

Acute Care

ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

Call to action: Longstanding strategies to prevent accidental daily methotrexate dosing must be implemented

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—for example, 12 g/m² per dose when treating osteosarcoma. 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 just once or twice weekly—for example, 7.5 mg per week when treating rheumatoid arthritis.

Relatively few medications are dosed weekly; thus, 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, severe myelosuppression, gastrointestinal bleeding, life-threatening pulmonary symptoms, and, in some cases, death.

Since early 1996, harmful or fatal errors with daily oral methotrexate for nononcologic use have been reported to ISMP and published in more than 60 of our *ISMP Medication Safety Alert!* newsletters. Thus, oral methotrexate for nononcologic use has been included on the **ISMP List of High-Alert Medications** (www.ismp.org/node/103) since the inception of the list in 2003. Although the risk of errors with oral methotrexate for nononcologic use has been known for a long time, harmful and fatal errors are still occurring today. Descriptions of recently reported events follow.

Methotrexate Errors**Medication reconciliation and transition-in-care error**

The most recent event involved an error that was caught during hospitalization but continued upon discharge when an incorrect entry for daily methotrexate on a patient's home medication list was not corrected. An elderly man with rheumatoid arthritis was admitted to a hospital with renal failure. At home, he had been taking oral methotrexate 2.5 mg twice weekly (Mondays and Wednesdays). The admitting nurse began creating a list of the patient's home medications. The admitting physician noticed that methotrexate was missing from the home medication injection list in the patient's electronic health record and added it. However, he mistakenly documented that the patient had been taking 2.5 mg of oral methotrexate twice daily instead of twice weekly. He then made this an active order during the patient's hospitalization.

Noticing the daily order for methotrexate, a pharmacist in the central pharmacy contacted the physician to let him know that he must prescribe daily methotrexate on a hospital-mandated chemotherapy order template. However, the pharmacist did not verify that the patient had an appropriate oncologic indication for the order.

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ELIGARD (leuprolide acetate for injectable suspension) is a gonadotropin-releasing hormone (GnRH) agonist indicated for the palliative treatment of advanced prostate cancer. The drug is given subcutaneously, which provides continuous release of leuprolide acetate over a 1-, 3-, 4-, or 6-month treatment period based on one of four available dosage strengths (see below).

Dosage	Recommendation
7.5 mg	1 injection every month
22.5 mg	1 injection every 3 months
30 mg	1 injection every 4 months
45 mg	1 injection every 6 months

The Eligard carton contains two syringes in separate overwraps that must be mixed together prior to injection. Syringe A is pre-filled with **ATRIGEL**, a polymeric (non-gelatin containing) delivery system. Syringe B is pre-filled with leuprolide acetate powder. However, it is easy to miss the wording on the front of the carton, "Must be constituted before use," and a full description of the syringe contents is only mentioned in small print on the back of the carton (**Figure 1**). Also, the Atrigel overwrap emphasizes the name Eligard, not the Atrigel delivery system.



Figure 1. Eligard outer carton front panel does not clearly indicate the contents of the two syringes.

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The physician simply complied with the pharmacist's request and prescribed the daily methotrexate via a chemotherapy order template. Fortunately, an oncology pharmacist identified the error after talking to the patient and corrected the active order, changing the dose from twice daily to twice weekly. However, it never crossed his mind to correct the methotrexate entry on the patient's home medication list.

The patient received the correct dose—one 2.5 mg tablet—of methotrexate on Wednesday during his 5-day hospital stay before being transferred to a skilled nursing facility (SNF). Upon discharge, the physician reconciled the patient's list of home medications for continuation upon discharge. In doing so, he pulled the erroneous methotrexate entry over to the list of medications to continue upon discharge, thus prescribing oral methotrexate 2.5 mg twice daily for the patient while at the SNF. The patient received twice daily methotrexate for more than a week before he was rehospitalized with a change in mental status, severe neutropenia, and mucositis. Sadly, he never recovered and died in the hospital about a week later.

