ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

May 6, 2015 — Data from 2014 Quarter 2

NEW SAFETY PERSPECTIVES

Zolpidem (AMBIEN) safety profile shows widespread unsafe use
Adverse event signals for canagliflozin (INVOKANA), a new diabetes medication
20,632 incomplete rosiglitazone (AVANDIA) reports of heart attack and stroke

Executive Summary

In this issue, we examine why unsafe use of zolpidem (AMBIEN), a largely generic drug taken by more than 5 million people as a sleep aid, accounts for more emergency department visits for adverse effects than any other psychoactive drug. Also, early signals for a new kind of diabetes drug, canagliflozin (INVOKANA) raise questions about whether enough is known about this agent to be assured that its benefits outweigh its risks. Finally, a flood of low-quality manufacturer reports for another diabetes drug—rosiglitazone (AVANDIA)—provide a notable example of why the U.S. Food and Drug Administration (FDA) needs to modernize its essential postmarket surveillance reporting program.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors adverse drug events reported to the FDA. We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS) that are released for public research use. These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of therapeutic drugs after FDA marketing approval.

This issue of QuarterWatch analyses the latest FDA release of FAERS data–covering 2014 Q2. In this three-month period the agency received a total of 221,958 case reports of adverse drug events from all sources. Of this total we selected for our primary analysis 75,643 new domestic reports of fatal, disabling or serious injuries in which a marketed drug was a primary suspect. Totals included 7,071 patient deaths, 1,596 reports indicating sustained harm or disability, and 16,717 cases severe enough to require hospitalization. This group of reports identified 960 different drugs with a median of 7 cases per drug, but with some drugs accounting for hundreds of cases. Our primary analysis excludes foreign reports, injuries not classified as serious, and cases identified as originating in legal claims.

Zolpidem (AMBIEN) and Unsafe Use

The sleep medication zolpidem is notable for both its wide exposure and unequalled number of emergency department visits for adverse drug effects. We estimate approximately 5 million people are taking zolpidem, mostly as a low-cost generic, but also in brand name forms of AMBIEN, AMBIEN CR, INTERMEZZO, EDLUAR, and ZOLPIMIST. When the Centers for Disease Control and Prevention (CDC) surveyed what psychiatric medications were most frequently identified as the reason for emergency department visits, zolpidem ranked first with an estimated 10,212 annual visits, 25% of which required hospital admission. In addition, over the 12 months ending with 2014 Q2 we identified 1,030 serious adverse

event cases in which zolpidem was the primary or secondary suspect drug. The key problem, QuarterWatch concluded, is a broad pattern of unsafe use that was not in accord with FDA and manufacturer recommendations.

We conducted an analysis of zolpidem use using one of the most detailed profiles of therapeutic drug exposure in the United States–a major survey of the federal Agency for Healthcare Research and Quality (AHRQ) called the Medical Expenditure Panel Survey (MEPS). Our analysis showed most zolpidem use was not in accord with safety recommendations. Zolpidem is recommended for short-term use, based on pivotal efficacy trials of 21-37 days. We found 68% of zolpidem patients were sustained users, with 3 or more prescriptions/refills and a mean of 229 days supply. The prescribing information warns against concomitant use of other drugs (or alcohol) that can depress the central nervous system (CNS). The survey data showed that 22% of sustained zolpidem users were also sustained users of opioids. In 2013 the FDA recommended that women and the elderly use the lower dose, 5 mg of the generic or 6.25 mg of the extended release version. In 2012, only 5% of women and 10% of the elderly were dispensed the lower dose—although by 2014 a modest improvement had occurred. Another safety concern is concomitant use of other drugs active on the same neuroreceptors targeted by zolpidem (such as benzodiazepine sedative/anxiolytics and some anticonvulsants). We found that 23% of sustained use zolpidem patients were also in sustained use of another drug targeting the same receptors.

Unanswered Questions about Canagliflozin (INVOKANA)

In March of 2013, the FDA approved the first drug in a new class of oral agents to lower blood sugar in patients with Type 2 diabetes. It was called canagliflozin (INVOKANA) and its mechanism of action was to inhibit a normal function of the kidney, which is to return any glucose to the blood circulation while excreting other undesirable substances. Instead, canagliflozin causes substantial amounts of sugar to be excreted in the urine. In the first year of adverse event data, we saw reports indicating serious injuries involving kidney function, and reports of serious hypersensitivity reactions. Most could have been reasonably anticipated, given the mechanism of action and pre-approval clinical trial data.

