



IMSN INTERNATIONAL
MEDICATION
SAFETY NETWORK

Global Targeted Medication Safety Best Practices

**Best practices to inspire and mobilize international adoption
of consensus-based risk-reduction strategies to prevent
fatal or harmful medication errors associated with:**

- **Potassium concentrate injection**
- **Vinca alkaloids**
- **Oral methotrexate for non-oncologic use**

IMSN Global Targeted Medication Safety Best Practices

Establishing Effective Medication Risk-Reduction Strategies Everywhere Around the World

Specific medication safety issues are well known to cause harmful and fatal errors in patients despite knowledge of repeated occurrence and warnings. These deadly events have the following common characteristics:¹

- They are recurring, likely to happen to another patient if not addressed
- They are identifiable, easily recognized, clearly defined, and attributable to known causes
- They are avoidable by appropriate practices, measures, and organizational barriers

Preventing these deadly events is possible by the implementation of risk-reduction strategies that reduce or eliminate the possibility of errors, make errors visible, and minimize their consequences.² The primary goal is to redesign the medication management process to make it harder for errors to reach the patient. The fact that such deadly adverse events can be prevented by using specific measures and organizational checks and balances has led numerous facilities to call them “never events.” In this expression, “never event” is a clear call-to-action, rather than an expectation of perfect performance or an attempt to blame if such an event happens. For this call-to-action, the **International Medication Safety Network (IMSN)** has identified three risk-reduction strategies, herein called the **Global Targeted Medication Safety Best Practices**, to inspire and mobilize widespread, international adoption of consensus-based best practices for specific medication safety issues that continue to lead to harmful and deadly medication errors.

2

International Medication Safety Network (IMSN)

The International Medication Safety Network (IMSN) is an international network of safe medication practice centers established with the aim of improving patient safety. This is achieved by operating medication error reporting programs and producing guidance to minimize preventable harms from medication use in practice. IMSN promotes the international exchange of good-quality information concerning safe medication practices to improve patient safety globally.

For more information, visit: <https://www.intmedsafe.net/>.

The First Three IMSN Global Targeted Medication Safety Best Practices

The first three IMSN **Global Targeted Medication Safety Best Practices** are:

- **Best Practice 1:**
Remove potassium concentrate injection from drug storage areas on all inpatient nursing units/wards
- **Best Practice 2:**
Prepare and dispense vinca alkaloids in a minibag, never in a syringe
- **Best Practice 3:**
Prevent inadvertent daily dosing of oral methotrexate for non-oncologic conditions

continued on page 3 ►

Establishing Effective Medication Risk-Reduction Strategies – continued from page 2

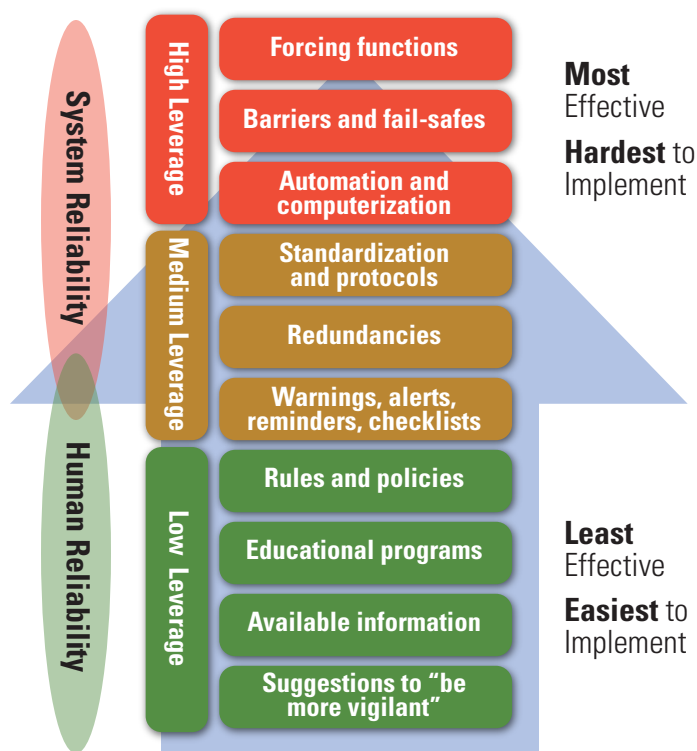
Focusing on these three high-alert medications—**potassium concentrate injection, vinca alkaloids, and oral methotrexate used in non-oncologic conditions**—is emblematic of the changes in systems and practices that should be undertaken as a priority around the world. High-alert medications bear a heightened risk of causing patient harm when used in error.