Misunderstood instructions

Another recent error involved a correctly filled outpatient prescription for weekly methotrexate with an escalating dose change 2 weeks later. Unfortunately, the patient misunderstood the instructions on the label and took the medication daily. An 8-week supply of 2.5 mg tablets (30 tablets) had been dispensed with label instructions that said, "Take 3 tablets by mouth one day for 2 weeks then increase to 4 tablets by mouth 1 day per week thereafter." Despite counseling, the patient was confused by the label instructions and took 3 tablets (7.5 mg) daily for 5 days before serious symptoms led his doctor to identify the error.

Overall complexity with titrated methotrexate doses or divided weekly doses have previously caused confusion. For example, in 2017, a patient with rheumatoid arthritis was hospitalized after mistakenly taking methotrexate 3 tablets twice a day for 4 days instead of 3 tablets in the morning and 3 tablets in the evening once a week. The prescription label said, "Take 6 tablets by mouth weekly. Take 3 tablets in AM and 3 tablets in PM." In the labeling for methotrexate, single oral doses of 7.5 mg once weekly are recommended for initial treatment of rheumatoid arthritis. However, divided oral doses of 2.5 mg at 12 hour intervals for 3 doses, given as a course once weekly, are also recommended. It appears that the use of divided doses has added to patient confusion.

Look-alike, sound-alike issues

Some of the recently reported errors have also involved accidentally selecting methotrexate instead of the intended diuretic metOLazone. Both drug names start with "m-e-t" and have overlapping tablet strengths of 2.5, 5, and 10 mg. In one case, a pharmacy technician who was entering a telephone prescription for oral metOLazone 2.5 mg daily accidentally selected methotrexate 2.5 mg daily. She had searched for metOLazone using the first three letters of the drug name and the strength and selected methotrexate 2.5 mg by mistake since it met both criteria. The computer system did not flag the methotrexate order to require verification of an appropriate oncologic indication since the dosing frequency was daily. The medication was dispensed without the pharmacist noticing the error. The patient's husband picked up the medication and was asked if he had any questions. When he had no questions, counseling was not provided. The patient took methotrexate 2.5 mg daily as directed on the label and died less than a month later. Mix-ups between these two medications have been previously reported in this newsletter.

Assessment of Best Practices

To prevent accidental daily dosing of oral methotrexate, ISMP has long recommended defaulting computer order entry systems to a weekly dosing regimen, requiring pharmacist verification of an appropriate oncologic indication for daily dosing of

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ISMP has received two complaints about the overwraps looking identical, with both labeled primarily as Eligard (**Figure 2**). In one case, a hospital pharmacist found only one syringe in an Eligard carton stored in the refrigerator and dispensed that for a patient. The dispensed syringe contained only the Atrigel delivery system. Fortunately, the patient's nurse was aware that two syringes were needed for dose preparation and intercepted the dispensing error before administration. However, when the medication was returned to the pharmacy, the



Figure 2. Overwraps for Eligard powder and the Atrigel delivery system are both prominently labeled as containing Eligard.

second syringe was not found. This led pharmacy staff to suspect that, previously, someone may have dispensed only the syringe containing leuprolide powder.

This product has difficult mixing instructions that require attaching the syringes to one another, shifting the Atrigel directly into the leuprolide, and then mixing back and forth between the two syringes. The product must then be administered within 30 minutes or discarded, which may require nurses in certain settings to mix the products together immediately before use. Preparation and handling errors may lead to lack of efficacy.

We have contacted the manufacturer, Tolmar Pharmaceuticals, to suggest label improvements: the Atrigel delivery system overwrap should prominently be labeled as such, with Eligard deemphasized; and the front panel of the carton should list the contents of the two syringes and clarify that they need to be mixed before administration.

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methotrexate, and educating patients about the weekly dosing regimen. These best practices have also been on the national to-do list with the ISMP **Targeted Medication Safety Best Practices for Hospitals** since 2014 (see best practice #2 [a, b, c] at: www.ismp.org/node/160).

Although implementation of these best practices has been rising since 2014 (www.ismp.org/ext/69), the most recent data (**Table 1**) from the **ISMP Medication Safety Self Assessment® for High-Alert Medications** demonstrate opportunities to improve implementation of these and other best practices that could prevent errors with methotrexate in many hospitals. In the recent self assessment, methotrexate for nononcologic use scored lowest among the 11 high-alert medications included in the assessment. For the 501 US hospitals that submitted data to ISMP for this medication, a mean percent score of only 50% was achieved. Participating hospitals scored particularly low on defaulting to a weekly dosing regimen with computer order entry systems, requiring verification of an appropriate oncologic indication for daily dosing of methotrexate, educating patients about the weekly dosing regimen, prescribing the medication in quantities that do not exceed a 30-day supply, and verifying that all lists and instructions provide the correct dosing instructions.

