ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES QuarterWatch
Monitoring FDA MedWatch Reports

October 5, 2016 — New data from 2016 Q1

PROBLEMS WITH A PATCH AND A SELF-INJECTION PEN

Lessons from why new patch for migraines was withdrawn after nine months
Consumers struggle with the self-injection pen for a new diabetes drug

Executive Summary

In this issue we examine two signals for problems with devices that administer drugs to patients rather than the underlying risks of the drugs themselves. The Zecuity transdermal patch delivered sumatriptan for acute migraines with a novel technology using small electrical currents to deliver the drug ions through the skin and into body circulation. The Zecuity patch was withdrawn after just nine months on the market because of burns, scarring, and other skin injury. Also, we discovered patients were struggling to use the once-weekly self-injection pen for albiglutide (TANZEUM), a recently approved drug for type 2 diabetes.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all adverse drug event reports submitted to the U.S. Food and Drug Administration. We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval. We also receive dispensed outpatient prescription data from IMS Health Inc.

In the first quarter of 2016 the FDA received 320,102 new case reports about drug adverse events identifying 1,411 different primary suspect drugs, an increase of 19.2% cases over the previous quarter and 33.8% over the same quarter in 2015. However, there was a decline in the number of reports indicating fatal, disabling, or serious outcomes. In this key subset, the total of 74,834 new cases was 4% lower than the previous quarter, and 20.8% below the same quarter in the previous year. After many years of being relatively stable, reports directly volunteered to the FDA have increased in recent quarters and reached a record high of 12,864 new cases in 2016 Q1. Overall, 96% of the reports received into FAERS were prepared by drug manufacturers, who are required to report all adverse events that they learn about. However, these reports may be influenced by marketing and educational activities that cause companies to learn about more adverse event cases through contacts with health professionals and consumers. Reports sent directly to the FDA largely avoid these influences, are more complete than manufacturer cases reports, and more accurately capture the current safety concerns being identified by health professionals and consumers.

Lessons from Zecuity Patch Safety Withdrawal

The Zecuity iontophoretic transdermal patch combined something old with something new. The drug–sumatriptan–had been available for more 20 years to counter migraine headaches, a neurological disorder that impairs the quality of life of at least 35 million Americans. Sumatriptan was already available as a tablet, a self-administered injection, and a nasal spray. However, the Zecuity product got the drug into systemic circulation with a novel transdermal patch device that included two lithium batteries, a microprocessor, and

two large electrode pads saturated with the drug, and with a sodium formulation. It had to be assembled and activated by a patient already experiencing a migraine headache, which can be debilitating for many. Then the patch, about the size of a wide armband, had to be wrapped around the upper arm or affixed to the thigh and activated for four hours.

The Zecuity patch came to our attention because of adverse drug event reports that the patch was causing burns, scars, welts, blistering, and severe pain. Further inquiry showed the FDA's Office of Surveillance and Epidemiology had already identified this problem and issued a Drug Safety Communication in June 2016, saying it was investigating. A week later, the patch was withdrawn by the manufacturer, Teva Pharmaceutical Industries. When further research showed the burns and other skin injuries had been a concern to the FDA both before and at the time of drug approval, we conducted a case study to examine why the Zecuity patch had to be withdrawn after just nine months on the market. The full study appears in the main report and probes the tensions between getting new products on the market quickly and ensuring they are adequately tested.

Problems Using the Albiglutide (TANZEUM) Self-Injection Pen

We identified more than 1,500 adverse event reports in the 12 months ending in 2016 Q1, indicating that consumers were struggling to achieve correct use of the albiglutide (TANZEUM) self-injection pen. The drug, manufactured by GlaxoSmithKline, was approved in April 2014 for second-line treatment of type 2 diabetes. Albiglutide is one of four approved drugs that lower blood sugar through their effect on glucagon-like-peptide-1 (GLP-1) receptors. But it was the first to offer weekly rather than daily self-injections.

Examination of the 10-page albiglutide patient instruction leaflet[*] revealed it was indeed challenging to assemble the self-injection pen for weekly use. The process took more than 30 minutes, required more than a dozen separate steps, including gently shaking and then twisting the pen assembly to dissolve and prepare the drug injection. By comparison, the second new GLP-1 agonist weekly injection drug–dulaglutide (TRULICITY)–involved these steps: 1) Uncap the pen; 2) Place the clear base against the skin; 3) Unlock by turning the lock ring; 4) Press and hold the injection button.

