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ISMP 25 YEARS ADVANCING MEDICATION SAFETY

Acute Care ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

QuarterWatch™ (includes new data from Quarter 4, 2018 and Quarter 1, 2019)

Focus on four new drugs: Xofluza, Aimovig, Ajovy, and Emgality

The latest issue of ISMP's QuarterWatch™ (see description in box below) focuses on the safety profiles of four new drugs that were approved in 2018:

- **XOFLUZA** (baloxavir marboxil), a new antiviral treatment for influenza (flu) symptoms, for which severe allergic reactions have been reported
- **AIMOVIG** (erenumab-aooe), **AJOVY** (fremanezumab-vfrm), and **EMGALITY** (galcanezumab-gnlm), three new biological products intended to reduce the frequency of migraine headaches, for which previously underestimated adverse effects have been reported

During the first few years after product launch, postmarket surveillance is especially crucial since there are still many unanswered questions about the drugs due to limits on pre-approval clinical testing. For this reason, we also evaluated manufacturer performance in reporting the adverse effects of these four new drugs since their launch. The following is a summary of the full QuarterWatch™ report, which can be found with references at: www.ismp.org/node/482.

Report Totals

The new data for this report consisted of 327,308 new adverse drug event reports received by the US Food and Drug Administration (FDA) in Quarter 4, 2018; and 334,395 new reports received in Quarter 1, 2019. We combined the data from the two quarters since FDA made the excerpts available more promptly and did not want to defer analysis of the latest set of data. The highest priority safety concerns are reflected in the US reports with serious or fatal outcomes—78,684 in Quarter 4, 2018; and 87,119 in Quarter 1, 2019.

A New Treatment for the Flu

Influenza is the most aggressive and successful viral predator of the human species. It combines effective transmission with the ability to mutate rapidly to evade immune, vaccine, and antiviral defenses. More than 1 in 10 adults and children were infected by influenza during the 2018-2019 season, and 1 in 1,000 who were infected died. Our primary preventative defense is vaccination; however, an estimated 43% of those vaccinated last season still contracted the flu. Effectiveness varied by age and flu type, ranging from 61% effective in children to 8% effective in adults 50 years and older with influenza A.

Antiviral drugs are a major treatment for the flu, with oseltamivir (**TAMIFLU**) used more widely than zanamivir (**RELENZA**) and peramivir (**RAPIVAB**). In October 2018, FDA approved a new antiviral treatment for the flu, Xofluza (baloxavir marboxil), which is man-

continued on page 2—QuarterWatch >

What is QuarterWatch™?

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

SAFETY briefs

HIGH-ALERT

Insulin and tranexamic acid mix-up.

A hospital reported two serious medication errors due to look-alike 100 mL bags of insulin and tranexamic acid that had been compounded in the pharmacy and stored in a refrigerator. The first error occurred when a pharmacy technician retrieved a 100 units/100 mL bag of insulin from the pharmacy refrigerator instead of the tranexamic acid that was also stored there. The bag of insulin was delivered to the operating

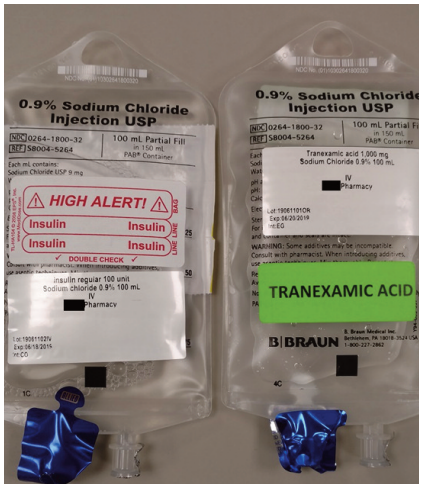

Figure 1. Because the drug names do not stand out on the small, white pharmacy labels on insulin (left) and tranexamic acid (right) bags, the pharmacy now affixes auxiliary labels. (A patient-specific label [insulin] and an additional auxiliary label [tranexamic acid] are also on the back of the bags.)

room (OR) where barcode scanning is not utilized. A 1 g dose of intravenous (IV) tranexamic acid was to be given over 15 minutes, but the insulin was administered in error. Staff in the post-anesthesia care unit (PACU) recognized the error, discontinued the insulin, and monitored the patient's blood glucose level. Dextrose IV was administered, and the patient suffered no permanent harm.

