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ISMP

Community/Ambulatory Care ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

QuarterWatch™ (2016 Quarter 1 Data)

Lessons learned from withdrawal of the Zecuity patch Patient difficulties using the Tanzeum pen

The latest issue of ISMP's QuarterWatch™ (see box below) provides a review of new drug safety issues reflected in adverse drug events reported to the US Food and Drug Administration (FDA) during the first quarter of 2016. This report examines two signals for problems with devices that administer drugs to patients rather than the underlying risks associated with the drugs themselves:

- **ZECUITY** (**SUMA**triptan iontophoretic transdermal system), which uses small electrical currents to deliver **SUMA**triptan through the skin to treat migraine headaches, was withdrawn after just 9 months on the market because of burns, scarring, and other skin injury.
- Patients with type 2 diabetes are struggling to use the recently approved, once-weekly self-injection **TANZEUM** (albiglutide) pen.

Overall QuarterWatch™ report totals

In the first quarter (Q1) of 2016, FDA received 320,102 new case reports about adverse drug events involving 1,411 different primary suspect drugs, an increase of 19.2% over the previous quarter and 33.8% over the same quarter in 2015. However, the number of reports indicating fatal, disabling, or serious outcomes declined. In this key subset, a total of 74,834 new cases in Q1 was 4% lower than the previous quarter and 20.8% below the same quarter in the previous year. Overall, 96% of the reports received by FDA were prepared by drug manufacturers, who are required to report all adverse events about which they learn. The remainder were voluntarily submitted directly to FDA by health professionals and consumers.

Zecuity patch withdrawal: A case study of the perils of innovation

Zecuity paired a drug for migraines that has been available for more than 20 years with a novel iontophoretic patch delivery system that included two lithium batteries, a microprocessor, and two electrode pads—one saturated with the drug and the other with a salt formulation. A patient experiencing a migraine headache had to assemble the system, wrap it around their upper arm or affix it to their thigh, and activate it for 4 hours by pressing a button. The iontophoretic technology had been used

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What is QuarterWatch™?

QuarterWatch™ is an independent ISMP surveillance program that monitors adverse drug events reported to FDA by manufacturers, health professionals, and the public. The agency releases excerpts of all reports it receives into the FDA adverse event reporting system (FAERS) for research and data analysis. The goal is to identify signals that may represent important drug safety issues which require further investigation to determine their frequency and establish a causal relationship to the suspect drug.

SAFETY briefs

Buprenorphine can look like HYDROmorphone. A physician wrote by hand a prescription for buprenorphine. However, the pharmacist misinterpreted the drug name (**Figure 1**) as **HYDRO**morphone and dispensed this instead of buprenorphine. The patient experienced some withdrawal symptoms as a result of the error. The dosage form or route (in this case sublingual), purpose of the drug, and brand name were not included on the

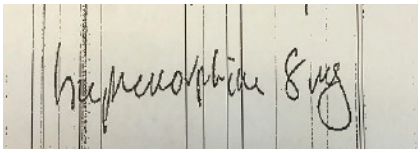

Figure 1. Handwritten prescription for buprenorphine misread as **HYDRO**morphone.

prescription, which may have helped prevent this error. Prescribers and pharmacies should pursue electronic prescribing of controlled substances (EPCS) to eliminate the role of handwritten medication errors and combat prescription fraud and abuse. Every state in the US allows EPCS. If you have not yet implemented EPCS in your practice, check with your vendor to make sure your system is certified and approved for EPCS and work with them to get your practice up and running for EPCS. You can find more information about getting started with EPCS at: www.getepcs.com.

Don't give Zurampic without allopurinol. **ZURAMPIC** (lesinurad) is indicated for hyperuricemia associated with gout. It is used when patients have not achieved target serum uric acid (sUA) levels with a xanthine oxi-

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for at least one other product, the **IONSYS** (fenta**NYL** iontophoretic transdermal system) patch used by hospitalized patients, which was first marketed in 2015. However, the drug, patch design, and treatment setting differ for the two patches.

Adverse event reports. The Zecuity patch came to our attention when adverse drug event reports submitted to FDA indicated that the patch was causing skin injury, including application site burns (n = 117), severe pain (n = 125), and smaller numbers of skin exfoliation, vesicles, scars, bruises, and chemical injuries. Reports were also submitted for battery issues (n = 63) and device leakage (n = 59). Within the first 6 months on the market, 389 adverse drug event reports were submitted to FDA. This number of reports might be considered modest if the drug was being used by hundreds of thousands or even millions of people. But only 7,235 prescriptions for Zecuity were dispensed during this time period, according to data from IMS Health. Additional patients could have been exposed if provided with free samples of the device.

The FDA's Office of Surveillance and Epidemiology had issued a Drug Safety Communication in June 2016, saying it was investigating the issue. A week later, the patch was withdrawn by the manufacturer, Teva Pharmaceuticals. When further research showed that burns and other skin injuries had been an FDA concern both before and at the time of drug approval, we conducted a case study to examine the problem.

