

Adverse Event Reporting News

The Biweekly Guide to the Reporting of Adverse Events for Drugs, Devices, Biologics & Dietary Supplements

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User fees/orphan drugs

Orphan drug fast-track seen as part of user fee reauthorization bill

Sen. Kay Hagen (D-NC) is trying to expand FDA's "orphan drug" provisions to allow more accelerated review of products for treating rare diseases, as part of the user fee reauthorization discussions going on in Congress.

The measure, supported by **Biotechnology Industry Organization (BIO)** and **GlaxoSmithKline**, a major employer in North Carolina, is factoring in Congressional talks to reauthorize the Rx drug user fees, according to a Nov. 16 **Bloomberg** report.

While FDA occasionally grants exemptions, "the experience of many biotechnology companies is that

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Drug shortages

House panel to probe drug shortages; study finds U.S. problem concentrated

Rep. Trey Gowdy (R-SC), chairman of the House Oversight Subcommittee on Health Care, will hold a hearing Wednesday (Nov. 30) to examine the causes of the drug shortage crisis.

The hearing gets under way at 10 a.m. in the Rayburn House Office Building, Room 2247.

No FDA witnesses are on the list. Those scheduled to testify are:

- Dr. Michelle Hudspeth, division director of Pediatric Hematology/Oncology, **Medical University of South Carolina**

Drug shortages, continued on page 2

Drug safety

FDA revokes Avastin approval due to safety concerns

FDA Commissioner Margaret Hamburg, M.D., said Nov. 18 she is revoking the agency's approval of the breast cancer indication for Avastin (bevacizumab) after concluding that the drug has not been shown to be safe and effective for that use.

Avastin will still remain on the market as an approved treatment for certain types of colon, lung, kidney and brain cancer (glioblastoma multiforme).

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the criteria for utilizing this type of regulatory flexibility are unclear and unpredictable,” according to the biotech industry group’s document, a copy of which was obtained by Bloomberg.

Diseases that may be targeted are rare disorders affecting fewer than 200,000 patients in the U.S. About 360 drugs exist for 7,000 such conditions, according to the **National Organization for Rare Disorders** in Danbury, CT.

Hagan’s plan, based on the biotech group’s proposal, would expand on an FDA accelerated-approval program used mainly for AIDS and cancer treatments, according to a draft proposal.

Manufacturers under accelerated approval can conduct shorter trials on patients based on a measured effect of a drug instead of an actual clinical outcome. For some cancer medicines, tumor shrinkage is considered a sufficient sign of survival to justify approving a product. The agency requires companies to prove the anticipated benefit once the treatment is cleared.

Hagan would allow agency approvals based on the second of three phases of clinical trials, when data can’t be “ethically, feasibly or practicably generated,” according to the draft.

Glaxo, which employs about 3,500 individuals in Research Triangle Park, is reviewing the senator’s proposal, said company spokeswoman Melinda Stubbee.

The London-based company has set a goal of winning approval for five rare-disease drugs each year for a decade, including therapies for Duchenne muscular dystrophy—one of nine varieties of the degenerative disease—and an immune deficiency sometimes referred to as “bubble boy disease.”

FDA already has many tools in place to expedite approval of promising drugs, said Karen Riley, an agency spokeswoman, in an e-mail. The regulator also allows patients access to unapproved medicines through clinical trials and physician-submitted applications, she said.

FDA has approved 85 rare-disease treatments since 2006, 75% of which were based on more-limited trials, John Jenkins, director of the agency’s Office of New Drugs, told a conference in Washington last month.

The agency’s “orphan drug” program offers tax breaks and a seven-year market monopoly for rare illnesses that affect fewer than 200,000 patients.

“I’m worried that a policy where we define flexibility will lock us in,” Jenkins said at the rare disease conference, discussing unspecified calls for faster reviews.

FDA officials discussed the possibility of expediting approvals for treatments showing “exceptional promise” in an innovation report the agency released Oct. 5.

The report said the agency plans to release guidelines

for an expedited pathway for high-risk breast cancer treatments. The President’s Council on Jobs and Competitiveness backed a progressive approval system in its interim report last month.

Hagan and the biotech group’s proposals may be wrapped into a renewal of the law that funds FDA’s reviews, according to the two aides. The agency and the drug industry have agreed to a 6% fee increase as part of a plan that would run through fiscal 2017. Drugmakers would pay \$712.8 million in fiscal 2013 under the deal Congress must approve before Sept. 30, 2012.

Drug shortages, from page 1

- Ted Okon, executive director, **Community Oncology Alliance**
- Scott Gottlieb, resident fellow, **American Enterprise Institute**
- Walter Kalmans, president, **Lontra Ventures**

The hearing comes a week after **IMS Institute for Healthcare Informatics** found that out of 168 drugs cited by President Obama as having shortages, industry was able to provide stable supplies for 56, and 31 became “more available.” However, some 75 of the drugs were on a big decline in supply.

This means the problem is more concentrated than overall figures suggest, **Reuters** reported.

IMS found that more than 80% of all affected drugs were generic injectable medications without patent protection that generally treat acute disease. In fact, half of the generic injectable drugs sold in the United States were on the shortages list, according to the report.

Although all major therapy areas were affected, cancer drugs took the biggest hit, accounting for 16% of all medications in shortage and putting more than a half million patients at risk for unexpectedly losing access to potentially life-saving treatments, the report said.

“It’s a finite and relatively small number of products that are causing the disruption,” said Murray Aitken, executive director of the IMS Institute for Healthcare Informatics.

“Not to diminish the issue of disruption because these products are very important ... it’s useful to be more specific and focused in looking at the part of the market that is especially affected.”

The problem has authorities and experts perplexed and led Obama late last month to sign an executive order to address it. Just 56 drugs were reported as scarce in 2006, FDA has said.

The IMS report found great volatility in the availability of some drugs in recent years, likely linked to the simple fact that some drugmakers just stopped making those

medicines.

Although almost 100 companies in all were supplying the 168 products in short supply, half of those drugs were made by only one or two suppliers, the report found.

Of the troubled 75, a single company or two companies were supplying 65% of them, Aitken said.

“Some (companies) have decided to stop production of these types of drugs, and if it leaves one or two suppliers, that doesn’t provide a lot of flexibility when one might have a manufacturing problem of some sort,” he said.

“Part of the story is there may not be sufficient economic incentive currently in this sector of the market.”

The corporations supplying the most number of drugs from the shortage list were **Hospira** and **Teva Pharmaceuticals**. Others included **Novartis**, **Watson Pharmaceuticals**, **Pfizer** and **Baxter Healthcare**, according to the report.

The companies most commonly report manufacturing problems, discontinuation or suspension of production and increased demand as the cause of drug shortages, said the report by IMS, a healthcare research company.

Researchers in the report based their analysis on the lists of drugs in shortage compiled by FDA and **American Society of Health-System Pharmacists**.

Avastin, continued from page 1

“This was a difficult decision. FDA recognizes how hard it is for patients and their families to cope with metastatic breast cancer and how great a need there is for more effective treatments. But patients must have confidence that the drugs they take are both safe and effective for their intended use,” Hamburg said. “After reviewing the available studies it is clear that women who take Avastin for metastatic breast cancer risk potentially life-threatening side effects without proof that the use of Avastin will provide a benefit, in terms of delay in tumor growth, that would justify those risks. Nor is there evidence that use of Avastin will either help them live longer or improve their quality of life.”

Avastin’s risks include severe high blood pressure; bleeding and hemorrhaging; heart attack or heart failure; and the development of perforations in different parts of the body such as the nose, stomach and intestines.

The decision, outlined in Hamburg’s 69-page opinion, involves Avastin used in combination with the cancer drug paclitaxel for those patients who have not been treated with chemotherapy for their form of me-

tastatic breast cancer known as HER2 negative. This indication must now be removed from Avastin’s product labeling.

Hamburg’s decision is based on an extensive record, which includes thousands of pages submitted to a public docket, data from several clinical trials and the record from a two-day hearing held in June.

Avastin was approved for metastatic breast cancer in February 2008 under FDA’s accelerated approval program, which provides earlier patient access to promising new drugs to treat serious or life-threatening conditions while confirmatory clinical trials are conducted. If the clinical trials do not justify the continued approval of the drug or a specific drug indication, the agency may revoke its approval.

In this case, the accelerated approval was based on promising results from one study that suggested that the drug could provide a meaningful increase in the amount of time from when treatment is started until the tumor grows or the death of the patient.

After the accelerated approval of Avastin for breast cancer, the drug’s sponsor, **Genentech**, completed two additional clinical trials and submitted the data from those studies to FDA. These data showed only a small effect on tumor growth without evidence that patients lived any longer or had a better quality of life compared to taking standard chemotherapy alone – not enough to outweigh the risk of taking the drug.

FDA’s Center for Drugs (CDER) ultimately concluded that the results of these additional studies did not justify continued approval and notified Genentech it was proposing to withdraw approval of the indication.

Genentech did not agree with CDER’s evaluation of the data and, following the procedures set out in FDA regulations, requested a hearing on the withdrawal proposal, with a decision to be made by the Commissioner. That two-day hearing, which took place June 28-29, included recommendations from FDA’s Oncologic Drugs Advisory Committee (ODAC), voting 6-0 in favor of withdrawing approval of Avastin’s breast cancer indication. After the hearing, the public docket remained open until Aug. 4. In an earlier meeting of the ODAC, that committee had voted 12-1 in favor of the removal of the breast cancer indication from the Avastin label.

“FDA is committed to working with sponsors to bring promising cancer drugs to market as quickly as possible using tools like accelerated approval,” Hamburg said. “I encourage Genentech to consider additional studies to identify if there are select subgroups of women suffering from breast cancer who might benefit from this drug.”