While **Best Practices 1 and 2** target the acute care setting, serious adverse events with potassium concentrate injection and vinca alkaloids have occurred in other settings, such as ambulatory practices and ambulatory procedure areas. **Best Practice 3**, associated with oral methotrexate, applies to all settings, including long-term care and home care.

These **Global Targeted Medication Safety Best Practices** have been reviewed and endorsed by experts from IMSN, an association of medication safety organizations, pharmacovigilance centers, regulatory agencies, and medication safety experts. They have already been successfully adopted by numerous organizations.³ For example, in the United States, the Institute for Safe Medication Practices (ISMP) has documented a steady progression between 2014 and 2017 of implementation of the **Targeted Medication Safety Best Practices for Hospitals** associated with two of the three targeted high-alert medications, vinca alkaloids and oral methotrexate (www.ismp.org/ext/224).

Risk-Reduction Strategies for Preventing Deadly Medication Errors

Selecting the best risk-reduction strategy is not easy.⁴ As illustrated below, risk-reduction strategies tend to focus on system design, which are often most effective, and/or human factors principles,⁴⁻⁷ which are less effective than system design strategies.



© 2019 Institute for Safe Medication Practices (ISMP)

continued on page 4 ►

Establishing Effective Medication Risk-Reduction Strategies – continued from page 3

- High-leverage strategies that focus on the system and ‘design out’ hazards are most effective because they can eliminate the risk of errors and associated harm. They do not rely heavily on individual human attention and vigilance. Such strategies include forcing functions, barriers and fail-safes, constraints, and automation and computerization. These strategies may involve complex implementation plans because they often require system redesign.
- Medium-leverage strategies do not eliminate hazards but reduce the likelihood of errors or minimize harm. They are relatively easy to implement but may need periodic updating and reinforcement to maintain knowledge and the currency of the process or product. These strategies are highly dependent on the behavior of people using the system. They include standardization; redundancies (e.g., independent double checks); reminders and checklists; warnings, alerts, and alarms; and patient counselling.
- Low-leverage strategies are often easy and quick to implement but need constant updating and reinforcement to maintain knowledge and currency. They aim to improve human performance and are more effective when combined with other medium- or high-leverage strategies. Low-leverage strategies include rules, policies, procedures, guidelines, protocols, education and training, and information documents. Suggestions to “be more vigilant” have little value in reducing the risk of errors.

Acknowledgments and Disclosures

All reviewers were volunteers and received no compensation for their contribution to this work. IMSN is grateful for these volunteers and acknowledges their expertise and assistance in reviewing these **Global Targeted Medication Safety Best Practices**.

- William Allan, Medication Safety Specialist, Health Quality and Safety Commission, New Zealand
- Michael Cohen, Chair of IMSN, President, Institute for Safe Medication Practices (ISMP), United States
- Helen Dowling, Pharmacist Advisor, eHealth and Medication Safety, Australian Commission on Safety and Quality in Health Care (ACSQHC)
- BarbraKaryne Nchinda Fobi, International Medication Safety Fellow, ISMP, United States
- Michael Hamilton, Physician Lead and Medication Safety Specialist, Institute for Safe Medication Practices Canada (ISMP Canada)
- Ciara Kirke, Health Service Executive Quality Improvement Division, Ireland
- Pia Knudsen, Senior Patient Safety Officer, Danish Patient Safety Authority
- Ursula Köberle, Pharmacovigilance Analyst, Drug Commission of the German Medical Association
- Christina Michalek, Medication Safety Specialist, ISMP, United States
- Maria Jose Otéro Lopez, President, ISMP Spain
- Gregory A. Poff, Chairman, Saudi Medication Safety Center, Saudi Food and Drug Authority
- Stephen Routledge, Patient Safety Improvement Lead, Canadian Patient Safety Institute
- Étienne Schmitt, Head of Programme Éviter l'Évitable (Preventing the Preventable), Prescrire, France
- Diana Shipp, Senior Project Manager, eHealth and Medication Safety, ACSQHC
- David U, General Secretary of IMSN, Medication Safety Advisor, ISMP Canada