In the first year after approval, canagliflozin was launched with considerable success, reaching 426,859 outpatient prescriptions in 2014 Q2, according to data from IMS Health. In the same period we identified 457 serious adverse event reports, including 5 different adverse effects directly or indirectly related to the renal toxicity of canagliflozin. This included kidney failure or impairment (n = 54), dehydration and fluid imbalances (n = 54), kidney stones (n = 11), urinary tract infections (n = 50), and abnormal or other weight loss (n = 52). A single case could involve more than one of these event groups. In addition, we identified 50 reported cases of serious hypersensitivity of two different types. Some involved angioedema, a rapid swelling of the tongue, lips, face, or throat. Others involved skin rashes, urticaria, and in 2 reported cases, skin exfoliation. If not excessive, the typical weight loss of 5-6 lbs. in clinical trials could be seen as a benefit in a largely overweight patient population.

We shared our results with Janssen Pharmaceuticals, which is licensed to market canagliflozin in the United States. The company said that the prescribing information for the drug already contained warnings or other alerts about these adverse effects, with the exception of kidney stones, about which the company said available information was insufficient to assess a causal role.

The unanswered question about canagliflozin—shared in part by other diabetes medications—is whether it has clinical benefits, and whether those benefits outweigh its risks. The clinical benefits of a Type 2 diabetes drug would be a reduction in the risk of macrovascular events (e.g., reduced numbers of heart attacks and strokes), or fewer microvascular complications (e.g., a lower risk of impaired vision, or kidney or peripheral nerve damage). At the time of FDA approval, canagliflozin had not been tested in a sufficient number of patients for a long enough period of time to answer that question. In the face of that uncertainty about benefit was increasing evidence that canagliflozin is associated with adverse effects in appropriate clinical use. In clinical trials, the most frequent measured adverse effect was urogenital infections—primarily fungal infections—in both women and men. The rates were high: 14% of women and 3.9% of men with near-

normal kidney function developed fungal infections at rates 4-6 times higher than comparator group patients. In addition, treatment reduced kidney estimated glomerular filtration rates (eGFR) by small amounts over the short term, with unknown effects over longer treatment periods. Higher dose animal studies in rats with uncertain applicability to human exposure showed long-term kidney damage, kidney and testicular cancers, and bone abnormalities.

Adverse Event Reporting System

20,632 Incomplete Rosiglitazone (AVANDIA) Reports

One of the goals of QuarterWatch is to review and help improve FAERS–the primary system through which the safety of marketed drugs is monitored. The last issue of this publication was devoted to an examination of the growing defects in the current reporting system and the steps needed to modernize and update it. Among the major problems are outdated regulations and guidances, flawed inspection and enforcement programs, and the low quality of reports from many drug manufacturers. All of these problems are illustrated in a single episode in 2014 Q2 when GlaxoSmithKline (GSK) submitted 20,632 incomplete adverse event reports for the diabetes drug rosiglitazone (AVANDIA), 99% during April 2014.

When a typical drug that QuarterWatch monitors accounts for a median of 7 reports, and 160 reports in a calendar quarter places it in the upper 5% of all drugs, discovering more than 20,000 cases for rosiglitazone immediately attracted our attention. The rosiglitazone adverse drug events described were primarily myocardial infarction (n = 12,159) and stroke (n = 5,169). The report quality was among the poorest ever seen for a large group of reports. The elementary essentials of patient age, gender, and event date were missing in 100% of these case reports, which also had other deficiencies.

We analyzed the data and sought additional information from both the manufacturer submitting the reports and the FDA. GSK told us that the case reports were from a legal settlement in federal district court in 2012. Published reports indicate that the company paid more than $2 billion to an estimated 40,000 patients who alleged rosiglitazone caused heart attacks, strokes, and other cardiovascular problems. Two years later the company discovered the 20,632 cases—originally supplied by lawyers for the patients—and said this was all the information that was available. However, it was the FDA's decision to insist that the company file a separate adverse event report for each individual patient, even though the immediately available information was of minimal safety value. The company told us the reports were being updated with additional information, beginning in the second half of 2014.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The FAERS data combine reports originated by drug manufacturers with cases submitted directly by consumers and health professionals through the agency's MedWatch program. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

The analysis of the sedative-hypnotic zolpidem illustrates a different dimension of drug safety. Apart from the question of whether a medication might cause adverse effects is whether the pattern of clinical use is consistent with minimizing its known risks. Our findings that most zolpidem use does not follow safety

recommendations should be a concern. It illustrates that to minimize harms from drug treatment requires not only accurate information about adverse effects, but also adherence to recommended prescribing practices.