Merck will pay \$950M to settle Vioxx investigation

The U.S. Department of Justice said Nov. 22 that drug maker **Merck** will pay \$950 million to resolve investigations into its marketing of the painkiller Vioxx, the **Associated Press** reported.

The agency said Merck will pay \$321.6 million in criminal fines and \$628.4 million as a civil settlement agreement. It will also plead guilty to a misdemeanor charge that it marketed Vioxx as a treatment for rheumatoid arthritis before getting FDA approval.

Merck stopped selling Vioxx in 2004 after evidence showed the drug doubled the risk of heart attack and stroke. In 2007, the company paid \$4.85 billion to settle around 50,000 Vioxx-related lawsuits.

The Justice Department said the settlement resolves allegations that Merck made false, unproven or misleading statements about Vioxx's safety to increase sales and made false statements to Medicaid agencies about its safety.

Merck said the settlement does not constitute an admission of any liability or wrongdoing, and it said the government acknowledged that there was no basis to conclude that Merck's upper-level management was involved in the violations.

Merck also entered into an agreement about its sales, marketing, publication and government pricing activities. The Justice Department said that agreement strengthens oversight of the company. It will require top officials to complete annual compliance certifications, and the company will post information about physician payments on its Web site.

The company took a charge of \$950 million in the third quarter of 2010 to cover the anticipated settlement payments.

Vioxx was approved by FDA in 1999, but the government did not initially approve the drug for use in rheumatoid arthritis. That meant doctors could write prescriptions for Vioxx for rheumatoid arthritis patients, but Merck could not promote the drug for that use. The Justice Department said Merck promoted Vioxx for rheumatoid arthritis for three years and continued to do

so after getting an FDA warning letter in 2001. The drug was approved as a treatment for rheumatoid arthritis in 2002.

The government will get \$426.4 million from the settlement, and \$202 million will be distributed to state Medicaid programs for 43 states and the District of Columbia.

Merck also settles Vioxx claims with NY, FL

According to a court filing, **Merck**, which paid \$4.85 billion to resolve patient lawsuits contending its Vioxx painkiller caused heart attacks, settled claims by New York and Florida alleging the company misled state officials about the drug's safety, Bloomberg reported Nov. 14.

Merck agreed to pay an undisclosed sum to the states of Florida, New York and South Carolina to resolve suits alleging the drugmaker failed to adequately warn patients of Vioxx's risks before halting sales in 2004, Russ Herman, a lawyer for former users of the drug, said in the Nov. 10 filing.

"Payments from Merck to these governmental entities may be imminent," Herman said in a request to U.S. District Judge Eldon Fallon in New Orleans to set aside some of the settlement funds for legal fees.

Merck pulled Vioxx off the market in 2004 after researchers linked it to an increased risk of heart attacks and strokes. Former users also criticized the company for downplaying the drug's health risks and manipulating studies to help promote it.

Merck officials countered that Vioxx wasn't the cause of users' heart attacks and the company had properly warned doctors and consumers about its risks. Still, the drugmaker paid \$4.85 billion to resolve more than 27,000 suits over the drug.

In the only state case seeking Vioxx reimbursements to go to trial, Fallon ruled in June 2010 that Merck didn't have to refund money that the state of Louisiana paid for the medication through state health-care programs. The judge heard the case without a jury and denied the state's bid to recover more than \$20 million.

New York's, Florida's and South Carolina's settlements are part of an effort by Fallon to resolve state claims over the drug, lawyers said earlier this year at court hearings in New Orleans.

The judge halted litigation by attorneys general from around the U.S. in November 2010 to launch a "global mediation," Fallon said at the time.

In June, Patrick Juneau, a special master appointed by Fallon to handle issues in the consolidated Vioxx cases, said talks between the states and the company had bogged down.

The company announced this month that it agreed to pay \$49.5 million to settle suits filed on behalf of former and current employees of the drugmaker over losses to their retirement funds tied to the company's handling of Vioxx.

Merck said in filings with the U.S. Securities and Exchange Commission that it paid the money to resolve allegations that executives violated legal duties by making false and misleading statements about the painkiller.

Merck set aside \$950 million to resolve a federal criminal probe into its handling of Vioxx, company officials said in October 2010. The company noted that prosecutors in Boston had identified the company in March 2009 as a target of a grand jury investigation, and that witnesses had been called in the probe.

Pfizer reaches agreements in principle with U.S. over bribery probe

Pharmaceutical giant **Pfizer** said it reached agreements-in-principle with U.S. authorities to resolve a foreign bribery investigation, "The Wall Street Journal" reported Nov. 16.

The company said in a securities filing it expects to enter into and announce final agreements with the Securities and Exchange Commission and the Justice Department by the end of the year. The alleged misconduct has to do with "potentially improper payments made by certain Pfizer and **Wyeth** subsidiaries" connected to sales outside the U.S., the filing said.

Wyeth was acquired by Pfizer in 2009.

The company, in an e-mail, said, "it would be premature" to disclose the terms of any agreement. "Pfizer has been voluntarily providing the [Justice Department] and SEC with information since 2004," it said in the e-mail to the Journal.

Pfizer is one of many pharmaceutical companies under investigation for possible foreign bribery, with a widely-reported sweep of the industry underway. The industry has had trouble dealing with the term "foreign official" under the Foreign Corrupt Practices Act, a Corruption Currents industry profile found.

The first company to settle was **Johnson & Johnson**, which agreed to pay \$70 million to resolve charges. It admitted illegal conduct in a criminal case, but neither admitted nor denied wrongdoing in a connected civil settlement. **Eli Lilly & Co.** is close to settling a case

against it, and **AstraZeneca** is cooperating with U.S. authorities in its case, but doesn't know when it will end.

Adverse events

Common drugs key in emergency admissions for seniors

Better management of antithrombotic and antidiabetic drugs could help avoid thousands of emergency admissions for adverse drug events in older adults every year, according to research reported by "MedPage Today" Nov. 23.

Every year, nearly 100,000 adults 65 or over have an emergency hospital admission, mainly because of a few commonly used drugs or drug classes, according to Dan Budnitz, M.D., of the Centers for Disease Control (CDC) in Atlanta.

High-risk and inappropriate drugs, on the other hand, only accounted for a small fraction of the emergency admissions, Budnitz and colleagues reported in the Nov. 24 issue of the "New England Journal of Medicine."

The implication, Budnitz said in a statement, is that "focusing safety initiatives on a few medicines that commonly cause serious, measurable harms can improve care for many older Americans."

The main culprits, accounting for more than two-thirds of all such admissions, are warfarin, insulins, oral antiplatelet agents and oral hypoglycemic agents, the researchers reported.

But drugs designated as high-risk for older people in the 2011 Healthcare Effectiveness Data and Information Set only accounted for 1.2% of emergency admissions. Drugs defined as "potentially inappropriate" for older adults in the Beers criteria led to 6.6% of admissions.

The findings are an analysis of data from a nationally representative sample of 58 hospitals that took part in the CDC's National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project between 2007 and 2009.

Budnitz and colleagues reported that the hospitals saw 5,077 emergency admissions over the study period, yielding a national estimate of 99,628 a year.

Nearly half of those admissions (48.1%) were among adults 80 or older and 65.7% were due to unintentional overdoses, they found.

Four medications or medication classes were implicated, either alone or in combination, in 67% of all

emergency admissions for drug adverse events, the researchers found. Specifically:

- Warfarin accounted for an estimated 33,171 admissions a year, or 33.3% of the total.
- Insulins were blamed for 13,854 admissions a year, or 13.9% of the total.
- Oral antiplatelet agents accounted for 13,263 cases, or 13.3%.
- Oral hypoglycemic agents led to 10,656 admissions, or 10.7%.

Those remained the most common causes of admission regardless of age, Budnitz and colleagues reported.

Nearly all admissions involving warfarin, insulins or oral hypoglycemic agents involved accidental overdoses at 95.1%, 99.4% and 99.1%, respectively, the researchers found.

More than half of the admissions involving “inappropriate” Beers-criteria medications were caused by digoxin, the researchers found. When digoxin was excluded, Beers-criteria medications were implicated in only 3.2% of admissions.

The study implies, Budnitz and colleagues concluded, that improved management of antithrombotic and antidiabetic drugs could have “sizable, clinically significant, and measurable effects” on public health.

They cautioned that the analysis probably underestimated the true number of emergency admissions, because the database would leave out some cases, including those in which the drug at issue was identified through patient interview after admission.

The study also did not have direct estimates of person-year exposure to medications, they noted.



Small overdoses of Tylenol can add up to deadly damage

A new study says taking even slightly too much Tylenol over a period of several days can lead to an overdose with deadly consequences, **MSNBC** reported Nov. 23.

The study looked at what are called “staggered overdoses,” in which a person repeatedly exceeds the daily recommendation through small overdoses. This is

in contrast to the more familiar single overdose, when a person takes too many pills at once.

In the study, staggered overdoses of acetaminophen, found in Tylenol and other pain relievers, were more deadly than single overdoses, even though people who experienced staggered overdoses typically took smaller total amounts of acetaminophen than those who experienced a single overdose.

Doctors may not identify staggered overdoses right away, researchers added. People with a staggered overdose may have levels of the drug in their blood below what a standard blood test would indicate as an overdose, even when their liver is badly damaged.

People taking acetaminophen should stay within the recommended limits of the drug and take even less of it when they are on other painkillers, said study researcher Kenneth Simpson of the **University of Edinburgh** in Scotland. The researchers defined an overdose as taking more than 4,000 milligrams of acetaminophen in a 24 hour period. FDA also sets the maximum dose at 4,000 milligrams.

And, Simpson said, doctors should realize the crite-

A total of 60 patients died from a staggered overdose, and 140 patients from a single overdose. This equates to a mortality rate of 37.3% among the staggered overdose group, and 27.8% in the single overdose group.

ria used to identify overdose patients do not work as well for staggered overdoses.