References

- 1) The Canadian Patient Safety Institute (CPSI). Never events for hospital care in Canada—safer care for patients. September 2015. www.ismp.org/ext/219
- 2) Cohen MR, Smetzer JL, Tuohy NR, Kilo CM. High-alert medications: safeguarding against errors. In: Cohen MR, ed. *Medication Errors*. 2nd ed. Washington, DC: American Pharmaceutical Association; 2007;317-411.
- 3) ISMP. 2018-2019 Targeted Medication Safety Best Practices for Hospitals. www.ismp.org/node/160
- 4) Institute for Safe Medication Practices (ISMP). Medication error prevention “toolbox”. *ISMP Medication Safety Alert!* 1999;4(11):1.
- 5) ISMP. Your high-alert medication list—relatively useless without associated risk-reduction strategies. *ISMP Medication Safety Alert!* 2013;18(8):1-5.
- 6) Institute for Safe Medication Practices Canada (ISMP Canada). Designing effective recommendations. *Ontario Critical Incident Learning: Improving Quality in Patient Safety*. 2013;(4):1-2. www.ismp.org/ext/220
- 7) Health Quality & Safety Commission New Zealand. Error prevention strategies. *Medication Safety Watch*. 2015;(13):1-3.

continued on page 5 ►

Global Targeted Medication Safety Best Practice 1

Remove potassium concentrate injection from drug storage areas on all inpatient nursing units/wards.

Background

Potassium is an electrolyte replenisher required for the maintenance of several physiological processes in the body.¹ Frequently used to treat hypokalemia and other electrolyte abnormalities, intravenous (IV) potassium is available in vials or ampules as a concentrate for dilution.¹ Improper administration of concentrated electrolytes is dangerous.² Tragic errors have occurred due to rapid IV administration of concentrated potassium solutions or wrong product selection (potassium concentrate mistaken for another drug).³ Vials or ampules of potassium have also been accidentally used instead of sterile water or normal saline (0.9% sodium chloride) to dilute vials of powdered or lyophilized drugs. Outcomes have often been fatal in children and adults, and errors still occur worldwide to this day.

As a consequence, many organizations in countries such as Australia, Brasil, Canada, Denmark, New Zealand, Northern Ireland, Spain, United Kingdom, and United States have added concentrated potassium injections to their list of high-alert medications²⁻⁷ and have implemented risk-reduction strategies to prevent errors and mitigate patient harm.

Goal

The goal of this best practice is to prevent fatalities involving the inadvertent injection of concentrated potassium on nursing units/wards (most often potassium chloride, potassium acetate, and potassium phosphate injections).

Best Practice Description

IMSN strongly advocates for the elimination of potassium concentrate injection on nursing units/wards in favor of using premixed or pharmacy-prepared solutions containing potassium.

- a) Remove potassium concentrate injections from all inpatient drug storage on nursing units/wards.⁷
- b) Purchase and use premixed potassium solutions (already diluted in typical strengths for IV potassium replacement).^{2,3,5,6}
- c) Wherever possible, standardize potassium solution concentrations to eliminate the need for preparing potassium solutions that are not premixed or pharmacy-prepared.
- d) When necessary, prepare potassium solutions in the pharmacy for distribution internally within each hospital.
- e) In scenarios where premixed solutions are not commercially-available, when a pharmacist and pharmacy preparation area is not available to prepare these solutions, or when 24-hour pharmacy service is unavailable:
 - ☐ Potassium concentrate vials or ampules should not be stored on nursing units/wards but instead be stored centrally, outside the pharmacy, in a locked cabinet.
 - ☐ Potassium concentrate vials or ampules should be placed in a clear plastic bag with warning stickers and instructions for dilution.
 - ☐ Only qualified and trained individuals (e.g., physician, nurse) should have access to these vials or ampules to prepare potassium solutions.^{3,7}
- f) Segregate and label storage locations of concentrated potassium injections in pharmacy preparation areas.^{3,6,7}