One of the barriers to defaulting to a weekly dosing regimen with computer order entry systems appears to be that some systems present common orders for oral methotrexate in both daily and weekly dosing frequencies, without an option to edit the display of these orders. When searching for the intended drug, a clinician may pick the first choice that matches the desired dose, without noticing that the frequency of administration listed is daily, not weekly.

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Table 1. Implementation of best practices associated with methotrexate (nononcologic use), n = 501 US hospitals

Best Practice	Implementation†		
	None	Partial	Full
Computer order entry systems default to a weekly rather than daily dosage regimen.*	19%	18%	63%
Computer order entry systems require a hard stop verification and mandatory entry of an appropriate oncologic indication in order to override the weekly dosage regimen and select a daily schedule for a defined number of doses or days.*	44%	21%	35%
OR			
Pharmacists clarify daily orders for methotrexate if the patient does not have a documented oncologic diagnosis to ensure the frequency and duration is appropriate and safe.*	14%	25%	61%
Patients who are discharged on methotrexate receive verbal and written instructions that specify the weekly dosing schedule and emphasize the danger with taking extra doses.*	17%	38%	45%
Patients discharged on methotrexate repeat back the instructions to validate understanding of the weekly dosing schedule and toxicities if taken more frequently than prescribed.*	30%	40%	30%
Prescriptions for nononcologic methotrexate only include the number of tablets or other dosage forms needed for weekly dosing, not to exceed a 4-week (30-day) supply.	47%	22%	31%
A healthcare professional verifies all printed medication lists and discharge instructions to ensure they indicate the correct dosage regimen prior to providing them to the patient.	10%	32%	58%

†Implementation: None = A & B scores; Partial = C & D scores; Full = E scores

*This best practice has been included in the **Targeted Medication Safety Best Practices for Hospitals** since 2014

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Import of potassium chloride injection.

Because of the severe shortage of potassium chloride injection, the US Food and Drug Administration (FDA) has approved importation by Athenex Pharmaceuticals of 20 mEq/10 mL ampules (2 mEq/mL) of the product, which is manufactured and marketed in Italy by Galenica Senese. Complete information, including product access, photographs of the carton and ampule label, and comparison to the US product, is on the FDA drug shortages website at: www.ismp.org/ext/71.

It is important to recognize that the ampule label expresses the potassium chloride concentration as 2 mEq/mL, with 20 mEq/10 mL in parentheses (**Figure 1**), which is the opposite of how the concentration is expressed on the US vial label per USP <7>. Also, a barcode is not on the label, so alternate procedures are needed to verify product identification. Finally, this product is in an ampule rather than a vial

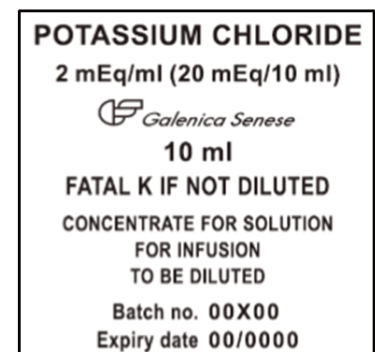


Figure 1. Concentration on imported potassium chloride injection is prominently expressed per mL as 2 mEq/mL, followed by the amount per total volume in parentheses (20 mEq/10 mL), the opposite of concentration expression on US labels.

and does not have a black band or series of black bands above the ampule neck constriction, as would a US product.

If these products are purchased, we highly recommend storing and utilizing these ampules only within the pharmacy.



Kudos to PA Patient Safety Authority for requiring patient weights.