In the albiglutide adverse event reports we identified 1,404 cases of a device use error, 490 mentions of accidental exposure, and more than 200 cases each of device leakage, product issue, and product preparation error. (One case report could contain several of these items.) By comparison, we did not identify device problems and medication errors for dulaglutide, although injection site reactions were reported.

Adverse Event Reporting System

In the 2016 Q1 data we saw further evidence of the need to improve report quality of manufacturer submissions, especially among the growing numbers of cases reported as non-serious adverse events. In 2016 Q1 we identified 175,342 manufacturer cases with non-serious outcomes. Among these cases, 83,830 (47.8%) were missing patient age, gender, or both, suggesting a limited interaction with the person reporting the event. It was notable that one drug–adalimumab (HUMIRA)–accounted for 19,530 or 23.3% of the incomplete non-serious reports. The adalimumab total was increased in part because the manufacturer, AbbVie, was reporting non-serious events just once a year, thus increasing the quarterly total.

[*] Prescribing information for TANZEUM (albiglutide for injection), for subcutaneous use. GlaxoSmithKline, 2016.

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 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. While the sheer numbers of case reports have scientific weight, because of variation in reporting rates, they reveal little about how frequently the events occur in the broader patient population. 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 approval and rapid withdrawal of the Zecuity migraine patch illustrates the tension between the political and industry pressures to get new drugs on the market as quickly as possible and the need to ensure that new drugs with uncertain risks are properly tested prior to marketing approval. As our full report documents in detail, the FDA had already observed unacceptable numbers of burns, scarring, and other skin injuries with the patch. But it was uncertain whether a redesigned patch had remedied the defects. Rather than require an additional round of premarket testing, the agency decided to address the safety question through enhanced monitoring once the patch was on the market. The result was that thousands of patients were unnecessarily exposed to a defective device and hundreds were reported injured. However, both the FDA and Teva, the manufacturer, did act promptly when the safety issue became clear.

We recommend that GlaxoSmithKline substantially improve its patient education program to reduce the number of problems consumers are encountering with the albiglutide self-injection pen. Physicians and patients might also compare the albiglutide product with dulaglutide if a drug in this class is indicated. However, we have previously reported and continue to see three major safety concerns with all the GLP-1 agonists: risk of pancreatitis, pancreatic cancer, and thyroid cancer.

This issue provides additional evidence that the FDA needs to reassess its regulations and guidance for drug manufacturer reporting of non-serious drug adverse events. There is need for more detailed instructions for capturing clinically significant adverse events, which at present might be coded as “other medically serious” or given lower priority as non-serious events. In addition, report quality can be improved by better guidance for manufacturers who have education and marketing programs that will place the company in repeated contact with thousands of consumers. Such programs should have protocols in place to systematically collect basic information such as age and gender and clarify the medical problem reported. With 47.8% of non-serious reports missing age, gender, or both, it is clear that report quality needs improvement.

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Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to the 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 under FDA regulation [2] if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening, or had other medically serious consequences. In addition, we include as serious manufacturer reports that are coded as "Expedited," defined as new, serious adverse drug events for which adequate warnings do not currently exist. Cases without these outcomes were classified as "not serious," and all new cases were included in this analysis unless indicated otherwise. Earlier QuarterWatch issues have focused primarily on a subset of adverse events, those that are domestic and coded with serious outcomes. We continue to monitor domestic, serious reports as an important subset of the newly released case reports.

In these data, the adverse events reported 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.[3] 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.[4] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also 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 2015 to MedDRA version 18.1.

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 2016 (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."

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 drugs used is normally the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations unless specifically indicated.

Results

In 2016 Q1 the steady long-term growth continued in the number of adverse drug event reports received into the FDA's Adverse Event Reporting System (FAERS). It received 320,102 new case reports in the calendar quarter, a 19.2% increase over the previous quarter, and a 3-fold increase over the same quarter five years earlier, when the agency received 105,816 reports. However, most of the recent growth was driven by increased numbers of non-serious reports. As noted in the previous issue of the QuarterWatch,[5] these report increases were partly a result of technology changes that permitted the agency to monitor reports that had been previously available in other forms, but not available for surveillance purposes because they were not the FAERS system. Also contributing to the increased totals are various forms of manufacturer interactions directly with consumers, which causes companies to learn of more adverse events that they have to report.