Remove Potassium Concentrate Injection from Drug Storage Areas on All Inpatient Units/Wards – continued from page 5

Rationale

Removal of concentrated potassium injection products from all patient care areas is a high-leverage, key safeguard. This strategy becomes an even more effective intervention when unit dose drug distribution systems are established as a standard of practice in inpatient settings, and when the pharmacy provides IV admixture services.⁷ This potent constraint has been supported by the World Health Organization (WHO), Joint Commission International, United Kingdom, Australia, The Joint Commission, ISMP, ISMP Brasil, ISMP Canada, ISMP-España, and others.^{2,7-12} The successful implementation of this best practice has avoided fatal errors;¹³ however, ongoing access to concentrated potassium injection in nursing units/wards risks human lives and continues to result in fatalities from the direct injection of this product. In the United States, The Joint Commission does not permit potassium concentrate injection storage (including potassium chloride, potassium phosphate, and potassium acetate) in patient care areas.¹³

Providing premixed potassium solutions in standard concentrations is an additional high-leverage risk-reduction strategy. However, limiting storage of the concentrated potassium injection outside of the pharmacy but allowing exemptions in certain areas such as critical care and pediatrics provides less protection from errors than removing the product from all nursing units/wards.

Improving Availability of Premixed Potassium Solutions

In North America and in some other parts of the world, the pharmaceutical industry provides commercially premixed potassium solutions in multiple concentrations and base solutions. Along with pharmacy IV admixture services, this enables complete removal of potassium concentrates from nursing units/wards. However, these premixed solutions are not available in many countries globally, making it difficult to comply with a ready-to-use, ready-to-administer approach. Unnecessary deaths from direct injection of concentrated potassium will continue to occur until the pharmaceutical industry makes these premixed solutions available everywhere, at minimal expense. IMSN urges the global pharmaceutical industry to make premixed potassium solutions available everywhere as soon as possible.

References

- 1) Potassium chloride, potassium acetate, potassium phosphate. Mechanism of action. In: *Micromedex*. Greenwood Village, CO: Truven Health Analytics. Accessed December 15, 2018, from: <http://www.micromedexsolutions.com/>.
- 2) World Health Organization (WHO), The Joint Commission (TJC), Joint Commission International (JCI). Control of concentrated electrolyte solutions. *Patient Safety Solutions*. 2007;1(5):1-3. www.ismp.org/ext/240
- 3) Grissinger M. Potassium chloride injection still poses threats to patients. *PT*. 2011;36(5):241-302.
- 4) Danish Patient Safety Authority. Health professionals and authorities. Risk situation drugs. November 13, 2018. www.ismp.org/ext/241
- 5) Australian Council for Safety and Quality in Health Care. Intravenous potassium chloride can be fatal if given inappropriately. *Safety & Quality Council Medication Alert*. 2003;Alert 1:1-3. www.ismp.org/ext/243
- 6) New Zealand Medicines and Medical Devices Safety Authority. Medication alert. Concentrated potassium chloride injection can be fatal if incorrectly administered! *Quality and Safe Use of Medicines*. July 2008. www.ismp.org/ext/244
- 7) Cohen MR, Smetzer JL, Tuohy NR, Kilo CM. High-alert medications: safeguarding against errors. In: Cohen MR, ed. *Medication Errors*. 2nd ed. Washington, DC: American Pharmaceutical Association; 2007;317-411.
- 8) National Health Services (NHS) National Patient Safety Agency (NPSA). Patient Safety Alert (PSA 01). July 23, 2002. NPSA London. www.ismp.org/ext/242
- 9) Institute for Safe Medication Practices Canada (ISMP Canada). Concentrated potassium chloride: a recurring danger. *ISMP Canada Safety Bulletin*. 2004;4(3):1-2.
- 10) Reeve JF, Allinson YM. High-risk medication alert: intravenous potassium chloride. *Austr Prescr*. 2005;28(1):14-16.
- 11) Ministerio de Sanidad y Consumo. Recomendaciones para el uso seguro del potasio Intravenoso. Madrid, Ministerio de Sanidad y Consumo. 2019. <https://www.seguridadelpaciente.es/formacion/tutoriales/MS-C-CD4/>
- 12) Lankshear AJ, Sheldon TA, Lowson KV, Watt IS, Wright J. Evaluation of the implementation of the alert issued by the UK National Patient Safety Agency on the storage and handling of potassium chloride concentrate solution. *Qual Saf Health Care*. 2005;14(3):196-201.
- 13) The Joint Commission. Medication error prevention—potassium chloride. *Sentinel Event Alert*. 1998;(1):1-2.