With approval of the Pennsylvania (PA) Department of Health, the PA Patient Safety Authority issued draft recommendations on July 14, 2018, to licensed acute care facilities in PA to ensure accurate patient weights (www.ismp.org/ext/70). The Au-

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Recommendations

Ongoing errors with oral methotrexate for nononcologic use suggest that more needs to be done to reduce the risk of patient harm. Most of the wrong frequency and wrong drug errors with methotrexate could be prevented by fully implementing the **Targeted Medication Safety Best Practice** associated with methotrexate and other related risk-reduction strategies in the **ISMP Medication Safety Self Assessment® for High-Alert Medications**, including:

- Defaulting to a weekly dosing schedule in prescriber and pharmacy order entry systems
- Requiring verification and entry of an appropriate oncologic indication in order entry systems for daily orders
- Educating patients and providing them with verbal and written instructions that specify the weekly dosing schedule and emphasize the danger with taking daily or extra doses
- Asking patients to repeat back the instructions for taking oral methotrexate to validate understanding
- Verifying the dose and frequency of all medication lists and discharge instructions
- Limiting the prescription quantity to a 30-day supply (e.g., dispensing just eight 2.5 mg tablets for a 5 mg weekly dose would reduce the risk of a serious overdose)

Other important risk-reduction strategies for clinicians, technology/drug information vendors, and the US Food and Drug Administration (FDA) are provided below.

Clinicians: Medication reconciliation

- Update and edit the patient's home medication list as needed throughout the patient's hospitalization so it can accurately guide medication reconciliation.
- Create a daily list of active orders and discharge prescriptions for oral methotrexate generated from the order entry system, and require a pharmacist to review the orders and prescriptions to verify the dose and frequency based on the patient's diagnosis.

Clinicians: Prescribing

- Provide clear directions on oral methotrexate prescriptions. Avoid "take as directed" instructions, include the strength and dose in mg, provide clear instructions for weekly dosing, and limit the number of tablets to a 4-week (30-day) supply.

Clinicians: Dispensing

- Provide clear instructions on pharmacy labels for weekly dosing, and specify the day of the week (written in full, not abbreviated) the medication should be taken. Affix an auxiliary warning label (preferably preprinted) to remind patients that the dose should be taken weekly.
- When available and covered by the patient's insurance, dispense oral methotrexate for nononcologic use in outpatient settings in a dose pack that helps guide patients to take the proper dose weekly. Dispensing loose tablets of methotrexate for nononcologic use in prescription vials is highly discouraged in outpatient pharmacies if methotrexate dose packs are available and covered by the patient's insurance.

Clinicians: Patient education

- Provide all patients with a copy of the free ISMP high-alert medication consumer leaflet on oral methotrexate (found at: www.ismp.org/ext/68).
- When possible, provide the patient with a visual calendar to clarify the weekly dosing schedule.

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thority is recommending that acute care facilities in PA have processes in place to weigh each patient as soon as possible on admission, when a patient experiences a change in condition that may lead to significant weight changes, and during each appropriate outpatient or emergency department encounter (except in critical situations). The use of an estimated, historical, or stated weight should be avoided. This includes all encounters in which the patient is being seen by a licensed independent practitioner, excluding life-threatening situations where the delay in weighing the patient could lead to serious harm (for example, major trauma). It excludes laboratory and other services where medications are not prescribed or administered.

Also, organizations must have a process in place to measure and document a patient's weight in metric units (for example, grams or kilograms) only. This would include documentation in computer information systems, infusion pumps and other medication devices, and printouts and preprinted order forms that prompt users to record patient weight.

The draft recommendations have a 30-day comment period. Once finalized, the Authority is responsible for issuing guidelines to acute care facilities in PA.



Contrived drug names wreak havoc.

An emergency department physician verbally requested "Neostick" from a bedside clinical pharmacist. However, the pharmacist misheard the request as "neostig" and retrieved neostigmine when the provider wanted phenylephrine (**NEOSYNEPHRINE**, a former US brand of phenylephrine). We were surprised by how many hits we received when we searched "Neostick" on Google. Apparently, it's a very popular slang term. ISMP has occasionally received medication error reports in which other contrived drug names were an issue, such as "Ketofo!" (ketamine and propofol combined in a syringe), "levo" (**LEVOPHED** [norepinephrine], levothyroxine, or levo**FLOX**acin [**LEVAQUIN**]), and "nitro" (nitroglycerin or nitroprusside). The hospital that reported use of the contrived name, Neostick, has discouraged further use of any made-up drug names and abbreviations.