The study was published online in the “British Journal of Clinical Pharmacology.”

Simpson and colleagues examined information from 663 patients with liver problems caused by acetaminophen—(also known as paracetamol—who were admitted to an Edinburgh hospital between 1992 and 2008.

The researchers found that nearly a quarter of them (161 patients) had taken staggered overdoses.

On average, staggered overdose patients took 24 grams of acetaminophen, typically over several days. Single-overdose patients consumed 27 grams at once, or six times the recommended dose for a whole day.

A total of 60 patients died from a staggered overdose, and 140 patients from a single overdose. This equates to a mortality rate of 37.3% among the staggered overdose group, and 27.8% in the single overdose group. Staggered overdose patients also were more likely to

have liver and brain problems, require kidney dialysis and need help with breathing.

Close to 60% of the staggered overdose group said they had taken the drug to relieve pain, including abdominal or muscular pains, headache or toothache.

During a staggered overdose, the drug likely builds up in the liver and kills the cells, Simpson said.

Staggered overdose patients may have fared less well because they did not receive the appropriate treatment soon enough, or because they had been drinking alcohol along with acetaminophen, he said.

The new study “sheds light on the fact that the maximum recommended daily dose should be strictly adhered to,” said Joshua Lenchus, M.D., an associate professor of clinical medicine at the **University of Miami Miller School of Medicine**.

Acetaminophen also appears in combination with other drugs in certain prescription products. In January FDA asked all manufacturers of acetaminophen to lower the dose in a single tablet to 325 mg. Even at this dose, people who take two tablets every four hours for 24 hours come close to the 4,000 mg limit. (Packets of regular Tylenol pills, which contain 325 mg, say: “Do not take more than 12 tablets in 24 hours.”)

“It’s pretty easy for people to take just a couple of tablets every four hours,” Lenchus said.

Doctors need to consider the possibility of overdoses when patients come to the hospital after taking acetaminophen, even if the patients have not obviously taken many pills at once, Lenchus said.

Sanofi’s Multaq doubled deaths from heart disease in study

A study found that **Sanofi’s** Multaq, approved to treat patients whose hearts intermittently race with quick and inefficient contractions, doubled the risk of death in those with a permanent form of the erratic rhythm, **Bloomberg** reported.

Stroke and heart failure rates also rose significantly in those given Multaq during the trial of 3,236 patients, a blow for the drug that doctors thought would avoid the risks seen with earlier generations of anti-arrhythmic drugs. The research was halted in July because of the increased danger, and the results were presented at the **American Heart Assn.’s** annual meeting Nov. 14.

Doctors had hoped the drug’s ability to reduce deaths, strokes and hospitalizations in patients with occasional atrial fibrillation would carry over to those with the more serious form of the condition, said lead researcher Stuart Connolly, from the **Population Health Research Institute** in Hamilton, Ontario. The findings shoot down the hypothesis, he said.

The study, funded by Paris-based Sanofi, was published in the “New England Journal of Medicine.” There were 21 deaths from cardiovascular causes in the Multaq group, compared with 10 among those getting placebo.

A separate trial of Sanofi’s celivarone, a once-a-day drug thought to be a potential successor to Multaq, failed to prevent sudden deaths and inappropriate electrical shocks in heart patients with implanted defibrillators. The study was halted in July and the company has discontinued the drug’s development.

The results shouldn’t change the use of Multaq for patients with intermittent atrial fibrillation, said Deepak Bhatt, M.D., chief of cardiology at the **VA Boston Healthcare** system and director of the interventional cardiovascular program at **Brigham and Women’s Hospital** in Boston. Instead, the research will focus the drug’s use among doctors who are allowed to prescribe medicines even for conditions where they aren’t specifically approved, he said.

FDA is reviewing Multaq’s safety profile.

More sore throats in people on acne medication

A new study indicates that young adults who take oral antibiotics for acne may be more likely to get sore throats, **Reuters** reported Nov. 21.

While it’s not clear that the medications caused the achy throats, researchers say long-term use of antibiotics might change the balance of bacteria in the throat. In principle, that could allow infection-causing strains to multiply.

“These people are more prone to upper respiratory tract infections, but we certainly don’t know why,” said David Margolis, M.D., from the **University of Pennsylvania** in Philadelphia, who worked on the study.

He pointed out that people taking antibiotics for acne are generally young and healthy and may take them for months or even years on end—so it’s important to be aware of any possible consequences of their use.

So far, though, his research team hasn’t seen an extra risk of antibiotic resistance due to acne medications, the most common of which are tetracyclines. And any

chance of a sore throat, he added, may be worth the medication's benefits in many cases.

"Upper respiratory tract infections are pretty self-limited and mild," said Margolis, whose findings appeared in the "Archives of Dermatology."

He and his colleagues conducted two different studies of college and graduate students at Penn.

In the first, they surveyed a group of 266 students on whether or not they had acne, as well as if they were regularly using oral antibiotics. They also asked the students if they'd had a sore throat in the last month.

Ten of the 15 students who were taking oral antibiotics for acne reported having a sore throat recently. That compared to 47 of 130, or just over one-third of students with acne who weren't taking antibiotics who'd had a sore throat—and slightly fewer students with no acne at all.

In the second study, the researchers followed a different group of close to 600 students over the course of a school year, tracking how many had acne. They also recorded which students visited the health center with a sore throat, as well as the antibiotics students took.

More than 11% of the students taking oral antibiotics for acne also visited a doctor for a sore throat, compared to only about 3% of those not taking the medications. Students using topical antibiotics for acne, such as lotions and ointments, didn't have an extra risk.

The researchers couldn't pin the sore throats on a particular type of bacteria; only a few of the students tested positive for *Streptococcus*, for instance.

That puts a kink in the theory that antibiotics are throwing off the balance of bacteria in the throat and increasing infection risks, but it certainly doesn't disprove it, Margolis added.

"There's an unlimited number of bacteria... and we only looked at a few," he told **Reuters Health**.

"It's hard to know what it means because we don't know what the cause of the (sore throat) was, we just know what it wasn't, and that's strep throat," said Guy Webster, M.D., a dermatologist at **Jefferson Medical College** in Philadelphia who wasn't involved in the new study.

He said that while changes in throat bacteria is one possible explanation for the sore throats, another is that the antibiotics are causing a slightly upset and bloated stomach, and that stomach acid is coming up and irritating the throat.

Regardless, Webster told Reuters Health, people taking the drugs who get achy throats shouldn't worry.

"It's not a warning sign of anything evil going on, that's for certain," he said.

And the findings don't mean people should avoid oral antibiotics for acne treatment altogether, Margolis added.

"People always have to look at the risks and the benefits. Certainly acne can be a severe problem for

people. Certainly oral antibiotics are a time-honored therapy and I'm not trying to tell people not to use them," he said.

Antipsychotics linked to childhood diabetes

Diabetes may be substantially more likely for children taking second-generation atypical antipsychotics, according to findings from a recent study, "MedPage Today" reported Nov. 21.

Incidence of diabetes appeared to be more than four times higher among children on a second-generation antipsychotic than in those not using psychotropic medications, Susan E. Andrade, ScD, of the **University of Massachusetts** in Worcester, and colleagues found.

If real, the risk would pose an important drug safety and public health concern, the group noted in the December issue of "Pediatrics."

Such a link may be plausible, given that the newer generation of antipsychotics is known to cause metabolic problems and weight gain in both children and adults, along with insulin resistance and diabetes in adults, they

Incidence of diabetes appeared to be more than four times higher among children on a second-generation antipsychotic than in those not using psychotropic medications.

pointed out.

But the study couldn't draw any definite conclusions because of the low number of diabetes cases found.

In a retrospective administrative database analysis, just 57 diabetes cases developed among the 9,636 children ages 5 to 18 who started on a second-generation antipsychotic medication from January 2001 to December 2008.

The children were followed through medical, pharmacy and outpatient laboratory records of three health maintenance organization plans.

The rate of incident diabetes was 3.23 cases per 1,000 person-years in children on the antipsychotics;

0.76 cases per 1,000 person-years in children not on any psychotropic medication; 1.86 cases per 1,000 person-years in children on antidepressants.

The incidence rate ratio for diabetes with second-generation antipsychotic use in the unadjusted analysis was 4.24-fold that of children not on psychotropics. But while the association actually appeared stronger after propensity score matching, it lost statistical significance in that analysis.

Compared with children taking antidepressant medications, atypical antipsychotic use wasn't a bigger diabetes risk in either the unadjusted analysis or after propensity matching.

Children on antidepressants may have been a better comparison group because they were more similar in terms of healthcare encounters with the potential for detection or diagnosis of diabetes, Andrade's group noted.

But antidepressants themselves may present a risk for diabetes, based on some recent studies, though evidence is conflicting.

"If a causal association exists between antidepressant medication use and diabetes, then the use of this comparison group might have attenuated an actual association between second-generation antipsychotic use and diabetes in the present study," the investigators wrote in the paper.

Another problem was that both adjusted analyses

included fewer children on antipsychotics—2,531 for the comparison with no psychotropic use and 8,012 for the comparison with antidepressant use.

That further limited the statistical power, because only three and 13 diabetes cases developed in those two groups, respectively.

Long-term epilepsy meds take toll on arteries

According to a single-center study, the duration of anti-epileptic monotherapy was associated with accelerated atherosclerosis, although individual drugs had different underlying mechanisms in epilepsy patients, "MedPage Today" reported Nov. 17.

"The duration of monotherapy with the older generation of anti-epileptic drugs (AEDs) ... is at least one of the important and contributing risk factors to the atherosclerotic process," wrote Teng-Yeow Tan, M.D., from **Kaohsiung Chang Gung Memorial Hospital** in Kaoshiung, Taiwan, and colleagues in "Epilepsia."