Global Targeted Medication Safety Best Practice 2

Prepare and dispense vinca alkaloids in a minibag, never in a syringe.

Background

Vinca alkaloids (vin**BLAS**tine, vinorelbine, vin**CRIS**tine) are chemotherapy drugs that should only be administered intravenously (IV) and never by any other route.¹ Deaths have been reported throughout the world when a vinca alkaloid was dispensed in a syringe but administered into the spinal fluid instead of IV.

The inadvertent intrathecal administration of vinca alkaloids leads to the destruction of the central nervous system radiating from the injection site. Most of the time, the outcome is fatal. Even for the few who might survive with immediate spinal fluid washout, devastating neurological damage will likely occur.² Vin**CRIS**tine is particularly problematic and the most frequently reported vinca alkaloid associated with inadvertent intrathecal administration, because it is often ordered in conjunction with medications that are administered intrathecally (e.g., methotrexate, cytarabine, and/or hydrocortisone).²

The WHO indicated that, between 1968 and 2007, inadvertent intrathecal administration of vin**CRIS**tine has been reported 55 times in a variety of international settings.³ More recently, ISMP reported 135 fatalities worldwide due to inadvertent intrathecal administration of vin**CRIS**tine, all dispensed in a syringe.⁴ Despite warnings (“For Intravenous Use Only—Fatal If Given by Other Routes”) and extensive labeling requirements in some countries, inadvertent intrathecal administration of vin**CRIS**tine still occurs today.^{2,3}

Goal

The goal of this best practice is to ensure that vin**CRIS**tine and other vinca alkaloids (vin**BLAS**tine, vinorelbine) are only administered by the IV route.

Best Practice Description

IMSN strongly advocates the dilution of vinca alkaloids in a minibag containing a volume too large for intrathecal administration (e.g., 25 mL for pediatric patients and 50 mL for adults), instead of preparation and administration in a syringe.

Rationale

Administration via minibag serves as a strong forcing function to prevent inadvertent intrathecal administration. A minibag is also less likely to be confused with other drugs in syringes intended for intrathecal use. There have been no reported cases of inadvertent intrathecal administration of a vinca alkaloid when dispensed in a minibag.² Although patient safety might be improved by the use of neuraxial connectors, such devices are not readily available throughout the world and have not been tested as a preventive measure against the inadvertent intrathecal administration of vinca alkaloids.

Globally, many organizations have switched to preparing vinca alkaloids in minibags, overcoming concerns about extravasation⁴⁻⁷ and other complications.² However, some organizations still administer vin**CRIS**tine via syringe,¹ risking inadvertent intrathecal administration. For example, results from the *2012 International Medication Safety Self Assessment® for Oncology* indicated that 39% of participants still prepare and administer vin**CRIS**tine in syringes,⁸ and more recent surveys in the United States (2017) and Shanghai (2015) indicate that approximately 20% of participants still prepare and administer vin**CRIS**tine and/or other vinca alkaloids in syringes.^{9,10}

continued on page 8 ►



Prepare and Dispense Vinca Alkaloids in a Minibag, Never in a Syringe – continued from page 7

Indisputably, the best practice to alleviate the risk of inadvertent intrathecal administration is to globally adopt the preparation and administration of vinca alkaloids in minibags. This is fully supported by the WHO;³ in the United States by The Joint Commission,¹ ISMP,² Oncology Nurses Society,¹¹ and National Comprehensive Cancer Network;¹² and in other countries by the UK National Health Service (NHS),¹³ ISMP Canada,¹⁴ Australia Commission on Safety and Quality in Health Care,¹⁵ French Medicines Agency,¹⁶ ISMP-España,¹⁷ ISMP Brasil, and others.