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- If folic acid is prescribed along with methotrexate, educate patients about the differences between the medications and their respective administration schedules.¹
- Educate patients about the key symptoms of methotrexate toxicity and to whom to report the symptoms.

Clinicians: Patient monitoring

- If a methotrexate dosing error is discovered, ensure the patient receives immediate medical attention.^{2,3}

Technology/drug information vendors

- Build computer order entry systems to ensure clinicians have access to the functionality needed to prevent methotrexate errors (e.g., default to weekly dosing, hard stop for verification of indication with daily orders).

FDA (which is currently evaluating the need for regulatory action)

- Change and limit the approved dosing regimen to once weekly as a single dose (not divided doses 12 hours apart or twice weekly), if appropriate.
- Encourage manufacturers to package oral methotrexate for nononcologic use in patient dose packs that direct consumers to the correct weekly dosing.
- Require prominent warnings on the packaging of oral methotrexate for nononcologic use about weekly administration, as is done in other countries (**Figure 1**).

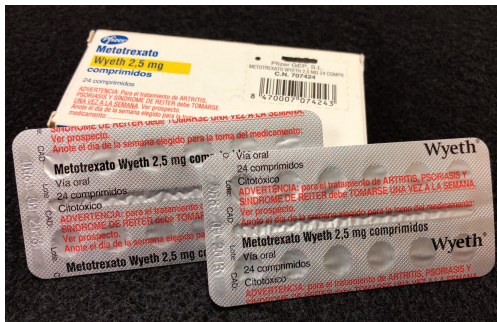


Figure 1. In Spain, blister packs of oral methotrexate limit the quantity of tablets available to patients. The outer carton and blister packs include the nononcologic indications and a specific warning that the dose is once a week for these approved indications (red text).

References

- 1) Harrison A, Jones P. Safer prescribing of high-risk medicines – methotrexate: potentially fatal in overdose. Best Practice Advocacy Centre New Zealand. *Best Practice Journal*. 2014;64:48-52. www.ismp.org/ext/72
- 2) Howard SC, McCormick J, Pui C, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. *Oncologist*. 2016;21(12):1471-82.
- 3) Bidakil R, Kian M, Owliaey H, Babaei Zarch M, Feysal M. Accidental chronic poisoning with methotrexate; report of two cases. *Emergency*. 2017;5(1):e67.

Special **Announcements**

Free webinar on global medication safety issues

Join ISMP on **September 26** for a **FREE** webinar, *Working Together to Address Global Drug Safety Issues with Packaging and Labeling*. Speakers will discuss drug product issues that contribute to medication errors around the world, and successful changes that some countries have made to reduce the risk of errors. Highlights from a recent international summit held by global regulators and the International Medication Safety Network (IMSN) will be presented. Practitioners outside the US are encouraged to attend. For details, visit: www.ismp.org/node/1113.

Revised ADC guidelines open for public comment

ISMP is seeking public comment from clinicians, vendors, regulators, and professional organizations on its revised *Guidelines for the Safe Use of Automated Dispensing Cabinets (ADCs)* through **August 31, 2018**. The guidelines, originally published in 2009, have been updated to reflect current safe ADC practices. To submit your comments, visit: www.ismp.org/node/1107.

Survey on IV push medications

If you are a practitioner who administers intravenous (IV) push medications to ADULTS, please take our survey on IV push medication practices by **August 31** by visiting: www.ismp.org/ext/49.

Accepting Cheers Awards nominations

Nominations for this year's **Cheers Awards** will be accepted through **September 7, 2018**. Outside and self-nominations are accepted. The awards spotlight efforts to improve medication safety from all health-care disciplines. To submit a nomination, visit: www.ismp.org/cheers-awards.

New ISMP white paper helps support the role of the medication safety officer

A recently released ISMP white paper, *The Case for Medication Safety Officers (MSO)*, stresses the need for an MSO to be included as an integral part of the healthcare team. The white paper provides detailed information for hospital leadership on the value of creating a dedicated position directly responsible for and empowered to lead medication safety strategy and implementation initiatives. It also describes key roles MSOs can play in optimizing safety, and comparable positions in other safety industries that can serve as models. The white paper can be downloaded at: www.ismp.org/node/1132.

If you would like to subscribe to this newsletter, visit: www.ismp.org/node/10



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