Even though canagliflozin was given to more than 10,000 patients in clinical trials prior to FDA approval, it remains unclear whether the adverse effects seen in many patients are outweighed by clinical benefits—which have yet to be measured.

As detailed further in this report, the history of diabetes drugs shows that most agents that lowered blood sugar did not demonstrate long-term benefits against clinical endpoints, and some have caused increased harm. Now comes another new drug with a new mechanism of action gaining rapid acceptance in clinical practice despite important unanswered questions about both risks *and* benefits.

The example of the incomplete reporting of rosiglitazone cases provides additional evidence as to why the FDA needs to modernize its adverse drug event reporting system and requirements. The reporting regulations and guidelines predate the age of digital marketing by manufacturers that involve many forms of contact with consumers and health professionals. The FDA has compounded the problem with compliance and inspectional actions that require reporting incomplete data about patient health problems without determining whether the drug was suspected of causing them. The modern digital age in which manufacturers know more and more about their patients ought to produce richer and better safety data from a broad population often excluded from clinical trials. Instead, the agency receives increasing numbers of incomplete reports of little or no value in assessing possible drug harms.

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Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to the Food and Drug Administration (FDA) by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source. [1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site. (http://www.ismp.org/QuarterWatch/detailedMethods.aspx)

The severity of the adverse event was classified as serious if the case indicated an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening or had other medically serious consequences. Cases without these outcomes were classified as not serious.

In these data, the adverse events that occur are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[2] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[3] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 26 categories. The QuarterWatch database was updated in November 2014 to MedDRA version 17.1.

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by IMS Health Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

"The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2014 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities."

In this issue, we utilize a new data source to provide a broader perspective on how drugs are used in medical practice, the Medical Expenditure Panel Survey (MEPS).[4] It is provided for research use by the Agency for Healthcare Research and Quality on an annual basis. This survey provides results from a large national survey of families and individuals and includes extensive self-reported data on the health status of the individuals, medical treatment, insurance, and prescribed medications. The most recent survey used for this issue was for 2012, and included data on a weighted sample of 38,974 individuals and 324,744 reported prescriptions. [5]

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology. When cited in the text, tables or charts, the brand name of a drug used is the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or formulation type (e.g., extended, immediate release).

Results

In the 2nd quarter of 2014, the FDA received 75,643 domestic reports with fatal, disabling or other serious outcomes, a 6.6% decrease from the previous quarter and a 48% increase from the 2nd quarter in 2013. The quarter's overall totals were heavily influenced by an unusual episode, the submission by GlaxoSmithKline (GSK) of 20,632 low-quality reports for rosiglitazone (AVANDIA) representing legal claims the company paid for myocardial infarction, stroke and other cardiovascular events resulting from a 2012 settlement in federal court. These are discussed separately in this report. If these GSK reports are excluded, the FDA received 55,020 new case reports, a 32% decline from the previous quarter, but a 7.6% increase from the same quarter one year earlier.

Quarterly report totals fluctuate because the agency allows drug manufacturers to submit periodic reports of serious adverse drug events annually instead of every quarter when the drug has been on the market at least three years. Reports sent directly to the FDA rather than through manufacturers totaled 5,663 cases, and were little changed from the previous 12 quarters.

Zolpidem (AMBIEN) and Unsafe Use

The Centers for Disease Control and Prevention (CDC) estimates that 50-70 million U.S. adults have chronic sleep disorders, and one CDC survey showed that 11% of adults said they were not getting enough sleep for every single night in the past month.[6] One of the most widely used pharmaceutical solutions to many sleep disorders is zolpidem, a sedative/hypnotic approved in 1992 under the brand name Ambien.* With 40 million dispensed outpatient prescriptions in 2013—98% generics according to IMS Health–zolpidem was the second most frequently dispensed psychoactive drug, surpassed only by alprazolam, a benzodiazepine, sedative, and anxiolytic. The Drug Enforcement Administration classifies zolpidem and alprazolam as Schedule IV controlled substances.

Safety Concerns Arise

In 2014, the CDC reported a survey of emergency department (ED) visits for adverse drug events resulting from use of all psychiatric medications taken by an estimated 26.8 million adults.[6] The investigators said they were surprised to discover that zolpidem ranked first in adverse drug event cases, accounting for 11.5% of all ED visits among all adults, and 21% in patients 65 years or older. The study estimated that zolpidem accounted for 10,212 annual ED visits, substantially more than the 2nd ranked drug, the antipsychotic quetiapine (SEROQUEL), with 6,900 ED visits.