References

- 1) The Joint Commission. Eliminating vincristine administration events. *Quick Safety*. 2017;(37):1-3. www.ismp.org/ext/231
- 2) Institute for Safe Medication Practices (ISMP). 2018-2019 targeted medication safety best practices for hospitals. Best practice 1. December 12, 2017. www.ismp.org/node/160
- 3) World Health Organization (WHO). Vincristine (and other vinca alkaloids) should only be given intravenously via a minibag. Information Exchange System, Alert No. 115. July 18, 2007. www.ismp.org/ext/232
- 4) ISMP. ISMP calls on FDA-No more syringes for vinca alkaloids! *ISMP Medication Safety Alert!* 2019;24(5):1-2.
- 5) Gilbar P, Chambers CR, Larizza M. Medication safety and the administration of intravenous vincristine: international survey of oncology pharmacists. *J Oncol Pharm Pract*. 2015;21(1):10-8.
- 6) Gilbar PJ, Carrington CV. The incidence of extravasation of vinca alkaloids supplied in syringes or mini-bags. *J Oncol Pharm Pract*. 2006;12(2):113-8.
- 7) Nurgat ZA, Smythe M, Al-Jedai A, et al. Introduction of vincristine mini-bags and an assessment of the subsequent risk of extravasation. *J Oncol Pharm Pract*. 2015;21(5):339-47.
- 8) Greenall J, Shastay A, Vaida A, et al. Establishing an international baseline for medication safety in oncology: Findings from the 2012 ISMP international medication safety self assessment for oncology. *J Oncol Pharm Pract*. 2015;21(1):26-35.
- 9) ISMP. 2016-2017 targeted medication safety best practices for hospitals survey results. Best practice 1. July 2017. www.ismp.org/ext/69
- 10) Yan M, Shen C, Zhang L, Ying Y, Sun P, Jiao Z. Vincristine drug safety administration survey: results from hospitals in Shanghai, China. *Eur J Hosp Pharm*. 2015;22(5):255-9.
- 11) Prischel C. New recommendations call for bagged vinca alkaloids. *ONS Voice*. November 16, 2016. www.ismp.org/ext/234
- 12) National Comprehensive Cancer Network (NCCN). Just bag it! NCCN campaign for safe vincristine handling. November 10, 2016. <https://www.nccn.org/JustBagIt/>
- 13) National Health Services (NHS) National Patient Safety Agency (NPSA). Using vinca alkaloid minibags (adult/adolescent units). *Rapid Response Report - NPSA/2008/RRR04*. August 11, 2008. www.ismp.org/ext/235
- 14) Institute for Safe Medication Practices Canada (ISMP Canada). Published data supports dispensing vincristine in minibags as a system safeguard. *ISMP Canada Safety Bulletin*. October 3, 2001. www.ismp.org/ext/233
- 15) Australia Council for Safety and Quality in Health Care. Vincristine can be fatal if administered by the intrathecal route. *Safety & Quality Council Medication Alert*. 2005;Alert 2:1-4. www.ismp.org/ext/236
- 16) Agence française de sécurité sanitaire des produits de santé (Afssaps). Recommandations destinées à prévenir les risques d'erreur d'administration intrathécale de vinca-alcaloïdes. May 2007. www.ismp.org/ext/238
- 17) ISMP-España, Grupo Español para el Desarrollo de la Farmacia Oncológica (GEDEFO). Alerta especial. Errores asociados a la administración de vincristina. Alerta Especial ISMP-España Y Gedefo. Julio 5, 2006. www.ismp.org/ext/239

Global Targeted Medication Safety Best Practice 3

Prevent inadvertent daily dosing of oral methotrexate for non-oncologic conditions.

Background

Methotrexate is a folate antimetabolite used in the treatment of neoplastic diseases and non-oncological conditions such as psoriasis, rheumatoid arthritis, and other conditions. When used to treat disorders such as psoriasis and rheumatoid arthritis, low doses are administered weekly by the oral route. However, for some cancer types, a more frequent or higher dose is used.¹ At high doses, oral methotrexate is known to be associated with serious and sometimes fatal blood dyscrasias, but similar adverse outcomes have been associated with the use of low-dose oral methotrexate when given daily.