A similar error happened when an anesthesiologist hung an insulin bag instead of tranexamic acid, both of

continued on page 2—SAFETY briefs >

> QuarterWatch—continued from page 1

ufactured in Japan by Shionogi and licensed in the US to Roche/Genentech. Compared to oseltamivir, baloxavir blocks a different step in viral replication and is taken in tablet form as a single dose within 48 hours of flu onset rather than twice a day for 5 days.

Premarket studies. FDA affirmed a claim that treatment with baloxavir shortened the duration of the flu from a median of 80 hours to 54 hours. However, limited pre-approval testing was required, making the assessment of risks and benefits a challenge. For example:

- The trials excluded patients with symptoms but who tested negative for the flu (verifying that a respiratory illness is the flu is generally not used in clinical practice) and adults over the age of 65 (a group with low response to flu vaccines)
- Only one Phase 3 trial was conducted, which included only 113 non-Asian patients despite observed ethnic differences in response to treatment (better results in Japanese)
- Only 710 patients were exposed to the recommended dose in Phase 2 and 3 studies, limiting the ability to detect less common adverse effects

Postmarket adverse event data. Our first look at baloxavir identified new reports of serious adverse drug events and raised questions about the limited clinical testing before approval. In the 12 months ending in Quarter 1, 2019; 382 reports were received identifying baloxavir as the primary suspect drug. All but 14 reports had a serious or fatal outcome, and about 20% involved children under 18 years of age. More than 90% of the cases were reported by health professionals during Quarter 1, 2019. Most of the cases originated from Japan where the drug was approved in early 2018 and where patient exposure was greater (6 million patients) compared to 93,000 prescriptions in the US while available during Quarter 1, 2019.

Of particular concern were 50 cases of anaphylactic shock, 7 fatal, which were all reported by healthcare professionals. When our preliminary data was shared with Genentech, the company confirmed that it has also seen a safety signal for hypersensitivity, including anaphylaxis, and has been closely monitoring these events.

In addition, we observed reports of central nervous system (CNS) symptoms similar to those described in FDA-required warnings for oseltamivir (e.g., altered consciousness, delirium, abnormal behavior, loss of consciousness, seizures). We also observed reports of gastrointestinal symptoms (e.g., colitis, blood in the stool, vomiting, diarrhea). Less weight was given to reported adverse events often associated with or complications of influenza itself (e.g., pneumonia, pyrexia, headache).

Conclusion. The first full calendar quarter of adverse event data following baloxavir approval provides signals for potentially important adverse effects that were not detected in pre-approval testing, particularly life-threatening hypersensitivity reactions after a single exposure. Neither the prescribing nor patient information material mentions this risk. In addition, we need to know more about the benefits and risks of this new drug, especially in non-Asian ethnic groups. The benefits of baloxavir remain unproven against influenza B, and reported gastrointestinal and CNS adverse effects require further investigation.

A New Class of Drugs for Migraine Prevention

In 2018, FDA approved 3 new biological products for migraines based on evidence they could reduce the number of headache days per month in many patients. The drugs were:

- Erenumab-aooe (Aimovig, Amgen), approved in May 2018, with 277,400 outpatient prescriptions in Quarter 1, 2019
- Fremanezumab-vfrm (Ajovy, Teva), approved in September 2018, with 79,700 prescriptions in Quarter 1, 2019

continued on page 3—QuarterWatch >

> SAFETY briefs

cont'd from page 1

which were stored in the OR automated dispensing cabinet. The error was caught after the entire insulin bag had been infused. Again, the patient was monitored once the error was noticed, IV dextrose supplementation was administered, and no significant harm occurred.

Two factors stand out as contributing to the above cases. Both medications were in 100 mL bags, and both had similar looking white labels with small text that was difficult to read. The information that stands out on the pharmacy label is the route of administration and the name of the pharmacy. No barcode was available on the pharmacy label; however, had the bags been scanned at the time of dispensing, at least one of these errors would have been prevented. Unfortunately, most hospitals have yet to deploy barcode scanning in the OR, which is critical for preventing these types of errors in this setting.

The hospital is now applying auxiliary labels to the bags that may help to identify their contents (**Figure 1**, page 1).

HIGH-ALERT

Bridion and light sensitivity. BRIDION (sugammadex) is packaged and supplied as 10 clear single dose vials per carton. There is a statement on the carton that mentions the medication must be discarded after 5 days when it is not protected from light. This has led some healthcare staff to discard the vials when they are found out of their carton on top of anesthesia carts exposed to light for an unknown period.

