The U.S. Food and Drug Administration (FDA) issues drug alerts and drug safety communications to help patients and practitioners stay abreast of rapidly changing medical knowledge. These communications may or may not have serious consequences as to how patients, caretakers, and prescribers respond. However, these alerts are important to increase safety awareness and initiate a dialogue between patients and providers.

Typically, drugs are FDA approved based on relatively short-term trials that are not designed to evaluate safety endpoints. Furthermore, for some drugs, assessing a postmarketing safety signal can be challenging due to lack of robust evidence, leaving a potentially harmful drug on the market. Over the past 9 years, the FDA has taken a more proactive approach to the reporting of potential adverse effects, readily disseminating preliminary information regarding drug safety issues as the information becomes available. With this increased transparency, however, it is important to place these safety alerts in context and to consider them not as conclusive mandates. This article will review some of the more relevant FDA drug safety alerts and ongoing safety concerns of 2015.

2015 New Drug Safety Alerts Resulting In Drug Labeling Changes

In May 2015, the FDA warned that the sodium-glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin and empagliflozin) used in the treatment of type 2 diabetes (T2D), may cause ketoacidosis requiring hospitalization.1 The concern originated from 20 reported cases of reported diabetic ketoacidosis (DKA), ketoacidosis, or ketosis that resulted in emergency room or hospital visits. SGLT2 inhibition causes a rapid increase in urinary glucose excretion including losses from daily carbohydrate availability.5 This results in an increased use of fat oxidation for energy production and eventually ketosis. Unlike the more typical presentation of DKA, many of these were accompanied by only mild to moderately elevated blood sugar levels (euglycemic DKA). The European Medicines Agency (EMA) further corroborated this risk.2

After a further safety review, the FDA added a warning to the label about the risks of ketoacidosis and of serious urinary tract infections.3 From March 2013 to May 2015, 73 cases of ketoacidosis were reported in the FDA Adverse Event Reporting System (FAERS) database with the use of the SGLT2 inhibitors. In all of these cases, patients were hospitalized or treated in the emergency room. The median time from drug initiation or dose change to symptoms was 43 days. Although these agents are currently only approved for T2D, fifteen cases were reported in patients with type 1 diabetes (T1D). The FDA also warned about serious urinary tract infections or urosepsis resulting in hospitalization that was reported in 19 cases from March 2013 through October 2014.3

Overall, the absolute risk of DKA in T2D associated with the use of SGLT2 inhibitors is relatively low.4 However, patients and practitioners should be aware of the risk as well as patient specific risk factors. The cause of ketoacidosis is usually multifactorial and potential contributing factors are concurrent illness, reduced food and fluid intake, reduced insulin doses, discontinuation of an oral insulin secretagogue, T1D or patients with long-standing T2D with marked B-cell insufficiency, and history of alcohol intake.4 In addition, because of the lack of accompanying severe hyperglycemia, euglycemic DKA can easily go unrecognized by patients and providers.5 Any patients with diabetes who experiences nausea, vomiting, shortness of breath or malaise on a SGLT2 inhibitor should be evaluated for ketosis, despite a normal glucose level. All patients taking SGLT2 inhibitors should be advised to check their ketone levels whenever they feel unwell, regardless of their glucose level. If ketones are detected, patients should be directed to seek immediate medical care, as it can be difficult to reverse at home. There are currently ongoing, long-term randomized controlled trials evaluating the use of SGLT2 inhibitors in T1D and insulin-treated T2D to help quantify the risk in these populations. Furthermore, in September 2015, the FDA also released a safety communication strengthening the warning for the SGLT2 inhibitor canagliflozin and the increased risk of bone fractures and decreased bone mineral density.7 SGLT2 inhibitors increase concentrations of phosphate through increased tubular reabsorption, which can adversely affect the bone.8 Confirmatory data from nine pooled clinical trials resulted in incidence rates of bone fractures of 1.4 and 1.5 per 100 patient-years of exposure for canagliflozin 100 mg and 300 mg, respectively. This is compared to a rate of 1.1 per 100 patient-years seen in the comparator group including placebo and active comparators. Fractures occurred as early as 12 weeks after initiation of therapy and were more likely to be from low trauma and affect the upper extremities. The FDA is continuing to assess the risk of fractures with the other SGLT2 inhibitors, including dapagliflozin and empagliflozin to determine if this is a class effect. The FDA also added new information about decreased bone mineral density at the hip and lower spine based on data from a postmarketing double blind placebo controlled trial in elderly patients with T2D (n=714).9

The FDA added a new Warning and Precaution that the dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin and alogliptin) may cause joint pain that can be severe and disabling.9 Cases have been reported in two similar locations as well as the FAERS database that have started anywhere from 1 day to years after starting a DPP-4 inhibitor.9,10,11 Symptoms resolve after discontinuation of the medication.

NSAIDs have been pivotal drugs for the treatment of pain management and are available by prescription and over the counter. However, ever since rofecoxib was withdrawn from the market in 2004, the cardiovascular (CV) safety of the class has been uncertain.12 After a recent review of the current safety data, the FDA opted to strengthen the label warning that non-aspirin NSAIDs do in fact increase the chance of a heart attack and stroke.13 A review of a meta-analysis of RCTs14 and observational trials were reviewed by the FDA Advisory Committee in 2014.15 Based on this review, the following conclusions were made: 1) A multitude of studies support the finding that NSAIDs can cause serious CV thrombotic events (relative risk [RR] 10% - 50%) and this risk is also evident in healthy individuals; 2) It appears there could be a significant risk within days to weeks of initiation and there may be a higher risk with longer NSAID use; 3) Some observational data suggests that naproxen may have a lower CV risk compared to other NSAIDs. However, this is based on limited data from studies not designed to compare the safety of one NSAID to another. The ongoing randomized safety trial comparing CV events with celecoxib, naproxen and ibuprofen among high CV risk patients16 will help determine if there are differences between individual agents; and 4) There is an approximately two-fold increase in hospitalizations due to heart failure with use of both COX-2 selective and nonselective NSAIDs.