Prescribing, transcribing, dispensing, and administration errors (including self-administration by patients) have led to daily instead of weekly dosing of oral methotrexate for non-oncological indications. Fatal dosing errors with oral methotrexate have been reported since early 1996, occurring both during hospitalization and after discharge.²⁻⁷

Goal

The goal of this best practice is to prevent errors involving inadvertent daily dosing instead of weekly dosing of oral methotrexate for non-oncologic conditions in the ambulatory and inpatient setting.

Best Practice Description

IMSN strongly recommends the following risk-reduction strategies to prevent inadvertent daily dosing of oral methotrexate for non-oncologic conditions:

- a) Prescribe, dispense, and administer oral methotrexate **ONCE WEEKLY** and specify the day of the week.
- b) Enter a weekly dosage regimen for oral methotrexate as a default into electronic systems to prevent the accidental prescribing or dispensing of the medication for more than once-a-week administration.
- c) Require an electronic hard stop verification of an appropriate oncologic indication for all daily oral methotrexate orders.
 - ☐ Require a pharmacist to consult prescribers for any oral methotrexate prescription indicating more than once per week dosing. The prescriber should specify the indication on the medication chart or prescription, which would alert nurses and pharmacists to any potential prescribing errors.
 - ☐ For manual systems and electronic order entry systems that cannot provide a hard stop, clarify all daily orders for methotrexate if the patient does not have an appropriate, documented oncologic diagnosis.
 - ☐ Where available (acute care or corporate pharmacies using information technology), work with information technology departments and software vendors to ensure that this hard stop is available. Order entry systems should be capable of this hard stop, as it is an important patient safety component of these systems.
- d) In the hospital setting, remove methotrexate from nursing units/ward stock and “after hours” cupboards.
- e) Dispense only the needed doses in safety packaging such as a dose pack, patient pack, or calendar pack.
 - ☐ For outpatients, dispense a maximum of 1 month’s supply.
 - ☐ Always verify the patient’s dose by comparing the dose and number of tablets dispensed. Many dosing errors occur during transitions of care where the patient administers or is inadvertently given the wrong number of tablets per dose.

Prevent Inadvertent Daily Dosing of Oral Methotrexate for Non-Oncologic Conditions – continued from page 9

- f) Provide specific patient and/or family/caregiver education for all oral methotrexate orders or new prescriptions.
 - ☐ Double check all printed medication lists and patient education materials to ensure they indicate the correct dosage regimen for oral methotrexate prior to providing the medication to the patient.
 - ☐ Ensure that the process for providing patient education includes clear written AND verbal instructions to specifically review the dosing schedule, emphasize the danger in taking extra doses, and specify that the medication should never 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 consumer leaflets on oral methotrexate (e.g., free ISMP high-alert medication consumer leaflet on oral methotrexate can be found at: www.ismp.org/ext/221).
- g) Educate clinical staff on the safe and appropriate use of methotrexate.
 - ☐ Clinical staff involved in patient care should be able to recognize potential signs and symptoms of toxicity or intolerance of methotrexate.
 - ☐ Prescribers should order full blood counts until the patient is stabilized and every 2-3 months throughout therapy. Other laboratory tests are also necessary when monitoring patients who receive methotrexate.

Rationale

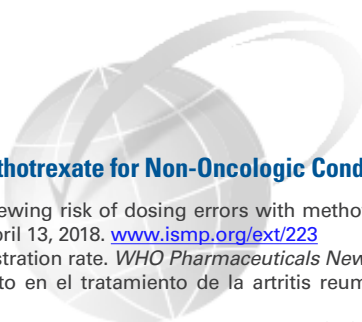
These selected risk-reduction strategies include constraints that can help avoid daily dosing of oral methotrexate, such as limiting the availability of methotrexate tablets by restricting quantities (e.g., dispensing blister forms as a weekly or monthly dose pack, dispensing only one dose at a time, removing methotrexate from nursing units/ward stock). The risk-reduction strategies also include high-leverage forcing functions and computerization, such as setting the default to a weekly dosage regimen for oral methotrexate in electronic systems and electronic hard-stop verification of the indication and posology of the medication. These key improvements must be accompanied by staff education, patient education and counselling, and warnings and reminders.^{2,8-16}