In their cross-sectional study, the authors looked

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specifically at four AEDs: enzyme inducers carbamazepine (CBZ) and phenytoin (PHT); enzyme inhibitor valproic acid (VPA); and nonenzyme inducer lamotrigine (LTG, Lamictal.)

The current results build on previous research by Tan's group, which demonstrated that common carotid artery intima media thickness (IMT) in patients with epilepsy seemed to be positively correlated with the duration of AED therapy.

The authors found that the mean common carotid artery IMT was significantly increased in patients taking an AED compared with controls.

In this study, the researchers enrolled 160 patients between July 2006 and December 2010 at an epilepsy outpatient clinic. All patients had received AED monotherapy for more than two years. Sixty healthy volunteers served as the control group.

Patients with idiopathic or cryptogenic epilepsy made up 63.1% of the study population, while the remaining 36.9% consisted of patients with symptomatic epilepsy.

Of the 160 patients, 41 were taking CBZ, 39 were taking PHT, 54 were using VPA and 26 were using LTG.

Patients on CBZ had been using the drug the longest, at 13.3 years, while those taking LTG had been using the drug for the shortest time, at 5.5 years. Duration of use came in at 10.7 years for PHT and 8.7 years for VPA.

Common carotid artery IMT was measured with ultrasonography, with both the left and right common carotid arteries scanned. Blood samples were taken after overnight fasting and analyzed for serum levels of triglycerides, total cholesterol, low-density lipoprotein (LDL), blood sugar, uric acid, folate and total homocysteine (tHcy).

The authors found that the mean common carotid artery IMT was significantly increased in patients taking an AED compared with controls.

However, the difference in mean common carotid artery IMT in the LTG monotherapy group was not statistically significant compared with controls.

There was a positive correlation between common carotid artery IMT and age and duration of AED; frequency of seizures; body mass index; uric acid levels; fasting blood sugar; total cholesterol; and LDL. But there was insignificant correlation between mean com-

mon carotid artery IMT and tHcy, folate and triglycerides.

The authors offered some possible reasons for the differences between AED and the progression of atherosclerosis.

"The augmented [common carotid artery] IMT observed in patients under long-term therapy ... with CBZ and PHT may be related to disturbances of cholesterol, tHcy and folate metabolism, alongside inflammation," they wrote.

On the other hand, elevated uric acid and tHcy levels, along with oxidative stress, may be the culprits in patients on long-term VPA therapy, they added.

Drug shortages

Patients facing shortage of some ADHD medications

For reasons that are unclear, among the medications that are in increasingly short supply are drugs for attention deficit/hyperactivity disorder (ADHD) such as Adderall, **NPR** reported Nov. 21.

Last week, methylphenidate, the active ingredient in Ritalin and generic equivalents, was officially declared in shortage.

"We've literally had hundreds per week of inquiries about this, so we know it's impacting a lot of patients," says Valerie Jensen of FDA's Office of Drug Shortages. "This has been throughout the nation. It's not a local issue. It's not a regional issue. Pharmacists are reporting it to us as well."

The advocacy group **Children and Adults with ADHD** says lots of patients can't get any of the drugs they need at all.

"People are going without. That's what we're hearing," says Ruth Hughes, the group's chief executive.

She says the implications go beyond kids driving their parents and teachers nuts.

"This isn't just 'Oh, I can't focus,'" Hughes says. "Because you can't focus, there are other very adverse circumstances that happen. Teen pregnancy or dropping out of school, drug abuse. Those are the kinds of things that happen when people have very poor impulse control."

And young adults with ADHD have three times more car accidents.

"So it's very important that they're taking their medication when they're driving, to control those symptoms," Hughes adds.

Nobody knows how many people are affected by the shortages. Up to 15 million children and adults are thought to have ADHD, and more than half of children with the disorder take medication for it.

Trying to figure out why there's a shortage is a big challenge. Different experts – even different federal agencies – give you very different reasons.

The Drug Enforcement Administration doesn't think there's a shortage at all.

"You know, I guess there's sort of an assumption out there that there is in fact a shortage," says Gary Boggs of the DEA's Office of Diversion Control.

DEA is involved because these medications are classified as potential drugs-of-abuse, and thus are controlled substances. The DEA sets an annual ceiling on how much of these drugs can be made.

The agency focuses on the aggregate amount of active ingredients being manufactured, not the number of pills sold under a specific company's label, dose or dosage form (such as "extended release"). And from that perspective, Boggs says, there *is* no shortage.

"There is plenty of the drug available out there," Boggs told NPR. "It's just how it's being marketed and how these companies make business decisions. And those business decisions that they make are completely outside of our control."

One company may have run out of its quota; another has plenty. One company sells only to **Rite-Aid**, another only to **CVS**. There might be plenty of 30-milligram extended-release in one locale, but none of the 10-milligram quick-release. And so on.

But ask some drug companies what the problem is, and you get a different answer. They say the DEA's annual quota hasn't been keeping up with demand, which has been escalating over the past decade as more people

get diagnosed with ADHD and the previous stigma associated with the diagnosis fades.

The DEA normally sets its aggregate ceiling on active ingredients once a year, although it may revise the quota once during the year if circumstances warrant. Individual manufacturers can (and do) apply to the agency for increases in their quotas.

But companies say they can wait two or three months for the DEA to respond to their quota requests. Once they get it (if they do), it takes 12 weeks to turn the raw ingredients into finished pills ready for distribution.

Physicians press U.S. to require reporting of drug shortages

Drugmakers should be required to establish plans to ensure the supply of crucial medicines such as cancer treatments, said a panel of doctors urging that the **American Medical Assn.** lobby for such a move, **Bloomberg** reported Nov. 14.

The group's House of Delegates is expected to vote to adopt the recommendation as its policy soon. The move by the largest U.S. physician lobby may increase pressure on lawmakers and manufacturers such as **Johnson & Johnson**, whose cancer drug Doxil has been in short supply this year.

Shortages of Doxil and other medicines "are a complex problem that will require a multipronged approach to solve," the AMA panel chaired by **Oklahoma University** medical professor Robert McCaffree, M.D., wrote in a report.

Johnson & Johnson supports "the concepts of identifying and describing shortages," said Lisa Vaga, a spokeswoman, in an e-mail. The company also wants quick FDA plant inspections to re-start production in the event of a shortage.

There have been 232 drugs in short supply so far this year, most generic injectable drugs for cancer and anaesthesia, said Bona Benjamin, director of medication-use quality improvement for the **American Society of Health-System Pharmacists**, in a presentation to AMA delegates. That is the highest number of shortages in at least a decade, according to the **University of Utah Drug Information Service**.

"We know there has been patient harm and even patient deaths" from shortages, Benjamin said. According to FDA, 54 % of the causes are due to "production quality issues" at drug factories.

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UK lawmakers to probe medicine shortages

A continuing shortage of some essential medicines in Britain is to be investigated by members of parliament, following complaints by pharmacists that vital supplies are being lost to exports, **Reuters** reported.

The **All-Party Pharmacy Group**, which announced its inquiry Nov. 21, said shortages in the supply chain had been occurring for two years and there was no sign of improvement.

The group said the reasons for drug shortages were complex but it was concerned that past efforts to resolve the problem had failed. It is seeking written evidence by Dec. 23, ahead of issuing a report in the new year.

Lloydspharmacy, a unit of Germany's **Celesio**, said earlier this month that a survey of 396 of its pharmacists around Britain found 80% were unable to dispense certain items because of shortages.

Low prices relative to other European countries have fueled exports from the country, leaving many pharmacies scrambling for supplies, it said.

The export trade has been encouraged by a weak pound, which means Britain is now a particularly cheap place for middlemen to buy medicines and sell them on at a profit in other European markets.

Such so-called parallel trade is legal under European Union law and has long been an irritation for drugmakers. In the past companies have complained about cheap parallel imports flooding into the country when British drug prices were relatively high.

The new alarm over drug shortages in Britain comes

hard on the heels of action by U.S. President Barack Obama to tackle an escalating shortage of life-saving medicines in the United States, due to manufacturing and supply issues.



FDA sees rare but serious issue with stents

FDA is investigating a rare but potentially serious problem with a newer class of heart stents that causes the tiny tubular devices made of wire mesh to shrink or lengthen after implantation, **Reuters** reported Nov. 18.

The problem appears to occur most frequently in the Promus and Ion devices made by **Boston Scientific Corp.**, FDA said. Promus Element is sold outside the United States. The company submitted a pre-market application with FDA earlier this year.

The agency said it still views the Ion stent, which it approved for use in the spring, as safe when used for its authorized indications.

“FDA is actively working with (drug-eluting stent) manufacturers, including Boston Scientific, to better understand longitudinal stent deformation with respect to its causes, predisposing underlying anatomic conditions, operator techniques that can reduce the likelihood of its occurrence, and treatment strategies should it occur,” the agency said in an emailed response to a Reuters inquiry.

Boston Scientific, the biggest manufacturer of stents with more than a third of the \$4 billion global market, declined to comment on discussions with FDA. Boston Scientific had a 36% share of the global market and a 49% share of the U.S. market at the end of the third quarter.

The company's business has struggled on several fronts in recent years, including a series of stent recalls that date to 2004 and a heavy debt load from its ill-fated acquisition of stent and pacemaker manufacturer **Guidant Corp.** in 2006.

Concerns about stent deformation were raised in two smaller cardiology journals published in the United States and Europe, and the issue was the subject of a discussion at the **Transcatheter Cardiovascular Therapeutics** meeting in San Francisco earlier this month.

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Drug-eluting stents prop open diseased arteries and deliver medicine to keep the vessel from reclogging. In the case of longitudinal deformation, the stents become deformed inside the vessel, creating a clotting risk that could lead to heart attack.

Some factors that appear to predispose a patient to the problem include calcification of coronary arteries, implantation in a twisted blood vessel and improper positioning of the stent, FDA said.