Zecuity approval history. The advantages, if any, of the new patch design were not immediately clear during clinical trials when compared to the tablet, nasal spray, and injection. In phase III efficacy trials, applying the patch resulted in an additional 8.5% of patients becoming pain free after 2 hours compared to placebo. This appeared to be an inferior result to both the **SUMA**triptan injection (50% pain free at 2 hours compared to placebo), and to the nasal spray (13%-33% pain free compared to placebo). While FDA approval requires substantial evidence of a benefit, it does not require evidence that a new drug treatment is more effective than existing drugs.

Nevertheless, FDA approval of the product was initially rejected due to extensive deficiencies, including 71 problems in chemistry and manufacturing. One of the critical clinical problems involved serious concerns about the potential to cause severe burns and permanent skin lesions. The problem, the company told the FDA, was that many of the burns were caused when the patient did not assemble the complex patch properly. One year later, a redesigned patch was submitted for review and approved. The results from two small usability trials (26 and 32 healthy subjects) indicated that no burns had occurred with the redesigned patch. FDA documents show, however, that the review team was uncertain whether problems with the patch had, in fact, been remedied, citing a lack of "clinical evidence" (as opposed to "engineering evidence").

Conclusion. In an era where pressures mount to speed up the approval of new drugs, this is the cusp of the regulatory dilemma that occurs when FDA has to balance rapid approval of innovative drug treatments against the amount of testing necessary to assess the risk of injury to patients. Since the patch had been extensively redesigned, FDA could have required a new long-term clinical trial. Instead, the agency required enhanced postmarketing surveillance and immediate reporting of

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dase inhibitor alone, such as allopurinol or febuxostat. In fact, the drug carries a boxed warning about the risk for acute renal failure when used without a xanthine oxidase inhibitor. Patients taking this medication alone during clinical trials experienced renal failure at a significantly higher rate than when taken in combination with a xanthine oxidase inhibitor. Given this risk, it seems odd that the drug was approved as a single entity tablet rather than a combination product with allopurinol. Without the combination product, sooner or later patients and healthcare providers will either not remember or not know that the two drugs must be given together.

We asked AstraZeneca, the product manufacturer, about this issue, and the company plans to submit a fixed-dose product containing both lesinurad and allopurinol this year. Given the current lack of a combination tablet, it seems that it would be a good idea to tie use of Zurampic with use of allopurinol or febuxostat by developing order sets that require both drugs and placing reminders in computer systems and on auxiliary labels affixed to containers. Patient education is critical to ensure patients understand the risks of Zurampic and the need to take a xanthine oxidase inhibitor while on the drug.

HIGH-ALERT

Clear methotrexate dose communication. We have written many times about errors involving methotrexate, often involving mix-ups between daily and weekly dosing of the drug. However, in the most recent event, it was the number of tablets prescribed for each dose that was confused. A rheumatologist sent a facsimile prescription to a pharmacy for methotrexate 2.5 mg, take 8 tablets per week. The "8" was misread as "6" and the prescription was dispensed with the

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any device problems. Patients unwittingly became test subjects to determine if the redesigned device would cause scars, burns, device leaks, erythema, and pruritus. The result was that thousands of patients were unnecessarily exposed to a defective device, and hundreds of patients reported injuries.

Problems using the Tanzeum self-injection pen

TANZEUM (albiglutide), a second-line treatment for type 2 diabetes from GlaxoSmithKline that lowers blood sugar through its effect on glucagon-like peptide-1 (GLP-1) receptors, was approved in April 2014. It's one of four currently available GLP-1 receptor agonists.

Adverse event reports. All of the GLP-1 receptor agonists carry an FDA warning for pancreatitis and thyroid cancer. There may also be an increased risk of pancreatic cancer. In 12 months of data ending with 2016 Q1 for all of the GLP-1 receptor agonists combined, we continued to see evidence of these adverse effects, including 555 reported cases of acute and chronic pancreatitis, 399 cases of pancreatic cancer, and 111 cases of thyroid cancer. What sets Tanzeum apart from the other GLP-1 agonists is more than 1,500 reports of patients having problems using the pen correctly.

By comparison, for **TRULICITY** (dulaglutide), also a GLP-1 agonist approved for weekly injection, FDA received 673 adverse event reports for the same 12-month period, but no reports of device issues, maladministration, or medication errors.

Patient directions for use. Examination of the Tanzeum patient instruction leaflet in the full prescribing information (www.ismp.org/sc?id=2815) reveals that the process to prepare the pen for use is lengthy and complicated. The process takes more than 30 minutes and requires more than a dozen separate steps, including gently rocking (but not shaking) and twisting the pen assembly in three separate steps to dissolve and prepare the drug for injection. If patients observe undissolved particles, they should not use the pen. After attaching the needle, patients must tap the cartridge to bring large air bubbles to the top, although "small" air bubbles can remain throughout the cartridge. Deciding between large and small bubbles seems problematic, as is identifying enough undissolved particles to render the pen unusable. We communicated with GlaxoSmithKline (Tanzeum manufacturer), but the company was unable to offer additional information about potential medication errors patients should be aware of when using the pen.