Limited Benefits

The limited efficacy of zolpidem can be seen in a pivotal trial in non-elderly adults submitted for FDA approval of the sustained released form (AMBIEN CR), with a 12.5 mg strength instead 10 mg.[7] This dosage form was designed to combine a rapid initial uptake similar to the immediate-release version, but extended plasma concentrations beyond the 3 hours seen with the immediate release formulation.[8] The primary endpoint was the reduction in awake time over eight hours measured by polysomnography in a sleep laboratory.

While zolpidem reduced mean awake time by 20 minutes compared to placebo on nights 1 and 2 of treatment, by days 15-16 efficacy was lost. After two weeks, the awake time difference from placebo was reduced to less than 3 minutes, a difference that was not statistically significant. The FDA nevertheless

* Zolpidem is currently marketed under the brand names Ambien CR, Edluar, Intermezzo, and Zolpimist.

accepted this as evidence of efficacy when a post hoc analysis showed that if the measurement period for sleep was reduced from 8 hours to 6 hours, it yielded a reduction in awake time of 16 minutes compared to placebo. In patient assessments of the refreshing quality of sleep and subjective total sleep time, no statistically significant difference could be seen between placebo and drug treatment after two weeks of continuous use. The results were similar in a second pivotal trial of 6.25 mg in elderly patients.

Also notable was the placebo effect. In the non-elderly adult trial, awake time in the placebo group was reduced by a mean of 18 minutes for nights 1-2, and increased to 20 minutes on nights 15 and 16. The trials were also conducted in a highly selected patient population. Investigators excluded 333/545 patients (61%) including heavy coffee drinkers, the overweight, and patients with concomitant use of any psychotropic drug. [8] In addition, the duration of trials for approval was short--just 21 days of treatment for the extended release formulation and 37 days for the original immediate-release version. As much as safety concerns, it appears that the declining effects of zolpidem–and short trial durations–account for the recommendation that the drug is indicated only for short-term use.

Does Clinical Use Follow Safety Recommendations?

To determine whether current clinical use of zolpidem was consistent with safe use recommendations from the FDA and product prescribing information, we used an annual health care survey from 2012 from the Agency for Healthcare Research and Quality.(See Methods Summary) [4] Our independent analysis of the MEPS survey shows that a substantial majority of clinical use of zolpidem involves multiple safety concerns.

Extensive Population Exposure

The MEPS data illustrate the wide extent of exposure of the U.S. population, with 25.3 million self-reported prescriptions in 2012 for 5 million adults. Women were more likely than men to report taking zolpidem, accounting for 59.4% of exposed persons, compared to 40.6% for males. Usage was also heavier in the elderly, who accounted for 12% of the population but 32% of zolpidem clinical use.

In addition to taking zolpidem, two thirds of patients were also prescribed at least one other drug acting on the central nervous system (CNS), or used for psychotherapeutic purposes.

These were the key safety concerns:

- **Long-term rather than short-term use**. Overall 68% of zolpidem patients met the criteria for sustained use, which we defined as 3 or more prescriptions/refills or more than 60 days supply. The sustained use group obtained a mean of 228 days supply.

- **Little use of lower dose.** The FDA now recommends the 5 mg (or 6.25 mg, extended release) lower dose of zolpidem for women and the elderly.[9] In 2012 only 5% of women and 10% of persons 65 years or older were dispensed the lower dose.

- **Also using other CNS depressants**. The prescribing information for zolpidem warns against also taking other CNS depressants such as opioids because of additive effects and greater risk to next-day alertness.[10] We found 22.3% of zolpidem patients with sustained use were also taking opioids on a sustained-use basis.

- **Other drugs active on GABA receptors**. Both benzodiazepine sedatives and anticonvulsants pregabalin and gabapentin target the same GABA (gamma-aminobutyric acid) neuroreceptors, with complex effects. Overall 23% of sustained users of zolpidem were also sustained users of another drug active on GABA receptors.

- **Depression and suicide risk**. The prescribing information warns of the possibility of worsening depression and suicidal thoughts and actions among patients with depression. Among sustained-use zolpidem patients, 34% were also taking an antidepressant on a sustained basis. Insomnia is not

only common in depression, it is also one of the most frequent side effects of antidepressant drugs, occurring in 5% to 16% of patients. [11]

These data provided no information about three other safety concerns. They do not address illicit or other inappropriate use. A zolpidem study in Taiwan reported evidence of "doctor shopping" among 24% of zolpidem patients—meaning patients were obtaining prescriptions from two different doctors with overlapping treatment periods.[12] No estimates were possible to measure the extent to which patients followed the recommendation to abstain from alcohol because of its additive depressant effect on the CNS. Nor was it possible to ascertain whether the zolpidem was being taken at least 8 hours prior to next-day activities requiring full mental alertness.

