September 2023 | Volume 22 ▪ Issue 9

ISMP
An ECRI Affiliate

Community/Ambulatory Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Another patient death: Implement strategies to prevent accidental daily methotrexate dosing

Methotrexate is a folic acid antagonist that was originally approved to treat a variety of cancers. Used for oncologic indications, methotrexate is administered in cyclical frequencies and in variable doses based on body surface area and the type of cancer being treated. The labeled indications for methotrexate later expanded to include the treatment of nononcologic conditions, including psoriasis (approved in 1971) and rheumatoid arthritis (approved in 1988). Other nononcologic off-label uses include the treatment of Crohn's disease, multiple sclerosis, inflammatory myositis, reactive arthritis (Reiter's syndrome), graft-versus-host disease, Takayasu arteritis, uveitis, and ectopic pregnancy. For most nononcologic indications, a low dose of methotrexate is administered weekly—for example, 7.5 mg per week when initiating treatment for rheumatoid arthritis.

Accidental daily dosing of oral methotrexate has occurred all too frequently. This type of wrong frequency error has originated in all stages of the medication-use process, from prescribing to self-administration. These errors have resulted in serious methotrexate overdoses that led to vomiting, mouth sores, stomatitis, serious skin lesions, liver failure, renal failure, myelosuppression, gastrointestinal bleeding, life-threatening pulmonary symptoms, and death.

Medication Incidents

A patient death recently reported in the media (www.ismp.org/ext/1260; www.ismp.org/ext/1261) is a stark reminder of the harm that can occur. A patient had been admitted to a rehabilitation facility following a fall at home. It appears that a prescription for methotrexate 20 mg daily was sent to the pharmacy instead of a prescription for methotrexate 20 mg weekly. According to the media reports, the prescriber approved the order and the pharmacy dispensing system allowed the pharmacist to bypass a high-dose alert. As a result, the patient received 20 mg of methotrexate daily for a week (a total of 100 mg over the span of the week). The patient became ill and died about a week later. Now, both the prescriber and pharmacist are facing second-degree manslaughter and second-degree neglect by a caretaker charges.

Since 1996, errors with daily oral methotrexate for nononcologic use have been reported to ISMP and published in dozens of our ***ISMP Medication Safety Alert!*** newsletters. For example, in one case, methotrexate 15 mg once weekly was prescribed for treatment of an autoimmune disorder in an elderly patient. The community pharmacy dispensed a 3-month quantity of medication but provided instructions on the label to take 15 mg (6 x 2.5 mg tablets) once daily. The error was discovered three weeks later during patient counseling with a pharmacist when the patient requested a refill. The error resulted in severe harm, which led to a long hospital stay and treatment with the rescue agent leucovorin calcium.

In another reported case, a rheumatologist decided to add methotrexate 10 mg weekly to an 80-year-old patient's arthritis regimen. Methotrexate 2.5 mg tablets were prescribed with instructions to take 4 tablets once every 7 days. The pharmacy label was typed incorrectly with directions to "Take four tablets once daily for 7 days." Although she was advised about the correct regimen to take by the physician, the patient followed the dosing instructions on the pharmacy label thinking she must have misunderstood the physician. She took 4 tablets (10 mg) daily for 4 days. On day 2 of therapy, she experienced severe fatigue. By day 3, she developed shortness of breath and swelling in her legs. Laboratory testing later ordered by the physician revealed thrombocytopenia.

continued on page 2 — Methotrexate >

SAFETY briefs

Confusing Fluzone High-Dose packaging led to a double dose. We have received multiple reports about this year's **FLUZONE** (influenza) High-Dose quadrivalent vaccine for adults 65 years and over by Sanofi Pasteur. The carton's primary display panel states it contains 10 single-dose prefilled syringes–five trays with two syringes sealed in one tray (**Figure 1**, page 2). The concern is that some may think both syringes are needed to administer a dose. This is exactly what happened in one case. A patient was given a double dose due to the confusing packaging.

We have notified the US Food and Drug Administration (FDA) and Sanofi Pasteur about this concern. If your organization

continued on page 2 — SAFETY briefs >

IMPORTANT! Read and utilize the Community/Ambulatory Care Action Agenda

One of the most important ways to prevent medication errors is to learn about problems that have occurred in other organizations and to use that information to prevent similar problems at your practice site. To promote such a process, selected items from the **May – August 2023** issues of the ***ISMP Medication Safety Alert! Community/Ambulatory Care*** newsletters have been selected and prepared for you and your staff to stimulate discussion and collaborative action to reduce the risk of medication errors. Each item includes a brief description of the medication safety problem, a few recommendations to reduce the risk of errors, and the issue date to locate additional information.