FDA said that only one instance of longitudinal stent deformation was reported from trials of more than 4,600 patients treated with a Promus stent. But it said it was also aware of recently published case reports on the problem and that an unspecified number of significant adverse events had been reported to the agency.

“At this time, additional data collection and analyses are ongoing, but the information available to date indicates that the Ion Paclitaxel-Eluting Platinum Chromium Stent remains safe and effective when used for its approved indications,” the agency said.

Heart stents have also come under scrutiny following research that shows taking conventional medication and exercise may help some patients more than the devices.

In June, **Johnson & Johnson** said it was getting out of the drug-eluting stent business. Other makers of drug-eluting stents include **Medtronic** and **Abbott Laboratories**.

Gregg Stone, M.D., a cardiologist at **New York Presbyterian/Columbia Hospital** who has led many clinical trials for all of the major stent makers, said the stent deformation seems to occur most often in complex cases of blocked blood vessels.

“It can happen with any stent if you’re aggressive enough with it,” he said. “The metal is very thin—it’s 3/1,000 of an inch thick, so depending on the material and configuration ... some are more prone (to deformation) than others.”

He would not characterize it as a design flaw or as user error. He cited instances where a balloon used to implant the device catches on the stent, pulls it and causes it to lose its proper form, or when the guide wire that carries the device pushes on the stent, causing it to shorten in length.

“It seems to be a rare phenomenon. Millions of these are implanted and there are just a handful of these cases,” he said.

Cindy Grines, M.D., a cardiologist at the **Detroit Medical Center Cardiovascular Institute** and editor of the “Journal of Interventional Cardiology,” said she reported the issues to FDA and to Boston Scientific when she first learned of it. She wrote an editorial on the problem in the latest issue of the Journal.

“The FDA was very interested and said they got other complaints and would do an extensive analysis,” Grines said in a telephone interview. “I’ve never seen

anything like this and I’ve been doing this for 25 years and I do a lot of complex cases.”

Abbott spokesman Jonathon Hamilton and Medtronic spokesman Joseph McGrath both stressed that longitudinal compression is caused by device design, and said it is not a class effect that applies to all stents.

Bill introduced to speed device approval

Sens. Al Franken (D-MN), Lamar Alexander (R-TN) and John Kerry (D-MA) introduced a bill Nov. 15 that eases some conflict of interest rules affecting outside experts on FDA review panels and lifts an FDA rule that caps profits for devices that treat rare conditions. Easing that rule is intended to encourage companies to develop devices that would otherwise serve a very small number of patients.

“My legislation would remove unnecessary barriers so that these critical medical devices get to the patients that need them as quickly and safely as possible,” said Franken in a written statement.

His legislation follows bills released by Sen. Amy Klobuchar (D-MN) and Rep. Erik Paulsen (R-MN) that are also intended to speed up the time it takes FDA to review medical devices. All three bills ease the conflict of interest rules for outside experts, albeit in different ways. Franken’s is the only bill to address the issue of treating rare conditions.

Off-label use

Bayer may have pitched contraceptive for unapproved use

Units of **Bayer**, Germany’s largest drugmaker, may have sought to market the Yasmin family of birth control pills for unapproved uses and misled women about the health risks the drug posed, according to company e-mails.

Bloomberg reported Nov. 21 that Bayer unit officials discussed promoting the contraceptive known as

Yaz, a spinoff of Yasmin, for treatment of all types of premenstrual syndrome, according to company files provided to lawyers for women suing Bayer. U.S. regulators approved Yaz only for the most severe form of PMS. Salespeople for Bayer unit **Berlex Laboratories**, acquired in the 2006 purchase of **Schering**, received an e-mail that year from a company official citing a “Woman’s Day” magazine article about Yaz.

“This article is a nice way of using YAZ for PMS treatment instead of just focusing on the specific” class of women battling premenstrual dysphoric disorder, the most severe form of PMS, wrote Matt Sample, a Berlex sales consultant, according to a copy of the e-mail produced as evidence.

The message and other internal company files were disclosed as part of litigation claiming the drug caused blood clots, heart attacks and strokes. Bayer faces more than 10,000 lawsuits over injuries allegedly caused by the contraceptives. Lawyers suing the drugmaker cited FDA reports of at least 50 deaths tied to the pills from 2004 to 2008.

Last month, FDA warned that women taking the pills were 74% more likely to suffer blood clots than women on other low-estrogen contraceptives. FDA examined data on 835,826 women who took pills containing the hormone, including Bayer’s Yasmin line of birth-control pills, according to the report. The agency has set a Dec. 8 hearing to discuss the findings.

Besides the off-label marketing allegations, attorneys for women suing Bayer alleged internal company files show Berlex and Schering officials withheld some information from patients, doctors and regulators about the drug’s risk for blood-clots. The lawyers also claim in court filings that company officials wrongfully touted Yasmin and Yaz to be just as safe as rival birth-control pills.

In January, Bayer is scheduled to face the first trials of lawsuits in which Yaz and Yasmin are alleged to have caused blood clots, which can lead to heart attacks and strokes. The trials are to take place in Illinois and Pennsylvania.

Bayer turned over Sample’s e-mail and other documents obtained by Bloomberg News to the plaintiffs’ lawyers as part of discovery in the consolidated Yaz cases.

The lawyers contend Sample’s e-mail about the Woman’s Day article amounts to an effort to have Yaz promoted for a use not approved by FDA. Under U.S. law, a doctor can prescribe a medicine for any condition, as long as it’s licensed by FDA and proven safe and effective.

Drug companies, however, aren’t allowed to promote a drug for uses other than those approved by the regulator.

In the e-mail, Sample encourages Berlex’s sales representatives to use the article to ask doctors “what per-

centage of your patient population suffers from” symptoms common to PMS, versus the more severe form of the disorder, and to seek information on “what they think the impact of Yaz will be.”

The attorneys contend the e-mail supports their arguments that the drugmaker sought to market the Yasmin line of contraceptives for unapproved uses.

FDA approved Yasmin only as a contraceptive. The regulator hasn’t cleared it as a treatment for any form of PMS or other ailments, according to the agency’s website.

FDA said Bayer made misleading claims about Yaz in television advertising, overstating the pill’s effectiveness and minimizing “serious risks associated” with it in two 60-second television ads. The regulator said the spots misled viewers about approved uses for the drug.

FDA officials ordered the company to pull the ads. The following year, Bayer agreed to run new ads stating Yaz hadn’t been approved as a treatment for all forms of PMS or acne as part of a settlement of a claims brought

Bayer unit officials discussed promoting the contraceptive Yaz for treatment of all types of premenstrual syndrome, according to company files. FDA approved Yaz only for the most severe form of PMS.

by 27 U.S. state attorneys general.

Nearly 12 million women in the U.S. and more than 100 million women worldwide use oral contraceptives, Scott Monroe, an FDA official, said last year.

About 10,400 suits have been filed over injuries allegedly caused by the contraceptives, Bayer officials said last month in a filing with the U.S. Securities and Exchange Commission.

FDA scheduled its December hearing on drospirenone-laden contraceptives, such as the Yasmin line, because of “the conflicting nature of the findings from six published studies evaluating this risk,” the agency said in September.

The FDA advisory committee will discuss “the benefits and risks” of contraceptives such as Yasmin and Yaz “in light of the emerging safety concern that the risk of venous thromboembolism (blood clots that can break loose and move within the circulatory system) associated with use of these products may be higher compared to oral contraceptives that contain the progestin, levonorgestrel,” Morgan Liscinsky, an FDA spokeswoman, said in a Nov. 18 e-mailed statement.

Synthes officers sentenced to prison for off-label marketing of bone cement

Two former **Synthes** executives were sentenced to nine months in prison and a third sentenced to five months in prison for their roles in the medical-device maker's promotion of a bone cement for unauthorized uses, "The Wall Street Journal" reported Nov. 22.

U.S. District Court Judge Legrome Davis sentenced Michael Huggins, who was chief operating officer of Synthes, and Thomas Higgins, former president of the Synthes spine division, to nine months in federal prison Monday.

John Walsh, former director of regulatory and clinical affairs in the Synthes spine unit, was sentenced to five months in prison. The sentencing hearing for a fourth man, Richard Bohner, former vice president of operations at Synthes, was postponed after his defense attorney collapsed in the courtroom.

"There's a real failure in this particular corporate culture ... as to the recognition of responsibility," Judge Davis said during Walsh's hearing. Judge Davis said he gave Walsh a shorter prison term because Walsh joined Synthes after some of the alleged violations had occurred.

Huggins was ordered to start serving his term immediately, while Higgins and Walsh were permitted to surrender at future dates.

The sentences were victories for the Justice Department as it steps up efforts to hold individual executives criminally responsible for corporate violations of food and drug laws. Federal sentencing guidelines called for prison terms of zero to six months, but the Justice Department had asked the judge to sentence the former executives to prison for up to a year, partly to serve as a deterrent to other health-care industry executives.

"We believe it sends the right message to the manufacturers of medical devices and drugs, that lying to FDA and disregarding patient safety has consequences," said Mary Crawley, an assistant U.S. Attorney who led the prosecution.

White-collar criminal defense lawyers said the sentences would make waves in the health-care industry. "This is the most significant sentence of an individual in the industry" among cases brought under the so-called responsible corporate officer doctrine, said Thomas Gal-

agher, a former federal prosecutor who specializes in white-collar criminal defense with **Pepper Hamilton** in Philadelphia, after the sentence for Huggins.

The doctrine holds executives in certain positions of authority criminally liable for alleged violations of food and drug laws, even if they didn't have direct knowledge of the underlying conduct.

Gallagher, who isn't involved in the case, said it has been rare for an executive to get any prison time for a case under this doctrine. In March, Marc Hermelin, former chief executive of **K-V Pharmaceutical**, was sentenced to 30 days in prison in connection with the company's shipment of oversized painkillers.