Limitations of Usage Profile

The statistics above are subject to sampling variability and were gathered during a single year, 2012. The definition of sustained use (for more than 60 days) makes it likely that different psychoactive drugs were used at the same time. However, the study design was not capable of affirming true concomitant use. These self-reported prescriptions may be an underestimate. Total prescriptions identified in the survey self reports totaled 25 million in 2012, compared to 34 million in the IMS Health data for all dispensed outpatient prescriptions.

Trends Toward Lower Dose

The FDA's safety recommendation for lowering the initial dose for women to 5 mg was published in May 2013—after the survey period.[9] A different and more recent information source, IMS Health data, showed that 29% of dispensed zolpidem prescriptions were for the lower dose in the 2nd quarter of 2014. However, the lower strength dispensed did not necessarily indicate that a single tablet was taken each night. The manufacturer of brand name Ambien, sanofi-aventis, opposed the lower dose recommendation, saying it would be ineffective.[13]

Adverse Event Profile

Observing the pattern of sustained use of multiple psychoactive medications, we selected all domestic, serious cases in which zolpidem was either the primary or secondary suspect drug. For the 12 months ending with the 2nd quarter of 2014, we identified 1,030 reported serious adverse drug events. Zolpidem was the primary suspect in 547 cases and secondary suspect in 483 cases.

Frequently reported adverse events included suicidal and self-injurious behavior (n = 159), sleep activities such as driving, walking, eating, or having sex[*] (n = 62), amnesia (n = 40), hallucination (n = 31), memory impairment (n = 25), fall (n = 35), road traffic accidents (n = 32), impaired driving ability (n = 18). A single case report could contain one or more of these event terms.

The multiple drug use reported above was also seen in the serious adverse events reported. The patients were taking a median of 4 different drugs and 25% of patients were taking 6 or more drugs. The other primary suspect drugs taken with zolpidem were similar to those raising safety concerns above: opioids, including hydrocodone, morphine, tramadol, oxycodone and fentanyl; benzodiazepines, alprazolam, diazepam and clonazepam; and antidepressants, paroxetine, trazodone and citalopram.

An unusual published medical journal report described two homicides,[14] and was included multiple times in the adverse event data because of duplicate reporting by generic drug manufacturers. In the two homicides a 45-year-old man and a 62-year old woman violently killed their spouses. The male stabbed his

[*] The specific sleep activities are described in the Medication Guide for patients but identified as "somnambulism" in the case report excerpts.

wife more than 20 times; the female hit her wheelchair-bound husband repeatedly with a metal pipe and put a plastic bag over his head. Neither had a previous history of violence. The 45-year-old male had no memory of the incident and the 62-year-old female reported only dream-like fragments and was discovered in a bathtub 24 hours later holding a knife to her own throat. On the night of the homicides, both took 2 or 3 10mg tablets of zolpidem and also had also been taking other psychoactive medications, notably paroxetine. Both were convicted and sent to prison.

Limitations of Adverse Event Reports

The cases cited above provide a useful perspective on the kinds of serious adverse events being currently reported for zolpidem. However, as QuarterWatch has previously noted, adverse event reporting for generic drugs is weak and of limited quality. In addition, duplicate reporting of cases in the scientific literature is common.[15] These cases confirm and extend the evidence of adverse effects already included in the prescribing information. However, these data typically do not provide useful information about how frequently such events may occur.

Conclusions

The safety profile of zolpidem today illustrates major shortcomings in the system intended to ensure the safe use of therapeutic drugs. The pivotal clinical trials for approval of zolpidem were notably short (21 to 37 days), illustrated benefits that decayed with time, and excluded patients taking any other psychoactive drug, or with a mental illness. The pattern of actual use, as measured here, is markedly different from the conditions under which the drug was tested. A majority of patients take zolpidem in sustained use and many have other psychoactive medications. Because it is a generic drug, postmarket surveillance is limited. The FDA has taken a substantial interest in increasing the safe use of zolpidem, but measures to date have been of limited effect. A drug that may have an acceptable safety profile for occasional short-term use still accounts for more ED visits than any other psychoactive drug, largely because of unsafe use.