The **Action Agenda** is available for download as an Excel file (www.ismp.org/node/100547).

> Methotrexate — continued from page 1

Recommendations

ISMP has identified methotrexate as a high-alert medication in community, long-term care, and hospital settings, even when used for nononcologic purposes such as rheumatoid arthritis. As with all high-alert medications, there is a heightened risk of significant patient harm when this drug is used in error. Most of these wrong frequency errors with methotrexate can be prevented by implementing known risk-reduction strategies. It is time for technology vendors, regulators, standards setting organizations, healthcare organizations, and practitioners to make the following system improvements outlined in *Best Practice* #3 in the ***ISMP Medication Safety Best Practices for Community Pharmacy*** (www.ismp.org/node/65345):

- Use a weekly dosage regimen default for oral methotrexate in electronic systems when medication orders are entered.
- Require verification and entry of an appropriate oncologic indication in order entry systems for daily orders.
  - Require a hard-stop verification of an appropriate oncologic indication for all daily oral methotrexate orders.
  - For systems that cannot provide a hard stop, clarify all daily orders for methotrexate if the patient does not have a documented appropriate oncologic diagnosis.
  - Work with software vendors and information technology personnel to ensure that this hard stop is available. Software vendors need to ensure that their order entry systems are capable of this hard stop as an important patient safety component of their systems.
- Create a forcing function (e.g., electronic stop in the sales register that requires intervention and acknowledgement by a pharmacist) to ensure that every oral methotrexate prescription is reviewed with the patient or a family member when a prescription is presented or refills are processed.
- Provide specific patient and/or family education for all oral methotrexate prescriptions.
  - Specifically ask the patient which day of the week they plan to take this medication.
  - Provide clear written instructions AND clear verbal instructions for oral methotrexate that specifically review the dosing schedule, emphasize the danger with taking extra doses, and emphasize that the medication should not be taken "as needed" for symptom control.
  - Require the patient to repeat back the instructions to validate that the patient understands the dosing schedule and toxicities of the medication if taken more frequently than prescribed.
  - Provide all patients with a copy of or hyperlink to the free ISMP high-alert medication consumer leaflet on oral methotrexate (found at: www.ismp.org/ext/221).

Healthcare practitioners should also consider other important risk-reduction strategies provided below:

Medication reconciliation

- Update and edit the patient's home medication list as needed throughout the episode of care so it can accurately guide medication reconciliation.

continued on page 3 — Methotrexate >

>SAFETY briefs

continued from page 1

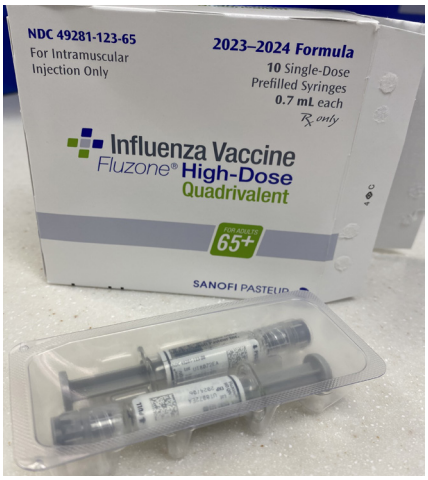

Figure 1. Fluzone High-Dose carton contains 10 single-dose prefilled syringes–five trays with two syringes sealed in each tray.

purchases this vaccine, notify staff about the potential for errors. Ensure barcode scanning is used when dispensing and administering. Consider adding auxiliary labels to each tray noting that each dose requires only one syringe. If stored outside the carton, consider removing the syringes from each tray.

Wrong prescription bag given to patient. Patients continue to receive medications intended for a different patient at the point-of-sale. ISMP receives reports of this from both pharmacies and consumers. Just recently, ISMP received another report of this type of error. A patient was supposed to receive atorvastatin but instead received **DESCOVY** (emtricitabine and tenofovir alafenamide), which is used to treat or reduce the risk of human immunodeficiency virus infection (HIV). When the patient approached the pharmacy counter, they provided their name and date of birth to the pharmacy technician. However, the technician inadvertently retrieved the wrong bag from the pharmacy's will-call area. Once back with the patient, the technician did not again verify the patient's name and date of birth or that the bag was the correct one. The patient ingested one dose of the incorrect medication before discovering the error.