Lawyers for the former executives had argued that prison terms would be excessive, and that probationary or fine-only sentences are sufficient. Each of the four men pleaded guilty in 2009 to a misdemeanor charge of shipping adulterated and misbranded bone cement into interstate commerce, and agreed to pay the maximum fine of \$100,000.

Federal sentencing guidelines called for prison terms of zero to six months, but the Justice Department had asked the judge to sentence the former executives to prison for up to a year, partly to serve as a deterrent to other health-care industry executives.

Synthes and its **Norian** unit agreed last year to plead guilty to charges that between 2002 and 2004 they conspired to conduct unauthorized clinical trials of the Norian bone cement in surgeries to treat vertebral compression fractures of the spine, a type of fracture that often occurs in the elderly.

The prescribing label for the Norian bone cement, however, specifically warned against using it for vertebral compression fractures, due to concerns it could cause dangerous blood clots. The cement was approved to fill bony voids or defects that weren't essential to bone stability.

Three patients died on the operating table after spine surgeons used the Synthes product in 2003 and 2004. The Department of Justice hasn't proved that the cement caused the deaths, but the agency has said the deaths should have raised red flags at Synthes about the product's safety risks.

To settle the corporate charges, Synthes and Norian agreed to pay \$23.2 million in fines, and Synthes sold Norian to **Kensey Nash Corp.** Synthes, which has its headquarters in Switzerland and has major operations in the Philadelphia suburbs, has agreed to be acquired by **Johnson & Johnson** for about \$21 billion in a deal expected to close next year.

The responsible corporate officer doctrine holds that executives can be held criminally liable if they failed to prevent or promptly correct certain corporate violations. The doctrine is controversial, however, because it doesn't require proof that a corporate officer had knowledge or awareness of the alleged wrongdoing.

The Justice Department alleged in court papers that in the Synthes case, the men were aware of and participated to some extent in the underlying criminal conduct, and that their conduct caused harm to the public.

But defense lawyers said in court filings that prison terms would be unusual and extraordinary for executives who have pleaded guilty to misdemeanors under the responsible corporate officer doctrine.

Lawyers for Huggins—the highest-ranking of the former executives—acknowledged in a court document he “failed to heed warning signs concerning Norian’s use in the spine” and “is painfully aware that three patients died during operations involving Norian.”

Huggins’ lawyers also said the evidence in the case “shows that Huggins committed a serious offense but does not show the sort of intentional misconduct that the government has alleged in this case.”

In a written statement read in court by his lawyer, Walsh said he accepted responsibility for failing to prevent the illegal conduct, but asked the judge for lenience, saying that he and his family have suffered as a result of the case, and that he wanted to pursue a career as a high-school teacher.

E-prescribing

New study finds e-prescribing is safe and efficient, but barriers remain

Physician practices and pharmacies generally view electronic prescribing as an important tool to improve patient safety and save time, but both groups face barriers to realizing the technology’s full benefit, according to a study funded by the U.S. Department of Health and Human Services’ (HHS) Agency for Healthcare Research

and Quality (AHRQ.) The study is published online in the “Journal of the American Medical Informatics Association.”

Electronic prescribing, or e-prescribing, has multiple potential benefits, including helping to reduce the risk of medication errors caused by illegible or incomplete handwritten prescriptions. The study focused on a key aspect of e-prescribing: the electronic exchange of prescription data between physician practices and pharmacies, which can save time and money by streamlining the way in which new prescriptions and renewals are processed.

Physician practices and pharmacies generally were positive about the electronic transmission of new prescriptions, the study found. However, prescription renewals, connectivity between physician offices and mail-order pharmacies and manual entry of certain prescription information by pharmacists—particularly drug name, dosage form, quantity and patient instructions—continue to pose problems.

“Physicians and pharmacies have come a long way in their use of e-prescribing, and that’s a very positive trend for safer patient care and improved efficiency,” said AHRQ Director Carolyn Clancy, M.D. “This study identifies issues that need attention to improve e-prescribing for physicians, pharmacies, and patients.”

Researchers at the **Center for Studying Health System Change** conducted 114 interviews with representatives of 24 physician practices, 48 community pharmacies and three mail-order pharmacies using e-prescribing. Community pharmacies were divided between local and national companies.

Physician practices and pharmacies used e-prescribing features for electronic renewals much less often than for new prescriptions. More than a quarter of the community pharmacies reported that they did not send electronic renewal requests to physicians. Similarly, one-third of physician practices had e-prescribing systems that were not set up to receive electronic renewals or only received them infrequently.

Physician practices reported that some pharmacies that sent renewal requests electronically also sent requests via fax or phone, even after the physician had responded electronically. At the same time, pharmacies reported that physicians often approved electronic requests by phone or fax or mistakenly denied the request and sent a new prescription.

The study noted that resolving e-prescribing challenges will become more pressing as increasing numbers of physicians adopt the technology in response to federal incentives. Physicians can qualify for Medicare and Medicaid electronic health record incentive payments by generating and transmitting more than 40% of all prescriptions to pharmacies electronically, excluding prescriptions for controlled substances, as part of the HITECH Act of 2009.

Other key study findings include:

- About three-quarters of physician practices reported problems sending new prescriptions and renewals electronically to mail-order pharmacies. Many practices were unsure which mail-order pharmacies accepted e-prescriptions and believed that, even when a mail-order company did accept them, the process was unreliable.
- Pharmacies noted the need to sometimes manually edit certain prescription information, such as drug name, dosage and quantity. One common cause reported by both physicians and pharmacists was that physicians must select medications with more specificity when e-prescribing and make decisions about such factors as packaging and drug form. Such decisions had typically been made by pharmacists for handwritten prescriptions.
- Nearly half of pharmacies reported that patient instructions typically had to be rewritten for patients to understand them.

The study, “Transmitting and processing electronic prescriptions: Experiences of physician practices and pharmacies,” concludes that a broad group of public and private stakeholders will need to work together to address these issues.



Contraindications and warnings

FDA listed the following drugs and drug products as having had modifications to the Contraindications and/or Warnings/Boxed Warnings sections during October 2011. For additional information or to read the full labeling of the drug products, visit:

<http://www.fda.gov/medwatch/>

Definity Vial for (Perflutren Lipid Microsphere) Injectable Suspension

BOXED WARNING

- Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration [see WARNINGS AND

PRECAUTIONS (5.1)]. Most serious reactions occur within 30 minutes of administration....

WARNINGS AND PRECAUTIONS

Serious Cardiopulmonary Reactions, and:

Anaphylactoid Reactions:

- minor changes in both sections....

ADVERSE REACTIONS

Postmarketing Experience

- Reported reactions included:

USE IN SPECIAL POPULATIONS

Geriatric Use

In clinical trials, the overall incidence of adverse reactions was similar for the <65 year age group and the ≥65 year age group. Of the total

Evamist (estradiol transdermal spray)

BOXED WARNING

- Unintentional secondary exposure.....added

WARNINGS AND PRECAUTIONS

Unintentional Secondary Exposure to Estrogen.....added

PATIENT COUNSELING INFORMATION

Unintentional Secondary Exposure to Estrogen...added

PATIENT PACKAGE INSERT

- extensive changes re: unintentional secondary exposure to estrogen

Selzentry (maraviroc) tablets

BOXED WARNING

- Hepatotoxicity (new)

WARNINGS AND PRECAUTIONS

Hepatotoxicity

- Hepatotoxicity with allergic features including life-threatening events has been reported in clinical trials and postmarketing. Severe rash or evidence of systemic allergic reaction including drug-related rash with....

May 2010

CONTRAINDICATIONS

- Selzentry should not be used in patients with severe renal impairment or end-stage renal disease (ESRD) (CrCl < 30 mL/min) who are taking potent CYP3A inhibitors or inducers.

WARNINGS AND PRECAUTIONS

- *Postural Hypotension in Patients with Renal Impairment* Patients with impaired renal function may have cardiovascular co-morbidities and could be at increased risk of cardiovascular adverse events triggered by postural hypotension. An increased risk of postural hypotension may occur in patients with severe renal insufficiency or in those with end-stage renal disease (ESRD) due to increased maraviroc exposure in some patients. Selzentry should be used in patients with severe renal impairment or ESRD only if they are not receiving a concomitant potent CYP3A

inhibitor or inducer. However, the use of Selzentry in these patients should only be considered when no alternative treatment options are available. If patients with severe renal impairment or ESRD experience any symptoms of postural hypotension while taking 300 mg twice daily the dose should be reduced to 150 mg twice daily.

USE IN SPECIFIC POPULATIONS

Renal Impairment

- Recommended doses of Selzentry for patients with impaired renal function ($\text{CrCl} \leq 80$ mL/min) are based on the results of a pharmacokinetic study conducted in healthy subjects with various degrees of renal impairment. The pharmacokinetics of maraviroc in subjects with mild and moderate renal impairment was similar to that in subjects with normal renal function. A limited number of subjects with mild and moderate renal impairment in the Phase 3 clinical trials ($n = 131$ and $n = 12$, respectively) received the same dose of Selzentry as that administered to subjects with normal renal function. In these subjects there was no apparent difference in the adverse event profile for maraviroc compared to subjects with normal renal function.
- If patients with severe renal impairment or end-stage renal disease (ESRD) not receiving a concomitant potent CYP3A inhibitor or inducer experience any symptoms of postural hypotension while taking Selzentry 300 mg twice daily, the dose should be reduced to 150 mg twice daily. No studies have been performed in subjects with severe renal impairment or ESRD co-treated with potent CYP3A inhibitors or inducers. Hence, no dose of Selzentry can be recommended, and Selzentry is contraindicated for these patients.

