Inhalation Aerosol)	Advisory highlighting transition and phase out of chlorofluorocarbon (CFC) propelled albuterol inhalers to HFA propelled albuterol inhalers. *www.fda.gov/cder/drug/advisory/albuterol_cfc.htm*
May 16, 2008	Mycophenolate mofetil (Cellcept) and Mycophenolic Acid (Myfortic)	Reports of infants born with serious congenital anomalies, including microtia and cleft lip/palate, following exposure to mycophenolate mofetil exposure during pregnancy. *www.fda.gov/cder/drug/infopage/mycophenolate/default.htm*
May 16, 2008	Varenicline (Chantix)	Update highlighting revisions to product labeling and new medication guide to address the risk of serious neuropsychiatric adverse events. *www.fda.gov/cder/drug/infopage/varenicline/default.htm*
May 14, 2008	Cefepime (Maxipime)	Update highlighting information on FDA's current analysis to re-evaluate the risk of death in patients treated with cefepime. *www.fda.gov/cder/drug/early_comm/cefepime_update_200805.htm*

FOOTNOTES:

1. Early Communication about Ongoing Safety Review.