Other notable FDA warnings that resulted in label changes include the safety caution of possible increased risk of heart attack and stroke with use of testosterone products.17 Further definitive high quality studies are needed to confirm this risk as the current data is conflicting and has many limitations.18 There were also two new concerns regarding treatments for hepatitis C. In March, the FDA warned of an increased risk of symptomatic bradycardia when sofosbuvir, with or without another direct acting antiviral, is used in combination with amiodarone.19 In October 2015, the FDA released a drug safety communication warning that hepatitis C treatments ombitasvir, paritaprevir and ritonavir +/- dasabuvir (Viekira Pak® and Technivie®) can cause serious liver injury, mostly in patients with underlying advanced liver disease.20 As a result, drug labeling was updated to include this risk. Lastly, the FDA made changes to the varenicline drug label warning that the prescription smoking cessation medication may react with alcohol, resulting in decreased tolerance or aggressive behavior. Rate reports of seizures were also reported.21 None of the cases involved excessive amounts of alcohol.

2015 in Review: Relevant Safety Updates and Ongoing Safety Concerns

By Megan Heinrik, Pharm.D, BCPS, Oregon State University College of Pharmacy, Drug Use Research and Management

The U.S. Food and Drug Administration (FDA) issues drug alerts and drug safety communications to help patients and practitioners stay abreast of rapidly changing medical knowledge. These communications may or may not have serious consequences as to how patients, caretakers, and prescribers respond. However, these alerts are important to increase safety awareness and initiate a dialogue between patients and providers.

Typically, drugs are FDA approved based on relatively short-term trials that are not designed to evaluate safety endpoints. Furthermore, for some drugs, assessing a postmarketing safety signal can be challenging due to lack of robust evidence, leaving a potentially harmful drug on the market. Over the past 9 years, the FDA has taken a more proactive approach to the reporting of potential adverse effects, readily disseminating preliminary information regarding drug safety issues as the information becomes available. With this increased transparency, however, it is important to place these safety alerts in context and to consider them not as conclusive mandates. This article will review some of the more relevant FDA drug safety alerts and ongoing safety concerns of 2015.
2015 Ongoing Safety Investigations

Tramadol and codeine in children

The FDA is investigating the use of tramadol and codeine cough and cold medicines in children <18 y/o because of the risk of respiratory depression in children.19,20 Although tramadol is not FDA-approved for use in children, it can be used off-label in this population. The FDA warns of a concern with both agents post-operatively after tonsillectomy and/or adenoidectomy. The risk with tramadol is thought to be increased as a result of some children being ultra-rapid metabolizers and subsequently having higher levels of the active form of the opioid than usual. Codeine is converted to morphine and tramadol to its active form (O-desmethyltramadol) in the liver by the cytochrome P450 CYP2D6 enzyme. Higher levels of the active opioid can lead to respiratory depression and possibly death. Fifteen deaths or overdoses of children who received standard doses of codeine have been reported in the U.S; all of which were found to have very elevated levels of morphine in their blood.23,24 Since routine genotype testing is not recommended to assess for ultra-rapid metabolizers, tramadol and codeine should be avoided in children (particularly those under 12 years of age) and only used if the benefits clearly outweigh the risks.

Rosiglitazone

After continued monitoring of rosiglitazone for the treatment of T2D, the FDA has eliminated the Risk Evaluation and Mitigation Strategy (REMS) which put prescribing restrictions in place due to the suggested increased risk of myocardial infarction (MI) with rosiglitazone.25 In 2013, the FDA determined that the rejudicated results from the RECORD trial did not show an increased risk of MI with rosiglitazone compared to metformin and sulfonylureas.26 Since 2013, no new pertinent safety information was identified and as a result, the FDA has deemed the REMS is no longer necessary.

Risk of cancer or death from cancer with clopidogrel

In 2014, results from the Dual Antiplatelet (DAPT) trial suggested a reduction in cardiovascular and cerebrovascular events, but also a possible increased risk of cancer or death from cancer from the long-term use (30 months) of clopidogrel following placement of a drug-eluting stent compared to 12 months.27 The increased risk of death was seen in patients given clopidogrel, but not those given prasugrel. However, in November 2015, the FDA determined that the long-term use of clopidogrel does not increase the overall risk of death in patients with high CV risk.28 A meta-analysis of other long term clinical trials did not result in a change in the overall risk of death with long-term DAPT (12 months or longer) with clopidogrel and aspirin compared to short-term (6 months or less) or aspirin alone (6.7% vs. 6.6%; respectively). There was also no apparent increase in the risk of cancer-related adverse events (4.2% vs. 4.0%) or cancer-related deaths (0.9% vs. 1.1%) with long term DAPT compared to short term DAPT, respectively. The American College of Cardiology/American Heart Association currently recommends DAPT for at least 12 months after drug eluting stent implantation.

References

12. Trelle S, Reinchenbach S, Wandel S, Hildebrand P. Cardiovascular safety of non-stero<ref