Signals for Canagliflozin (INVOKANA)

Treatment of diabetes ranks among the most prevalent drug therapies in the United States, with 21 million adults taking blood sugar lowering drugs in 2012, including 21% of all adults age 65 and older and 12% of adults 45-64.* More than 90% of those treated for diabetes have Type 2, and frequently are overweight. Oral hypoglycemic drugs are also notable for the paucity of scientific evidence of a direct clinical benefit. Four recent trials[16] failed to demonstrate that intensive treatment of Type 2 diabetes reduced the risk of macrovascular complications– heart attack and stroke–and other studies showed some agents might increase the risk.[17] [18] The primary evidence that intensive treatment prevented long-term injury to the eye, kidney and peripheral nerves—microvascular complications–is derived from a single clinical trial in Type 1 diabetes using insulin.[19]

Type 2 diabetes is diagnosed and treated on the basis of high levels of glycosaturated hemoglobin (HbA1c), and a reduction is usually the primary benefit measured in clinical trials. A common-sense criterion for diabetes drugs is that they should reflect inherently low risks since it takes years for either progression of the disease or possible but yet-unproven benefits of treatment to be manifest.

Canagliflozin (INVOKANA), marketed in the U.S. by Janssen Pharmaceuticals, was first in a new class of oral diabetes agent which the FDA approved for this patient population in 2013. [20] The drug blocks a key transport protein in the kidney filtration process—sodium glucose cotransporter-2 (SGLT2)–thereby causing some of the circulating blood glucose to be excreted in the urine rather than returned to blood

* Calculated from the Medical Expenditure Panel Survey described in the Methods Summary.

circulation. In clinical trials, the typical result was a modest lowering (of ~ 1%) in HbA1c, the primary laboratory measure. Furthermore, it caused a mean of 5-6 lbs. weight loss in an overweight population, unlike some diabetes agents such rosiglitazone (AVANDIA) and pioglitazone (ACTOS), which cause weight gain. In the 2nd quarter of 2014, IMS Health data showed the drug was being marketed successfully, accounting for 426,859 dispensed outpatient prescriptions just 12 months after marketing approval.

As might be expected from an agent that blocks a normal function of the kidney, evidence of renal impairment was seen in animal models. In repeat dose studies in rats, canagliflozin was associated with 10%-25% increased kidney weight and dilatation of the kidneys, pelvis and bladder.[21] While a 2-year carcinogenicity study in mice showed no increase in tumors, it did show urinary tract distension, kidney abnormalities, and dilatation of the ureter and bladders in male mice. In a carcinogenicity study in rats, kidney cancers were significantly increased at 12 times the human exposure to the drug, and testicular cancers occurred at all doses tested. Other abnormalities were seen in the adrenal glands, kidneys, bladder, bone, testes and ureters. A high-dose study in beagle dogs did not show similar renal adverse effects, which FDA toxicologists attributed to this species having a lower response to the drug. Adverse findings in animal toxicology studies typically trigger debates about whether the findings are applicable to humans or attributable to biological differences in the test species. Animal studies over a lifetime are an imperfect—but more readily available—surrogate for long-term human clinical studies.

In human clinical trials, evidence of renal impairment was seen with a laboratory measure of kidney function, the estimated glomerular filtration rate (eGFR).[22] At six weeks, eGFR was reduced 4-6%, compared to 2% in a placebo comparator group. The adverse effect appeared early and did not appear to worsen over 26 weeks. However, the reduction in eGFR was also related to the diuretic effect of canagliflozin, which in some patients also reduced intravascular volume and caused fluid depletion-related adverse effects of hypotension, postural dizziness, syncope and dehydration.[20]

In patients with near normal kidney function, 4% of patients at the 300 mg dose had at least one clinically significant decline in renal function (30% or more), approximately twice the rate seen in placebo treated patients [18] Janssen noted that the adverse effects on the kidney were not large and were seldom clinically significant. However, the FDA renal review noted *"the long term renal consequences of canagliflozin's effect on the eGFR are unknown.…It seems prudent to assume that the volume depletion and corresponding reduction in eGFR …places patients at increased risk for clinically significant episodes of acute kidney injury."* [23]

The most frequent adverse effect of canagliflozin on normal kidney function was indirect: Substantially increased glucose in the largely sugar-free urine caused high rates of urogenital infections in both men and women. In women, 14% with near-normal kidney function experienced genital fungal infections, compared to 3.2% of the comparators, and 23% of women with fungal infections had more than 1 over the 26 week period. In men, in whom urogenital fungal infections are normally quite rare, 3.9% experienced fungal infections. [23]

Adverse Event Results

For the 12 months ending with March 31, 2014 (Q2) we identified 457 domestic serious adverse events with canagliflozin as the primary suspect drug. This was a higher total than for 92% of the drugs we regularly monitor. The patients experiencing reported events were younger than many diabetes patients—a median age of 57—and the majority were also taking other diabetes drugs, notably metformin* (23.6%), and insulin (22.7%). Examining these cases we identified six signals, all but one involving direct or indirect adverse effects on the kidneys.