In addition to always verifying the patient's identity by asking for at least two

continued on page 3 — SAFETY briefs >

> Methotrexate — continued from page 2

- Verify the dose and frequency of all medications and patient instructions (including discharge and ambulatory care visit summaries).
- Ask patients about their use of specific prescription and over-the-counter medications that could increase the risk for methotrexate toxicity.

Prescribing

- Provide clear information on oral methotrexate prescriptions. Include the strength and dose in mg and provide clear instructions for weekly dosing. Avoid "take as directed" instructions.
- Consider specifying a day of the week in the directions to reduce the risk that the patient will receive instructions for daily use. If possible, avoid Monday as the day to take the weekly dose, since "Monday" may be misread as "morning."
- Include a specific clinical purpose (e.g., rheumatoid arthritis, psoriasis) within the prescription.
- Limit the prescription quantity to be dispensed to a 4-week (28-day) supply.

Patient and/or family education

- When possible, provide patients and/or families with a visual calendar to clarify the weekly dosing schedule.
- Educate patients and/or families about the key symptoms of methotrexate toxicity and to whom to report the symptoms.

Patient monitoring

- If a methotrexate dosing error is discovered, ensure the patient receives immediate medical attention.

Conclusion

Ongoing frequency and dosing errors with oral methotrexate suggest that more needs to be done to reduce the risk of patient harm. It is imperative for healthcare organizations, technology vendors, prescribers, nurses, and pharmacists to implement these effective strategies to safeguard the use of methotrexate as a high-alert medication and ensure that the medication is dispensed with the proper dosage regimen. While all community pharmacies routinely provide instructions to patients and/or families about a medication's use, special attention needs to be taken with oral methotrexate. It is critical to ensure correct instructions are provided to the patient and listed on the label of the prescription bottles, that patients and/or families are counseled, and that patients and/or families understand both the proper dosage regimen and potential toxicities that can occur if too much medication is taken.

Editors: Michael J. Gaunt, PharmD; Michael Cohen, RPh, MS, ScD (hon), DPS (hon); Shannon Bertagnoli, PharmD; Ann Shastay, MSN, RN, AOCN. ISMP, 5200 Butler Pike, Plymouth Meeting, PA 19462. Email: ismpinfo@ismp.org; Tel: 215-947-7797.

>SAFETY briefs continued from page 2

identifiers, one of the most effective ways to prevent this error is to open the bag of filled prescriptions at the point-of-sale and verify with the patient that the medications are correct and for the right patient. Talking with the patient about their medications can further reduce the risk of errors. If the prescription is delivered to the patient's home, educate them to open the package, check the contents before taking any of the medication, and call the pharmacist with any concerns or questions.

New expiration date format is official. Effective September 1, 2023, USP's General Chapter <7> *Labeling* new expiration date format became official. Manufacturers are required to provide a 4-digit year at the beginning of the expiration date format. Expiration dates may be presented in all numeric formats (YYYY-MM-DD [e.g., 2025-06-30]; YYYY-MM [e.g., 2025-06]) or alphanumeric formats (YYYY-MMM-DD [e.g., 2025-JUN-30]; or YYYY-MMM [e.g., 2025-JUN]). Thank you for your reports as they helped spur this change.

Special Announcements

MSI workshop for community, mail order, and specialty pharmacy

Don't miss the opportunity to register for a unique, virtual ***ISMP Medication Safety Intensive (MSI)*** workshop designed for those working in **community, mail order, and specialty pharmacies**. Learn how to identify risks before they cause harm and how to use data for continuous improvement. This program will take place on two consecutive Fridays, **October 20 and 27, 2023**, from **7:30 am – 4:30 pm ET**. For more details about the program, please visit: www.ismp.org/node/75243.

Foundations in Medication Safety

ISMP's new online, interactive program offers **community pharmacies** a standardized, cost-effective way to ensure pharmacy staff have the baseline knowledge needed to promote safe medication use. For details, visit: www.ismp.org/node/76167.

HITTING THE SAFETY HIGH NOTES

ISMP 26TH ANNUAL CHEERS AWARDS

When: Tuesday, December 5, 2023

Where: House of Blues – Anaheim

The Cheers Awards honor those who have hit the high notes in medication safety.

CHOOSE YOUR GROOVE

Showcase your commitment to medication error prevention with a donation to our ONLY fundraising event:

https://www.ismp.org/node/83407

FAN CLUB BENEFITS

- Branding as a prominent champion of patient safety
- Positioning as a strategic partner with ISMP
- Networking with patient safety leaders from varied practice settings

ISMP
Institute for Safe Medication Practices
An ECRI Affiliate