Sugammadex is indicated for routine reversal of rocuronium- or vecuronium-induced neuromuscular blockade post-procedure, or immediate reversal after a full dose of rocuronium. For example, reversal may be needed in situations when intubation was unsuccessful, making rapid response of the essence. If an anesthesia provider administers the contents of a vial that supposedly has lost potency due to light exposure greater than 5 days, the drug may be ineffective after the specified waiting period. Also, product labeling mentions that recurrence of neuromuscular blockade can occur, usually due to sub-optimal dosing. Thus, there would be no way of knowing if the recurrence was due

continued on page 3—SAFETY briefs >

> QuarterWatch—continued from page 2

- Galcanezumab-gnlm (Emgality, Eli Lilly), approved in September 2018, with 65,300 prescriptions in Quarter 1, 2019

All three drugs are genetically engineered monoclonal antibodies that target a highly prevalent signaling molecule, calcitonin gene-related peptide (CGRP). While CGRP has many functions vascularly, it has been linked to some migraine headaches. These drugs are given subcutaneously once a month (or fremanezumab-vfrm can be every 3 months).

Premarket studies. All three drugs reduced the number of migraine headache days by a median of 1 to 2 days per month compared to placebo in a group of episodic migraine patients who had been experiencing 8 to 9 headache days per month. Large variability in effects was a striking feature. Outcomes ranged from no effect in 15% of patients, to 20% who reported that treatment eliminated–or nearly eliminated–migraine headaches that had afflicted them for many years. Also, trials showed a substantial placebo effect.

Although the CGRP molecular target has other roles in the body (e.g., vasodilation, effects on gastrointestinal motility and wound healing, others not well understood), erenumab-aooe clinical trials revealed only a few adverse events occurring 2% more frequently than placebo: constipation, cramps/muscle spasms, and injection site reactions.

Postmarket adverse event data. Our primary analysis focused on erenumab-aooe, which was the first to gain FDA approval, has the largest patient population, and generated the most adverse drug event reports. The most striking feature of the erenumab-aooe adverse event data was the sheer number of case reports for the 12 months ending in Quarter 1, 2019: 10,508 case reports, including 1,458 with a serious outcome. Erenumab-aooe ranked first in the number of reports for the 33 new drugs approved in 2018 and accounted for more than twice as many cases as the other 32 new drugs combined. The large number of reports might be explained, in part, by a successful product launch and high number of outpatient prescriptions.

We identified a clear signal for constipation (n=1,169), which ranged from cases managed with laxatives to those requiring hospitalization and/or treatment discontinuation. This adverse effect was seen in clinical trials but at a very low rate (1% at the 70 mg dose). Participants in the trials may not have been asked about constipation, and higher incidences up to 20% have been documented when patients have been queried about this adverse effect. There was also a signal for alopecia (n=376; 64 classified as serious), even though this was seen in only 2 patients during clinical trials. Again, patients may not have been asked about this during trials, leading to underestimation of its effect.

We also identified a possible signal for cardiac arrhythmia (n=225), including palpitations, increased heart rate, and loss of consciousness. The risk of cardiovascular adverse effects was a concern during FDA-approval evaluations, but in pre-approval clinical studies, the agency did not identify a risk warranting a warning.

Muscle and joint pain, and hypersensitivity were seen both in clinical trials and early adverse drug event data. Large numbers of complaints about the drug not being effective (n=2,086) were also observed, which is expected given studies that showed limited or no benefit in 15% of patients and only modest reductions in headaches in many others.

Conclusion. The emerging safety profile of erenumab-aooe shows that certain adverse effects, such as constipation, may be more frequent for this migraine preventive than were seen in the clinical trials. Reports of hair loss were seen for all three drugs, but this adverse effect was not clearly identified in clinical testing for approval. Although the drugs are intended for long-term use, there are no multi-year studies of either long-term benefits or long-term adverse effects. There are at least theoretical risks that these new treatments could cause other health problems.

continued on page 4—QuarterWatch >

> SAFETY briefs

cont'd from page 2

to reduced potency of the drug or suboptimal dosing. Understanding the cause of the recurrence would be important.

We contacted Merck, the company that sells Bridion, asking for additional information about photostability of the product. Merck found a significant decrease in content over time in a light-exposed group, as compared to dark controls, which were wrapped either in the carton box or in black polyethylene foil. However, the lighting conditions used in the photostability study were extreme conditions, which do not correspond to light exposure during normal expected use of sugammadex. The findings from the photostability study were then used to estimate the degree of degradation of sugammadex products in usual hospital lighting conditions. It was estimated that over a 5-day period under normal hospital lighting, the expected degree of degradation would be no more than 0.2%, which is considered to be within acceptable limits. For all samples tested, the color of sugammadex did not change with exposure to ultraviolet (UV) radiation or cool white light.