* A combination product with metformin was approved in August 2014 with the brand name of Invokamet.

1. **Renal failure or impairment (n = 54**). The largest number of these cases in this HLT category indicated acute or unspecified renal failure, although some cases also involved dehydration, or hypotension.

2. **Kidney stones (n = 11).** These reported cases in the renal lithiasis HLT are a renal adverse effect that was not reported in FDA safety reviews or the prescribing information. The company said there was insufficient information to assess a drug role.

3. **Fluid/electrolyte issues (n = 54).** In these reported cases the diuretic effect of canagliflozin was suspected of serious adverse effects, measured by the High Level Group Term (HLGT) of that name. The primary term reported was dehydration (n = 36), and 13 cases also involved renal failure and were counted in the category above. These were severe events, with 54% requiring hospitalization.

4. **Urinary tract infections (n = 50).** Given 14% of treated patients reported fungal infections in clinical trials, the 50-case total illustrates that only a small fraction of events occurring are being reported. In these data, females accounted for 69% of infection cases and males 31%. Many of the infections were also included in reports of other adverse events described here.

5. **Weight loss (n = 52).** While the mean weight loss seen in clinical studies (~ 5-6 lbs. [20]) may be considered a benefit in a largely obese patient population, these effects apparently could be large enough to result in serious adverse events. Of the total, 13 cases specified "abnormal" weight loss while the others referred to general "weight decreased."

6. **Hypersensitivity (n = 50**). Since a few cases were reported in clinical trials, discovering serious cases in a larger patient population was to be expected. Two different types of hypersensitivity were described. Some were cases of angioedema–a medical emergency involving swollen tongue, lips, face or throat. However, adverse effects on the skin were also seen, ranging from rash (n = 11) and urticaria (n = 8) to the more severe skin exfoliation (n = 2).

We provided a summary of these results to Janssen Pharmaceuticals, which is licensed by Mitsubishi Tanabe Pharma to market canagliflozin in the US. Janssen told us that the specific adverse effects we observed in postmarketing reports were generally consistent with those seen in clinical trials and described in the prescribing information. Regarding case report totals, the company said "the number of serious adverse events ISMP identified are consistent with what Janssen has observed in our clinical trials and what we continue to see in our postmarketing analysis."

Conclusions

The central unanswered question about canagliflozin—which extends in a different form to other diabetes medications—is whether the drug does more good than harm in long-term treatment. While Janssen noted that the drug had now been tested in more than 10,000 patients, the data were still of insufficient duration to establish whether the drug had a measurable clinical benefit on the complications of Type 2 diabetes. The current data are also insufficient to address unanswered questions raised in the FDA reviews about whether long-term use might result in a steady decline in kidney function, increased risk of bone fractures, or more cardiovascular events. By contrast, we observe clear evidence of harm to some patients in terms of hypersensitivity reactions and an array of renal adverse effects.

20,632 Incomplete Reports for Rosiglitazone (AVANDIA)

The last issue of QuarterWatch focused on the need for the FDA and drug manufacturers to update the FDA Adverse Event Reporting System, FAERS.[15] Key problems included low-quality reports from drug manufacturers, outdated adverse event reporting regulations and guidelines, and ineffective and counterproductive FDA compliance activities.

A graphic and unusual illustration of the need to upgrade FAERS can be seen in a group of 20,632 low-quality reports submitted by GlaxoSmithKline (GSK) about heart attacks and strokes associated with rosiglitazone (Avandia). The reports, 99% submitted during late April 2014, were striking for several reasons. This is one of the largest numbers of serious injury reports for one drug to be submitted in a single calendar quarter. For comparison, in 2014 Q2, for all other 1,025 drugs we monitor, the agency received a total of 55,020 cases, a median of 7 reports per drug. Also, the GSK reports were devoid of basic detail, and were missing all of the following: age, gender and event date. Even the limited information that was provided was problematic. The occupation of source of the report was miscoded, indicating that the complaints had come from consumers when further inquiry revealed they resulted from litigation settlements, i.e. lawyers. They were also classified as expedited reports–the most serious and urgent cases–which FDA regulation requires to be submitted within 15 calendar days of the company learning of the event. [24] These case reports apparently originated in a federal district court settlement approved in 2012, but were not submitted until two years later.