QuarterWatch also examines report totals for signals of growing risks to patients, from new kinds of reactions, newly approved drugs, or other factors. We focus in particular on changes in domestic, serious adverse event reports. For 2016 Q1 we identified 74,834 new reports in this category, a decline of 4% from the previous quarter and 20.8% from the same quarter of 2015. In the section on the Adverse Event Reporting System below we consider the question of whether postmarket surveillance is strengthened by increasing numbers of reports about events that were apparently not serious, and many of which were incomplete.

Zecuity Migraine Patch Withdrawn

A Case Study on the Perils of Innovation

The FDA approval and voluntary safety withdrawal of a novel transdermal patch for migraine headaches provides a case study illustrating the need for thorough testing of innovative new drug products. The Zecuity patch was a new, high-tech device to deliver sumatriptan through ionic currents through the skin to relieve migraine headaches. It was voluntarily withdrawn in June 2016 after hundreds of adverse drug event reports of serious injury to the skin, including burns, scars, welts, blistering, and severe pain.[6] Key questions include: a) How valuable was this new treatment? b) Did the FDA identify the risk of skin injury prior to approval? c) Was a novel new delivery device adequately tested before marketing?

Migraine headaches impair the lives of more than 35 million people in the U.S. They affect 18% of the female population and 6% of males and 10% of children, with painful headaches lasting 4 to 72 hours, and may involve nausea, vomiting, sensitivity to light or sound, and vision disturbances, called aura.[7] Most of those with this disorder experience one or two temporarily debilitating migraines a month, but in some people they occur every day or two. The mainstay of acute treatment is sumatriptan, which is available in tablet, subcutaneous injection, and nasal spray formulations. At least six other chemically similar drugs are also FDA approved.

Zecuity was a newly designed patch to administer sumatriptan through the skin. It was the size of a broad armband, contained two lithium batteries, a

microprocessor, and two electrodes the size of small teacup saucers. To prepare the patch, the patient places and aligns with the electrode pouches two medication pads, one containing sumatriptan gel and the other soaked with a salt formulation. After peeling off the liner, the patient attaches the patch to the upper arm or thigh and presses a button to activate it. When activated, a red indicator light confirms that this device is at work for the next four hours. The iontophoretic technology had been used for at least one other product, the IONSYS fentanyl patch for use in hospitalized patients for patient-controlled analgesia, which was first marketed in 2015.[8] However, in this instance the drug, patch design, and treatment setting were different.

Benefits Compared

From a review of the Phase III efficacy trials of the Zecuity patch it was not immediately clear what if any advantages a new patch for delivery of sumatriptan offered compared to the tablet, nasal spray, and injection. Compared to a placebo, applying the patch resulted in an additional 8.5% of patients becoming pain free after 2 hours (17.7% Zecuity vs 9.2% placebo).[9] While no head-to-head trials were performed, this appeared to be an inferior result to both the sumatriptan injection (with 50% pain free at 2 hours compared to placebo),[10] and to the nasal spray (13%-33% pain free compared to placebo).[11] However, the legal standard for FDA approval requires substantial evidence of a benefit but does not require comparisons with existing drugs or evidence that a new drug treatment is more effective. Standard statistical comparisons showed that the patch had provided evidence of benefit compared to placebo, as required by law, even though the percentage of patients experiencing complete relief compared to placebo was small.

The novel Zecuity patch with its batteries, microprocessor, and electrodes was originally developed and tested as the lead product of a small Philadelphia area biotech startup called NuPathe. In October 2010 NuPathe submitted a New Drug Application (NDA) for marketing approval. After a multidisciplinary review lasting 10 months and involving 14 interactions with the sponsor, the FDA refused to approve it.[12] The FDA action letter which rejects an NDA until specific deficiencies are resolved is called a “Complete Response.”