Hepatic Impairment

Maraviroc concentrations are higher when Selzentry 150 mg is administered with a potent CYP3A inhibitor compared to following administration of 300 mg without a CYP3A inhibitor, so patients with moderate hepatic impairment who receive Selzentry 150 mg with a potent CYP3A inhibitor should be monitored closely for maraviroc-associated adverse events.

Demerol (meperidine hydrochloride)

CONTRAINDICATIONS

- Serotonin syndrome with agitation, hyperthermia, diarrhea, tachycardia, sweating, tremors and impaired consciousness may also occur
- DEMEROL is contraindicated in patients with severe respiratory insufficiency

PRECAUTIONS

General

- ...or renal function; and toxic psychosis (see PRECAUTIONS, Special Risk Patients) **Interactions with Other CNS Depressants**
Drug-drug interactions may result in respiratory depression, hypotension, profound sedation, coma or death if...

- **Interactions with Mixed Agonist/Antagonist Opioid Analgesics**
added...may precipitate withdrawal symptoms in these patients due to competitive blocking of receptors

- **Tolerance and Physical Dependence**
added...Meperidine has the potential to produce tolerance and drug dependence

- **Drug Interactions**
CNS Depressants: Concomitant use of CNS depressants with usual doses of Demerol may result in...
Phenytoin: ...were increased, thus caution should be exercised when...

- **Geriatric Use**
Reducing the total daily dose of meperidine is recommended in elderly patients...

ADVERSE REACTIONS

- Nervous System: Mood changes (e.g. euphoria, dysphoria), weakness, headache, agitation, tremor, involuntary muscle movements (e.g. muscle twitches, myoclonus), severe convulsions, transient hallucinations and disorientation, confusion, delirium, visual disturbances

WARNINGS

- ... Prolonged meperidine use may increase the risk of toxicity (e.g. seizures) from the accumulation of the meperidine metabolite, nor-meperidine.

PRECAUTIONS

Pediatric Use:

- ... If meperidine use is contemplated in neonates or young infants, any potential benefits of the drug need to be weighed against the relative risk to the patient.

ADVERSE REACTIONS

Allergic

Pruritus ... anaphylaxis, shock.

Hycamtin (topotecan) Capsules

CONTRAINDICATIONS

- ...should not be used in patients with severe bone marrow depression

WARNINGS AND PRECAUTIONS

Interstitial lung disease

- interstitial lung disease..... added

ADVERSE REACTIONS

Postmarketing Experience

Respiratory, thoracic, and mediastinal disorders: Interstitial lung disease.

Premarin (conjugated estrogens tablets, USP)**CONTRAINDICATIONS**

- ... angioedema
- ... known thrombophilic disorders

WARNINGS

- ... 7. angioedema
- ... 8. hereditary angioedema

PPI

How should I take.....

- added info about “tablet in stool”

also: selected sections changed to reflect recommended estrogen-class labeling

Suprenza (phentermine hydrochloride) ODT**CONTRAINDICATIONS**

- Known hypersensitivity, or idiosyncrasy to the sympathomimetic amines

Amturnide (amlodipine/aliskiren/hydrochlorothiazide) Tablets**WARNINGS AND PRECAUTIONS****Cyclosporine or Itraconazole**

- When aliskiren was given with cyclosporine or itraconazole, the blood concentrations of aliskiren were significantly increased. Avoid concomitant use of aliskiren with cyclosporine or itraconazole [see Drug Interactions (7)]

ADVERSE REACTIONS**Postmarketing Experience**

- Hypersensitivity: angioedema requiring airway management and hospitalization
- Aliskiren: Peripheral edema, Blood creatinine increased

DRUG INTERACTIONS**Aliskiren**

- Cyclosporine: Avoid co-administration of cyclosporine with aliskiren.

Itraconazole: Avoid co-administration of itraconazole with aliskiren. [See Clinical Pharmacology (12.3).]

Avelox (moxifloxacin hydrochloride)**WARNINGS AND PRECAUTIONS****Central Nervous System Effects/ Disorders**

Convulsions and increased intracranial pressure (including pseudotumor cerebri) have been reported...

Byetta (exenatide) Injections**WARNINGS AND PRECAUTIONS****Use with Medications Known to Cause Hypoglycemia**

- When Byetta is used in combination with insulin, the dose of insulin should be evaluated. In patients at increased risk of hypoglycemia consider reducing the dose of insulin [see Adverse Reactions (6.1)]. The concurrent use.....

ADVERSE REACTIONS**Clinical Trial Experience**

- Add-on to insulin glargine with or without metformin and/or thiazolidinedione.....For the 30-week placebo-controlled.....
- Table 5 added
- The most frequently reported adverse reactions leading to withdrawal for Byetta-treated patients were.....

PATIENT COUNSELING INFORMATION**Risk of Hypoglycemia**

- When Byetta is used in combination with insulin, evaluate.....

MEDICATION GUIDE

- These medical conditions can make you more likely to get pancreatitis in general. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking Byetta.
- The use of Byetta with short acting insulin is not recommended.
- The use of Byetta with rapid acting insulin is not recommended.
- Low blood sugar (hypoglycemia). Your risk for getting low blood sugar is higher
- The most common side effects with Byetta include: constipation, weakness

Also see: Instructions for Use

- Do not mix Byetta and insulin in the same syringe or vial even if you take them at the same time.

ADVERSE REACTIONS**Postmarketing Experience**

- Skin and Subcutaneous Tissue Disorders: alopecia

WARNINGS and PRECAUTIONS**Acute Pancreatitis**

- Based on postmarketing data Byetta has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of Byetta, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, Byetta should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Byetta should not be restarted. Consider antidiabetic therapies other than Byetta in patients with a history of pancreatitis.

Renal Impairment

- Byetta should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should

be used with caution in patients with renal transplantation [see Use in Specific Populations (8.6)]. In patients with end-stage renal disease receiving dialysis, single doses of Byetta 5 mcg were not well-tolerated due to gastrointestinal side effects. Because Byetta may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of Byetta from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Byetta or any other antidiabetic drug.

Clozaril (clozapine) Tablets

WARNINGS

QT Interval Prolongation

- section added

PRECAUTIONS

Drug Interactions and Pharmacodynamic-Related Interactions

- ... QT prolongation

Pharmacokinetic-Related Interactions

- ... QT prolongation

DRUG INTERACTIONS

Post-marketing Clinical Experience

Cardiovascular system

... QT prolongation

Cipro (ciprofloxacin hydrochloride)

Ciprofloxacin Tablets

Ciprofloxacin IV for Inusion Vial

Ciprofloxacin 0.2 % Solution in 5% Dextrose

Ciprofloxacin Oral Suspension

Cipro XR Tablet

WARNINGS

Central Nervous System Effects/ Disorders

- ... Increased intracranial pressure (including pseudotumor cerebri)

Factive (gemifloxacin mesylate) Tablet

WARNINGS

Central Nervous System Effects/ Disorders

... Although not seen in Factive clinical trials, convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis have been reported in patients receiving other fluoroquinolones.”

Gallium Citrate Ga 67 Injection

WARNINGS

Added.... The vial stopper contains dry rubber latex and may cause allergic reactions in provider or patients who are sensitive to latex.

Lactated Ringer

Lactated Ringer's injection in aviva plastic container

Lactated Ringer's in viaflex plastic container

Lactated Ringer's and 5% Dextrose in viaflex plastic container

Sodium Lactate (M/6 sodium lactate) injections in viaflex plastic container

WARNINGS

- Excessive administration of Sodium Lactate Injection, USP may result in hypokalemia

PRECAUTIONS

- Do not connect flexible plastic containers in series in order to avoid air embolism due to possible residual air contained in the primary container
- The osmolarity of Sodium Lactate Injection, USP is 334 mOsmol/L (calc). Administration of substantially hypertonic solutions may cause venous irritation, including phlebitis

ADVERSE REACTIONS

Class Reactions

- Other manifestations of hypersensitivity/infusion reactions: decreased heart rate, tachycardia, blood pressure decreased....

Levaquin (levofloxacin) Tablets and Oral Solution

WARNINGS AND PRECAUTIONS

Central Nervous System Effects/Disorders

- pseudotumor cerebri ... added

Lithium Carbonate 150 mg, 300 mg, and 600 mg capsules

WARNINGS

Unmasking of Brugada Syndrome

- ...the unmasking of Brugada Syndrome [added]

PRECAUTIONS

Information for the Patients

- ...the unmasking of Brugada Syndrome [added]

ADVERSE REACTIONS

Cardiovascular

...the unmasking of Brugada Syndrome [added]

Lithobid (lithium carbonate) Extended-Release tablets

WARNINGS

- the unmasking of Brugada Syndrome [added]

ADVERSE REACTIONS

- the unmasking of Brugada Syndrome [added]

PATIENT COUNSELING INFORMATION

the unmasking of Brugada Syndrome [added]

Nexavar (sorafenib)

WARNINGS AND PRECAUTIONS

Increased Mortality Observed with Nexavar Administered in Combination with Carboplatin/Paclitaxel

and Gemcitabine/Cisplatin in Squamous Cell Lung Cancer

- In a subset analysis of two randomized controlled trials in chemo-naïve patients with Stage IIIB-IV non-small cell lung cancer...

Risk of QT Interval Prolongation

- Nexavar can prolong the QT/QTc interval and increase the risk

ADVERSE REACTIONS

Additional Data from Multiple Clinical Trials

The following additional drug-related adverse reactions and laboratory abnormalities were reported from clinical trials of Nexavar (very common 10% or greater, common 1 to less than 10%, uncommon 0.1% to less than 1%):

- Cardiovascular: Common: congestive heart failure*, myocardial ischemia and/or infarction Uncommon: hypertensive crisis* Rare: QT prolongation*

Postmarketing Experience

- Dermatologic: Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN)

DRUG INTERACTIONS

Drug Metabolism

- Effect of Cytochrome P450 on Sorafenib : Rifampicin, a strong CYP3A4 inducer, administered.....