This adverse event reporting episode is still another chapter in the revealing history of the Type 2 diabetes drug rosiglitazone. It was approved in 1999 as the second in a new class of diabetes drugs that lowered blood sugar by causing adipose tissue (or fat cells) to absorb more circulating glucose, frequently causing weight gain in the process. [25] In later studies, it was also associated with edema, heart failure, and increased fracture risk. [25] The central unanswered question—shared by other oral diabetes treatments—was whether rosiglitazone would provide the hoped-for clinical benefit of reducing the risk of cardiovascular events. Given the mechanism of action, questions were raised early that it might possibly increase the risk. Cardiovascular risk became central to the future of rosiglitazone when the chairman of cardiology at the Cleveland Clinic published a meta-analysis in the *New England Journal of Medicine* that reported that rosiglitazone increased both the risk of myocardial infarction (HR (hazard ratio) 1.43) and death (HR 1.98). [26] This study triggered an extensive reexamination of the safety of rosiglitazone that ended with its safety withdrawal in Europe, restricted status in the US, and a boxed warning about the risk of cardiovascular events.[27] In additional tens of thousands of lawsuits were filed against GSK in state and federal courts, alleging the drug had caused myocardial infarction and stroke. [28]

This, however, did not end the story of rosiglitazone. Although not a single case came to trial in court, GSK paid more than $2 billion to an estimated 40,000 patients who alleged the drug had caused myocardial infarction and stroke.[29] GSK also paid an additional $2.3 billion to settle federal claims of fraudulent promotion of several drugs, including rosiglitazone. However, in an unprecedented action the FDA invited GSK to “re-adjudicate” the results of the largest open label rosiglitazone trial of cardiovascular outcomes, which had been previously published as an inconclusive “interim” analysis.[30] When thus re-evaluated, a small increased cardiovascular risk remained, but lost statistical significance. [31] The re-adjudicated data were presented to an FDA advisory committee that did not invite the Cleveland Clinic investigators to present their alternative views. After the committee voted that the evidence did not support an increased CV risk, the FDA removed the restrictions on rosiglitazone use.[32] However, the FDA’s turnabout on rosiglitazone risk had few practical consequences since the drug remained off the market in Europe, and according to IMS Health data, accounted for only 1,500 total prescriptions in 2014 Q2, indicating a patient population of only a few hundred.

The Report Submission

The reasons why GSK submitted 20,632 serious adverse event reports during a few weeks in 2014 proved to be as unusual as other aspects of the drug’s history. GSK told us that it discovered in 2014 that it had inadvertently not reported to the FDA cases from the settlement of the legal cases in 2012. Although the company offered to provide the FDA with a spreadsheet with the limited data the company received from the plaintiffs’ lawyers in the settlement, both the FDA and the company confirmed that the agency required them to file a separate adverse event report for each case.

Even more difficult to understand is the explanation of why so many reports did not contain elementary information such as age and gender. GSK said the information came from lawyers who represented the

patients who claimed injury. The FDA gave no indication it was concerned, saying *"The quality of the report varies with the information the company was able to obtain."* With a corporate outlay of an estimated $2 billion, it is difficult to believe that a major pharmaceutical company paid so much money to so many patients without knowing anything about them. A more likely explanation is corporate organizational problems. The company also told us that it was updating the reports with additional information in the second half of 2014.

It is standard practice in the pharmaceutical industry that when a lawsuit is filed on behalf of a patient alleging injury from a marketed drug, the company's legal department files an adverse drug event report summarizing the complaint, and coding it with occupation = lawyer. Why GSK did not follow this procedure is a question that both the company and the FDA should further examine not only for rosiglitazone but also for other GSK drugs.

QuarterWatch Team and Funding Sources

QuarterWatch is published by the Institute for Safe Medication Practices as a public service. It has no regular income, foundation grant, or other dedicated financial support and is provided to the public and health professions without charge. We seek outside peer reviewers for each issue but their identities are not disclosed. QuarterWatch's essential costs are funded from the general budget of ISMP, a non-profit organization dedicated solely to promoting the safe use of medication. ISMP, in turn, is supported by charitable donations, volunteer efforts, foundation grants, and subscription income from its other medication safety newsletters, for healthcare professionals in the acute, ambulatory, and long-term care settings, for nurses in hospitals, and for consumers.

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