The deficiencies were extensive. The Complete Response identified 71 specific problems in chemistry, manufacturing, and controls. It found six more problems involving risk of microbial contamination of the salt pads in one of the patch electrodes. The repeat dose study applying the patch to skin of miniature pigs was defective, the letter said. But the critical problems were nine deficiencies in the clinical testing in humans. The first listed was, “We have serious concerns about the potential of your product to cause severe burns and permanent skin lesions.” [12]

Patch Redesigned

One year later NuPathe amended their NDA, introducing a redesigned patch product. The problem, the company told the FDA, was that many of the burns were caused when patients did not assemble the complex patch properly.[13] To use the patch, the patient, while experiencing a likely debilitating migraine, has to open the patch package (3 steps), then open 2 foil packets to get the medication pads, and put them into the electrode reservoirs on the patch, taking care not to omit one pad or fold a pad. Then the patient was instructed to remove the assembled patch liner to expose the adhesive. In the redesign, the patch was modified so it was not supposed to activate if the medication pads were missing or misaligned.

Now the critical question for the FDA was to decide whether the redesigned patch had eliminated the safety problem, and how much evidence was required to address the issue. After a review, the FDA accepted two small usability trials, one in 26 healthy subjects, another in 32 healthy subjects. The FDA review documents indicated that that burns had not occurred in these tests.[14] In January 2013 the FDA approved the Zecuity patch. However, the patch still did not get to market immediately because the startup NuPathe did not have the capital to launch its new product. The company sought merger partners, and in 2014 was purchased by the Israeli pharmaceutical company Teva Pharmaceutical Industries for $144 million.[15] Teva launched the Zecuity patch in September 2015.[16]

FDA Concerns

Transparency is one strength of the FDA's drug approval process. Its disclosure of pertinent reviews is extensive and unequalled by any other global regulator. These same documents, however, also show that the review team was uncertain whether problems with the patch had, in fact, been remedied. This can be seen in the conclusion of the medical reviewer:

"Overall, the benefits derived from Zecuity marginally outweigh its risks of causing numerous adverse events at the application site." [14] The medical reviewer was persuaded the redesigned product probably mitigated the risks of severe burns, but not other application site injuries.

The senior FDA review official, who also recommended approval, noted the small studies provided "engineering evidence" that the burn/scar problem had been addressed but expressed concerns about "the lack of clinical evidence." [17]

This is the cusp of the regulatory dilemma that occurs when the agency has to balance promoting innovative new drug treatments versus an uncertain risk of injury to patients. So the agency compromised. Since the patch had been extensively redesigned, the FDA could have required a new long-term clinical trial similar to the original one that produced evidence that 43 (5.4%) of patients experienced severe skin reactions, only 4 of which were severe burns, and 1 a scar. A small biotech startup might or might not have been able to afford another long-term trial.

Instead of asking for more clinical testing, the agency required enhanced postmarket surveillance of the early patients who were unwittingly becoming test subjects to answer a specific scientific question that had been left on the table at drug approval. What kinds of scars, burns, device leaks, erythema, and pruritus were going to occur with the redesigned device? Instead of more testing, the agency required the sponsor to report immediately (within 15 days) any device problems it learned about from early consumers.

The Adverse Event Report Signal

In its first six months on the market, Zecuity patches accounted for 389 adverse drug event reports, according to QuarterWatch monitoring. Almost all indicated problems with the patch. These included application site burn (n = 117), application site pain (n = 125), battery issue (n = 63), and device leakage (n = 59). Smaller numbers of reports indicated skin exfoliation, vesicles, scars, device malfunction, bruises, and chemical injury. This number of reports might be considered as modest for a drug being used by hundreds of thousands or even millions of persons. However, dispensed outpatient prescription data from IMS Health shows that despite a potential patient population of 35 million, the launch was a limited success. Only 7,235 prescriptions for Zecuity were dispensed during the first six months after launch. However, additional patients could have been exposed with free samples.