Neomycin

- Neomycin administered at a dose of 1g three times daily for 5 days decreased.....

USE IN SPECIAL POPULATIONS

Patients With Hepatic Impairment

- In a trial of HCC patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, the systemic exposure (AUC) of sorafenib was

Patients With Renal Impairment

- No correlation between sorafenib exposure and renal function was observed following administration of a single 400 mg dose.....

PATIENT COUNSELING INFORMATION

QT Interval Prolongation

Inform patients with a history of prolonged QT interval that Nexavar can worsen the condition [see Warnings and Precautions (5.9) and Clinical Pharmacology (12.2)].

Noroxin (norfloxacin) tablets

WARNINGS

Central Nervous System Effects/ Disorders:

- added.....Convulsions have been reported in patients receiving norfloxacin. Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychoses have been reported in patients receiving drugs in this class.

OxyContin (oxycodone hydrochloride)

WARNINGS AND PRECAUTIONS

Difficulty Swallowing and Gastrointestinal Effects

- There have been post-marketing reports of difficulty ...
- There have been rare post-marketing reports of cases of intestinal obstruction...
- Use caution when prescribing OxyContin for patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction.

The administration of OxyContin may obscure...

Tasigna (nilotinib) capsule

WARNINGS AND PRECAUTIONS

Tumor Lysis Syndrome

- added ... new section; moved from Adverse Reactions, Postmarketing experience

MEDICATION GUIDE

"What are the possible side effects...?"

- updated to include tumor lysis syndrome

Veramyst, (fluticasone furoate) Nasal Spray

WARNINGS AND PRECAUTIONS

Local Nasal Effects

- section added

ADVERSE REACTIONS

Postmarketing Experience

Respiratory, Thoracic, and Mediastinal Disorders

- add : Rhinalgia, nasal discomfort (including nasal burning, nasal irritation, and nasal soreness), nasal dryness, and nasal septal perforation

PATIENT COUNSELING INFORMATION

Keep Spray Out of Eyes

- section added

Potential Drug Interactions

- section added

Votrient (pazopanib hydrochloride) Tablets

WARNINGS AND PRECAUTIONS

Hypertension

- In clinical studies, events of hypertension including hypertensive crisis have occurred... Votrient should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite antihypertensive therapy and dose reduction of Votrient.

ADVERSE REACTIONS

Clinical Trials Experience

- Potentially serious adverse reactions with Votrient included hepatotoxicity, QT prolongation and torsades de pointes, hemorrhagic events, arterial thrombotic events, gastrointestinal perforation, and fistula, and hypertensive crisis [see Warnings and Precautions (5.1-5.6)].

- Cardiac Dysfunction - Pazopanib has been associated with cardiac dysfunction (such as...)

MEDICATION GUIDE

see document for details

Vumon (teniposide) Injection

WARNINGS

- ...metabolic acidosis added
- ...Physicians should be aware of the possible occurrence of a hypersensitivity reaction variably manifested by chills, fever, urticaria, tachycardia, bronchospasm, dyspnea, hypertension or hypotension, rash

Male Fertility

- section added

ADVERSE REACTIONS

Central Nervous System

- ...neurotoxicity added

Hematological Toxicity

- ...Sepsis, sometimes fatal, may be a consequence of severe myelosuppression.

Other Adverse Reactions

- ... headache, confusion, asthenia
- ...for effects on male fertility and incorporate rash as a possible symptom of an anaphylactoid-type reaction, as well as sepsis as a consequence of myelosuppression.

Vytorin (ezetimibe/simvastatin) tablet

WARNINGS AND PRECAUTIONS

Myopathy/Rhabdomyolysis

- Vytorin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Vytorin therapy should also ...

Liver Enzymes

- There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury ...

ADVERSE REACTIONS

Post-Marketing Experience

- There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated...

PATIENT COUNSELING INFORMATION

Liver Enzymes

- ...All patients treated with Vytorin should be advised to report promptly any symptoms that may indicate liver injury, including...

PATIENT PACKAGE INSERT

“What are the possible side effects of Vytorin?”...

Your doctor should do blood tests to check your liver before you start taking Vytorin and if you have any....

Zocor (simvastatin) tablets

WARNINGS AND PRECAUTIONS

Myopathy/Rhabdomyolysis

- Zocor therapy should be discontinued if markedly ...
- Amiodarone added to TABLE 1

Liver Dysfunction

- There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients...

Endocrine Function

- Increases in HbA1c and fasting serum glucose levels have been reported ...

ADVERSE REACTIONS

Post-Marketing Experience

- fatal and non-fatal hepatic failure.....added
- There have been rare postmarketing reports of cognitive impairment....

PATIENT COUNSELING INFORMATION

Liver Enzymes

All patients treated with ZOCOR should be advised to report promptly any symptoms that may indicate liver injury...

Accupril (quinapril hydrochloride) Tablets

PRECAUTIONS

Drug Interactions

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase – 2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised...

Accuretic (quinapril HCl/hydrochlorothiazide)

PRECAUTIONS

Drug Interactions

Other Agents

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase – 2 Inhibitors (COX-2 Inhibitors): In patients who...

Azor (amlodipine and olmesartan medoxomil) Tablets

DRUG INTERACTIONS

Drug interactions with Amlodipine

added:

- Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily

Dexilant (dexlansoprazole) delayed-release capsules

DRUG INTERACTIONS**Clopidogrel**

- section added

also see:

CLINICAL PHARMACOLOGY**Pharmacokinetics**

Clopidogrel...

Exforge (amlodipine/valsartan) Tablets**DRUG INTERACTIONS****Drug/Drug interactions**

Studies with Amlodipine added:

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) tablets**DRUG INTERACTIONS****Drug/Drug interactions**

Studies with Amlodipine added:

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Intelence (etravirine) tablets**DRUG INTERACTIONS**

- table 3 modified

PATIENT PACKAGE INSERT

“Tell your doctor if you take other HIV medicines” section buprenorphine and buprenorphine/naloxone drug interaction.

Ixempra kit (ixabepilone) for injection**USE IN SPECIFIC POPULATIONS****Pediatric Use**

entire section updated; see PI

Leukeran (chlorambucil) Tablet**PRECAUTIONS****Use in Patients with Hepatic Impairment**

section added

Lotrel (amlodipine besylate and benazepril hydrochloride) Capsules**DRUG INTERACTIONS****Drug/Drug interactions**

- added: Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Macugen (pegaptanib sodium injection)**USE IN SPECIFIC POPULATIONS****Pregnancy**

- section revised

Pediatric Use

section revised

Norvasc (amlodipine besylate) tablets**DRUG INTERACTIONS****Simvastatin**

added..... Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Prevacid (lansoprazole) Delayed-Release Capsules and Prevacid Solutab (lansoprazole) Delayed-Release Orally Disintegrating Tablets**DRUG INTERACTIONS****Clopidogrel**

- Concomitant administration of lansoprazole and clopidogrel in healthy subjects had no clinically important effect...

also see:

CLINICAL PHARMACOLOGY**Pharmacokinetics**

Clopidogrel...

Protonix (pantoprazole sodium)**ADVERSE REACTIONS****Postmarketing Experience:**

- weight changes, hyponatremia, asthenia, fatigue and malaise, insomnia and somnolence

DRUG INTERACTIONS**Clopidogrel**

- co-administration of clopidogrel with pantoprazole reduces the pharmacological activity of clopidogrel

also see:

Pharmacokinetics: information about the drug-drug interaction between pantoprazole and clopidogrel.

Tekturna (aliskiren) and Tekturna HCT (aliskiren/hydrochlorothiazide) Tablets**USE IN SPECIAL POPULATIONS****Geriatric Use**

Of the total number of patients receiving aliskiren in clinical studies, 1,275 (19%)..... Blood pressure response and adverse effects were generally similar to those in younger patients.

Prezista (darunavir) tablet**ADVERSE REACTIONS****Clinical Trials Experience: Treatment-Naïve Adults**

Study TMC114-C211

- The safety assessment...

PATIENT PACKAGE INSERT**“What are the possible side effects of PREZISTA?”**

- ...rash when PREZISTA is taken in combination with raltegravir.

Reyataz (atazanavir sulfate)**ADVERSE REACTIONS****Clinical Trial Experience in Pediatric Patients**

- added safety data up to 96 weeks

also see:

CLINICAL PHARMACOLOGY**Pharmacokinetics, Pediatrics subsection****CLINICAL STUDIES****Pediatric Patients subsection****Saphris (asenapine) Sublingual Tablets****ADVERSE REACTIONS****Clinical Studies Experience**

- Other Findings: Oral hypoesthesia and/or oral paraesthesia may occur directly after administration of asenapine and usually resolves within 1 hour.

USE IN SPECIAL POPULATIONS**Geriatric Use**

In elderly patients with psychosis, asenapine exposure (AUC) was on average 40% higher compared to younger adult patients [see Clinical Pharmacology (12.3)].

Sprycel (dasatinib) tablets**ADVERSE REACTIONS****Postmarketing Experience**

- pulmonary arterial hypertension

Symbyax (olanzapine and fluoxetine HCl)**ADVERSE REACTIONS****Additional Findings Observed in Clinical Studies****Sexual Dysfunction**

There are no adequate and well-controlled studies examining sexual dysfunction with Symbyax or fluoxetine treatment. Symptoms of sexual dysfunction occasionally persist after discontinuation of fluoxetine treatment...

Humalog

Humalog (insulin lispro injection)

Humalog Mix 75/25 (75% insulin lispro protamine suspension/25% insulin lispro injection [rDNA origin])

Humalog Mix 50/50 (50% insulin lispro protamine suspension/50% insulin lispro injection [rDNA origin])

PATIENT PACKAGE INSERT**[Instructions for Use Leaflet, or Users Manual]**

added.....warning against the sharing of insulin pens and needles

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