By comparison, again, the use of Trulicity involves just four steps: 1) Uncap the pen; 2) Place the clear base against the skin; 3) Unlock by turning the lock ring; and 4) Press and hold the injection button.

Conclusion. Evidence shows that patients are struggling with use of the complex Tanzeum pen. Problems were first identified in adverse drug event reports, and the device compared unfavorably to the ease of use with the Trulicity pen. We recommend that GlaxoSmithKline substantially improve its efforts to educate patients about use of the pen. Physicians should consider the ease of use when prescribing a GLP-1 agonist pen if a drug in this class is needed, and ensure that patients know how to use the device if prescribing the Tanzeum pen. However, with all of these GLP-1 agonists, we continue to see concerns with the risk of pancreatitis, pancreatic cancer, and thyroid cancer.

The full report with references can be found at: www.ismp.org/sc?id=1702.

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wrong directions of "take 6 tablets per week." The patient, who was aware of her correct dose and the number of tablets she needed to take, caught the error and returned the medication to the pharmacy. The person who reported this error suggested, to make communication of methotrexate doses clear and precise, that prescribers should write out the dose in letters (e.g., eight tablets) and include the patient's total mg dose (e.g., 20 mg per week). We agree with the reporter's recommendations and encourage prescribers to employ this strategy.

Healthcare consumers are watching!

A consumer (also a nurse) reported that an unlabeled syringe was observed at a dermatologist's office during her son's appointment for a wart removal. The unlabeled syringe was on a table with a piece of paper under it. Her son asked the nurse if the injection was for him, and she replied, "No, that's for a different type of procedure." On another occasion, the consumer noticed an unlabeled syringe of what looked like propofol in an oral surgeon's treatment room, but it clearly was not needed for her procedure, which did not require sedation.

Then, more recently, another consumer took her mother to a neurologist for a nerve block to treat head and neck pain. A nurse holding two unlabeled syringes and a sheet of paper in her hand ushered them into a treatment area. They remained in the room for about 30 minutes, along with the 2 unlabeled syringes, until a physician assistant (PA) arrived in the treatment room. The consumer reported her concern about the unsecured and unlabeled syringes, suggesting several adverse scenarios that could happen as a result. First, a patient might try to divert or tamper with the unknown medications in the sy-

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Gone are those wonderfully unusual Target bottles

Back in 2005, Target Corporation took a bold step in redesigning the traditional pharmacy vial and container label. In fact, ISMP recognized Target for this change with a 2005 **CHEERS** Award. The innovative design was the basis of a 29-year-old graphic designer's thesis project. She recognized that traditional prescription vials and labeling could contribute to medication errors after her grandmother mistakenly took pills belonging to her grandfather. The redesigned vial and label were created to enhance patient safety and adherence. Key safety features included:

- A more patient-centered label with the most important information (i.e., patient name, medication name, strength, and instructions) printed at the top of the label while the pharmacy name and contact information were relocated to the bottom.
- The unusually shaped bottle provided wider front and back panels that allowed for better presentation of information, making it easier for patients to read.
- An abbreviated medication information card that included information such as the patient's name, drug name, description of the drug, instructions for use, and common side effects was tucked neatly between the back label and the bottle to keep information readily available.
- A patient's medication bottles were color differentiated from other family members' medications with patient selected and pharmacy applied color rings around the neck of the prescription bottle or a colored sticker added to the front label.

With CVS acquiring Target's pharmacies, these bottles and labels are now a thing of the past. They have been replaced with the same round, amber bottles and labels CVS uses in its pharmacies nationwide, a change that has upset many Target customers. However, we hope that the innovation displayed in the design elements of the Target bottle and label are not lost. We encourage CVS and other pharmacy operations to take another look at their bottles and labels. Explore ways to incorporate some, if not all, of the patient-centered safety features of the **CHEERS** winning Target bottle and label system. Technology (e.g., robotics) developers and vendors should also work to develop systems capable of filling and labeling different shaped prescription bottles, such as those formally used by Target. We continue to hope the Target effort will spark innovation and improvements throughout the community pharmacy industry.

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rings, or even self-administer the contents of one or both syringes; furthermore, a nurse could put the syringes of unknown medications into the wrong treatment room, where a PA or physician could assume the syringes contained the anticipated medications and inject the unknown medications without confirmation. The consumer probably ruffled some feathers in the office when she spoke up, brought this to the PA's attention, and did everything possible to address the risk she observed. However, soon after, the neurologist came into the room, proceeded to freshly prepare the needed medications, and assured the consumer that he would address the risk. Kudos to the consumer for speaking up! The proper labeling of prepared syringes of medications is absolutely critical to safety.

Always check each patient's pharmacy record before giving vaccines.

A patient's wife came into the pharmacy and asked why her elderly husband had been given a second flu shot. The pharmacist checked and she was correct. The patient had mild dementia and he didn't remember the one given to him a month before. Also, the patient's record had not been checked prior to giving the latest injection. It seems obvious but it's not always done as it should be – check the patient record before administering any vaccine and participate in your state's vaccine immunization information system to document or confirm vaccine administration.

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