The FDA and Teva Respond to Signal

FDA analysts in the Office of Surveillance and Epidemiology also identified the surge in Zecuity adverse event reports and acted promptly. On June 2, 2016, the agency published a Drug Safety Communication saying it was "investigating the risk of serious burns and permanent scarring." [18] A week later Teva withdrew the product and urged any patients with patches to discontinue use immediately.[6]

Safety Withdrawal Redefined

In recent years, the FDA has not publicly announced a single drug safety withdrawal, even though drug products have been taken off the market because of safety problems. For many years drug safety withdrawals have been described as "voluntary" because the FDA secures the consent of the manufacturer rather than using a formal regulatory proceeding. But the "voluntary" actions were publicly announced as safety withdrawals. Apparently the new but unofficial policy is to avoid using the word "withdrawal" and describe the action as "suspending sales and marketing" in the case of Zecuity. In another case, the 2013 safety withdrawal of peginesatide (OMONTYS), was described as a "recall of all lots." [19] This treatment for

anemia in kidney dialysis patients triggered a hypersensitivity reaction so severe that some patients died within minutes of receiving the first dose.[20] The policy of substituting these low-key descriptions of safety withdrawals also raises legal and regulatory questions about the conditions under which these withdrawn products can be returned to the market.

Conclusions: Testing in Unwitting Patients

The case of Zecuity is illuminating because the evidence clearly shows that the FDA was aware of application site problems and was uncertain whether they had been resolved. Management selected enhanced postmarket surveillance as a substitute for additional clinical testing. This also is an issue that would benefit from an independent expert review with access to all materials. In addition, the exact problem remains undetermined. Why do scars and burns occur with the redesigned patch? Do they occur with correct operation? Was device failure the issue? Were some of the corrections of the 71 manufacturing deficiencies not adequate?

In an era where pressures mount to reduce the amount of clinical testing to speed approval of new drugs, it is especially important to have clear, transparent policies to announce publicly safety withdrawals. In addition, new policies are needed to evaluate why patients were exposed to these risks, and set clear and open criteria for any possible reintroduction of the product.

Consumers Struggle with Albiglutide (TANZEUM) Self-Injection Pen

Albiglutide (TANZEUM) is a drug for type 2 diabetes, approved in April 2014, and is administered once weekly with a self-injection pen. It is one of four available synthetic glucagon-like-peptide-1 (GLP-1) agonists that lower blood sugar by stimulating the release of insulin from the pancreas and increasing storage of circulating sugar in the liver. All GLP-1 agonists require injections–daily in the case of liraglutide (VICTOZA) and exenatide (BYETTA)–and weekly for albiglutide and dulaglutide (TRULICITY).

GLP-1 Agonist Known Safety Issues

The GLP-1 agonists share a series of known and potential safety risks that resulted in the FDA classifying them as second-line drugs for type 2 diabetes. QuarterWatch examined these issues in depth in April 2013.[21] Two risks of these agents relate to likely adverse effects of steady state synthetic GLP-1 on receptors in the pancreas, causing abnormal growth of pancreatic tissue with risk of pancreatitis and pancreatic cancer. In addition, the prescribing information for all four agents warns of possible risk of thyroid cancer based on multiple animal studies. In the most recent 12 months of data for the four GLP-1 agonists combined, we continued to see evidence of these adverse effects. This included 555 reported cases of acute and chronic pancreatitis, 399 cases of pancreatic cancer, and 111 cases of malignant thyroid cancers. All four drugs share FDA warnings about the risk of pancreatitis and thyroid cancer. However, the increased risk of pancreatic cancer remains controversial and without an FDA warning. These new event totals did not distinguish among the four drugs.

The Albiglutide Injection Pen

Meanwhile, what set albiglutide apart from the other GLP-1 agents were more than 1,500 reports that consumers were having problems with the drug's injection pen. These cases were among 2,734 case reports overall for albiglutide for the 12 months ending in 2016 Q1. Injection pen problems included 1,404 mentions of a device use error, 490 cases noting accidental exposure, 293 complaints of device leakage, as well as smaller numbers of cases indicating that consumers found the device difficult to use, experienced device failure, or administered the wrong dose. (Some reports included multiple report terms.) GlaxoSmithKline (GSK), the manufacturer, prepared 99% of the reports, and 98% originated from consumers (rather than health professionals).

To investigate why albiglutide patients might be having trouble with the pen, we reviewed the instructions for use in the prescribing information [22] and watched the company's video tutorial. [23] By several measures the albiglutide pen was a complex device to use. The patient instructions were 10 pages long, the injection required more than 30 minutes to prepare, and required the pen, a clock timer, an empty cup, and a sharps disposal container. The overall preparation process contained more than a dozen separate steps. One step involves gently rocking (but not too hard) the pen to dissolve the medicine at two stages in preparing the injection. It also called for some practical judgments. After rocking the pen, if patients observe undissolved particles, they should not use the pen. After attaching the needle, the user should tap the cartridge to bring large air bubbles to the top. However, "small" air bubbles can remain throughout the cartridge chamber. Deciding the difference between large and small bubbles seems problematical, as is identifying enough undissolved particles to render the pen unusable.