Knowing the 5-day loss was only 0.2%, it seems like more extensive testing should be required for out-of-the-carton vials, say at 10 days, 30 days, and beyond. Otherwise, we will not know the true significance of any degradation over longer periods of time, and the label will continue to lead healthcare staff to discard any vial they see that has been exposed to light for an unknown amount of time. Marking vials with a date removed from the carton would be useful, although compliance with this type of strategy tends to be very low. Keeping the vials in an amber pharmacy bag might be helpful. However, visualizing the label through the bag would be challenging and could lead to errors if the wrong product is accidentally placed in the bag labeled as sugammadex.

The company should conduct additional testing or package the drug in amber vials. The US Food and Drug Administration (FDA) has also been contacted about these recommendations. Unfortunately, short of these actions, it does not seem that other recommendations for handling the product will be impactful.

> QuarterWatch—continued from page 3

Reporting of Adverse Events to FDA

The first few years after launch of a new drug are a critical period for postmarket surveillance through adverse drug event reporting and other methods. Some countries (notably Japan, United Kingdom) require various forms of enhanced surveillance during the early period after approval. However, FDA does not have such requirements unless specified in a Risk Evaluation and Mitigation Strategies (REMS) plan.

The reason early postmarket surveillance is most likely to identify new, more frequent, or more severe adverse effects is linked to the following weaknesses in clinical trials:

- Trials are too small or too short to capture less frequent effects
- Vulnerable patient populations are often excluded
- Unlike treatment benefits, a drug's adverse effects are not systematically collected with a checklist or other instrument
- Duration and severity of adverse drug events are rarely captured

For this reason, we evaluated the completeness of the adverse event reports for the four newly approved drugs that were the focus of this QuarterWatch™ report. The standard for minimally complete was defined as a report with age, gender, and at least some description of the adverse event (simply reporting "death" or "hospitalization" was not useful). Our findings appear in **Table 1** below.

Table 1. Completeness of reports submitted to FDA for four new drugs

Drug Name	Brand	Source	Report Total*	Complete (%)
Migraine Preventive Medications (Manufacturer)				
erenumab-aooe	Aimovig	Amgen	9,938	59
galcanezumab-gnlm	Emgality	Eli Lilly	1,020	20
fremanezumab-vfrm	Ajovy	Teva	457	41
Migraine Preventive Medications (Direct to FDA)				
All three		FDA (healthcare professionals, consumers)	639	94
Antiviral Flu Treatment (Manufacturer)				
baloxavir	Xofluza	Genentech	382	74

*12 months ending Quarter 1, 2019

Based on our analysis, the problem lies with drug manufacturers since 94% of the reports submitted directly to FDA from health professionals and consumers were minimally complete. The best results with manufacturers were for baloxavir, but almost all the reports came from Japan, not the US. Since Amgen submitted many more reports than the manufacturers for the other three drugs, the company's stronger performance in reporting for erenumab-aooe (59%) shows a system capable of collecting a large report volume without loss of quality.

Conclusion. FDA should strengthen and modernize its adverse event reporting system, starting with the development of better reporting requirements and protocols for the first few years after a drug is launched, when high quality data collection is most important and relevant. The key guidance and other requirements date back to 2001 before the internet era and other large-scale changes in the practice of medicine and marketing of drugs. Better performance is clearly feasible, and there is no reason product launch plans should not include enhanced and accurate postmarket surveillance processes.

Special Announcements

Accepting Cheers Awards nominations
Nominations for this year's Cheers Awards will be accepted through **September 6, 2019**. ISMP encourages outside nominations, including self-nominations. The prestigious Awards spotlight efforts from all healthcare disciplines, and winners have included representatives from hospitals, health systems, long-term care, ambulatory care, community pharmacies, professional associations, federal and state agencies, as well as individual advocates. Cheers Award winners demonstrate a willingness to share learning beyond the organization (e.g., professional presentations; articles in publications; tools shared on the internet). To submit a nomination, visit: www.ismp.org/node/1036.

Get intensive about medication safety
The **Medication Safety Intensive (MSI)** workshops sold out quickly last year! Act now to avoid being put on the waiting list in 2019; you won't want to miss this unique opportunity to maximize your error prevention efforts and learn to look at your organization through the eyes of leading safety experts. For information and to register, visit: www.ismp.org/node/127.

2019 MSI dates
- **September 12-13**—Orlando, FL
- **December 6-7**—Las Vegas, NV

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