Improving Oral Methotrexate Packaging Safety

Some European Union countries (e.g., Denmark, Spain, France) and Canada have added a visual warning on oral methotrexate medication package labels about weekly dosing of this drug (e.g., “Check dose and frequency—methotrexate is usually taken once a week”).^{4,6,17,18} The European Medicines Agency (EMA) is currently reviewing the risk of methotrexate dosing errors to determine required changes. Many medication safety organizations, including ISMP, ISMP-España, IMSN, Prescrire, and New Zealand’s Health Quality and Safety Commission, also recommend packaging oral methotrexate in blister forms as a weekly or monthly dose pack (or calendar packs) to help prevent inadvertent daily dosing.^{4,10-15} As a result, an international safety standard for safe labeling and packaging of non-oncologic oral methotrexate is currently part of an in-progress White Paper sponsored by the IMSN and the United States Food and Drug Administration (FDA) to prevent daily use and overdose.

References

- 1) World Health Organization (WHO). Methotrexate (low-dose) - blood dyscrasias and other adverse reactions: United Kingdom. *WHO Pharmaceuticals Newsletter*. 1997;11&12: www.ismp.org/ext/222
- 2) Institute for Safe Medication Practices (ISMP). Beware of erroneous daily oral methotrexate dosing. *ISMP Medication Safety Alert!* 2002;7(7):1-2.
- 3) Prescrire. Weekly methotrexate: still more deaths in France in 2011. *Prescrire Int*. 2012;21(123):15.
- 4) Prescrire. Weekly oral methotrexate therapy: raise awareness of fatal dosing errors. *Prescrire Int*. 2013;22(138):126.
- 5) ISMP. 2018-2019 targeted medication safety best practices for hospitals. Best practice 1. December 12, 2017. Available at: www.ismp.org/node/160



Prevent Inadvertent Daily Dosing of Oral Methotrexate for Non-Oncologic Conditions – continued from page 10

- 6) European Medicines Agency (EMA). EMA reviewing risk of dosing errors with methotrexate. Review prompted by continued reports of overdose [press release]. London, UK: EMA. April 13, 2018. www.ismp.org/ext/223
- 7) Attalla M. Methotrexate–Incorrect drug administration rate. *WHO Pharmaceuticals Newsletter*. 2019;(1):18.
- 8) ISMP-España. Errores asociados al metotrexato en el tratamiento de la artritis reumatoide. *Alerta Especial ISMP-España*. Junio 2003. www.ismp.org/ext/225
- 9) Prescrire. Oral methotrexate: preventing avoidable overdose. *Prescrire Int*. 2007;16(90):150-2.
- 10) Irish Medication Safety Network (IMSN). Oral methotrexate. *Safety Alert*. May 2010. www.ismp.org/ext/226
- 11) International Medication Safety Network (IMSN). Position statement: making medicines naming, labeling and packaging safer. October 2013;1-11.
- 12) Pharmaceutical Society of Ireland. Guidance for pharmacists on safe supply of oral methotrexate. Version 2. January 2015. www.ismp.org/ext/227
- 13) ISMP. Simple packaging change could help reduce drug diversion. *ISMP Medication Safety Alert!* 2016;21(7):4.
- 14) Health Quality & Safety Commission New Zealand. Reducing the risk of error and patient harm with low-dose oral methotrexate. *Medication Safety Watch*. 2016;(17):1-2.
- 15) Prescrire. Methotrexate: room for improvement in packaging and patient information. May 29, 2018. www.ismp.org/ext/228
- 16) Ministry of Health, New South Wales (NSW). Policy directive: high-risk medicines management policy. August 12, 2015. www.ismp.org/ext/230
- 17) Health Canada. Good label and package practice guide for prescription drugs. June 30, 2016. www.ismp.org/ext/229
- 18) Danish Medicines Agency. Latest news about medicines safety and medical devices. 2018;3(2):8.