Comparison with Dulaglutide

Albiglutide was one of two once-weekly self-injection drugs that the FDA approved in 2014. For comparison purposes we also examined the adverse event reports and instructions for using dulaglutide, the other product.

For dulaglutide we found 673 adverse event reports for the same 12-month period, but no reports of device issues, accidental exposure, maladministration, or medication error. However, both dulaglutide and albiglutide had reports of application site reactions such as pain, bruising, rash, and hemorrhage.

We also examined the dulaglutide self-injection pen instructions for use, [24] and the video tutorial.[25] It involved these steps: 1) Uncap the pen; 2) Place the clear base against the skin; 3) Unlock by turning the lock ring; 4) Press and hold the injection button.

Manufacturer Response

We shared our results with GlaxoSmithKline, the manufacturer, and sought any additional insights into specific problems consumers might be having with the self-injection pen. The company disagreed with our overall event totals, which we calculated from publicly released FDA data. The company said our 12-month totals were lower than those the company extracted from its global event database. After further investigation, we concluded the differences were likely the result of coding and report date calculations in two similar but different data systems. There were also differences in how the company and the FDA public release data coded the severity of the events, but this did not affect our analysis. GSK did not provide additional information about any potential medication errors patients should be aware of when using the self-injection pen.

Conclusions

Three different kinds of evidence show that patients are struggling with the complex albiglutide self-injection pen. Problems were first apparent in adverse drug event reports, confirmed by review of the lengthy instructions, and compared unfavorably to the dulaglutide pen in ease of use. We recommend that GSK increase its efforts to educate patients about use of the self-injection pen. Physicians and patients should consider ease of use in selecting a GLP-1 agonist self-injected medication. None of this new information addressed our long-standing safety concerns about the risks and benefits of this drug class.

Adverse Event Reporting System

As noted in the Results section, the growing number of adverse drug event reports received by the FDA is currently being driven by increases in reports about events that were not judged to be serious. Events that are not serious need to be reported only on a quarterly basis (rather than in 15 days), and after a drug is three years on the market non-serious reports can be submitted annually. Reporting of non-serious events is not required for foreign reports. Having domestic non-serious reports available also provides a double check

to ensure that serious events are not being miscoded by drug manufacturers to reduce the number of the most urgent and high-priority events. A check of 2016 Q1 non-serious manufacturer reports disclosed thousands of reports that are, at the very least, clinically relevant to assessing a drug adverse effect. Table 1 provides examples.

In addition to thousands of clinically significant events, we found that report quality was often poor. Overall, 47.8% of manufacturer non-serious reports (n = 83,830) were missing patient age, gender, or both. Just one drug–adalimumab (HUMIRA)–accounted for 19,530 of these cases or 23.3% of the incomplete report total. However, two factors contributed to the increased totals for adalimumab: A) The drug accounted for more cases overall than any other drug in several categories, including domestic, serious events. B) The manufacturer, AbbVie, was reporting one year's worth of non-serious events in this quarter. Nevertheless, we recommend the company develop protocols to improve the report quality for these large-scale interactions with patients and health professionals.

Table 1. Clinically signficiant but non-serious events, 2016 Q1*

Preferred Term	Mentions
Rash	3,780
Vomiting	2,867
Drug hypersensitivity	2,480
Depression	1,465
Memory impairment	1,333

* Selected manufactuer reports

The FDA should reconsider its reporting requirements and definitions, many of which date back to the mid-1990s, to better capture clinically significant adverse drug events. At present, events such as depression are being coded by some manufacturers as "other medically serious" and reported in 15 days, while others considered it a non-serious event. In addition, report quality should be improved for the clinically significant events. Finally, the agency should require manufacturers to develop protocols to collect higher quality information from large-scale interactions such as hot-lines, nurse assistance, and programs for getting insurance approval.

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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 four other medication safety newsletters, for pharmacists in the acute care and ambulatory care settings, for nurses, and for consumers.

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