

MEDICATION SAFETY IN SECONDS

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use

VINCRIStINE: WRONG ROUTE OF ADMINISTRATION ERRORS AND FATAL OR DEVASTATING NEUROLOGIC OUTCOMES

The Institute for Safe Medication Practices (ISMP) addressed the risk of death and serious neurological effects associated with the inadvertent intrathecal administration of vincristine or another vinca alkaloid instead of intravenously. Since 1968, published literature documents 17 cases in the United States (US) and 49 cases abroad, most with fatal outcomes or neurological devastation in the few survivors (i.e., persistent vegetative state and quadriplegia). Further, reports from the Food and Drug Administration (FDA) MedWatch, legal claims, non-US regulatory agencies, media, and personal communications account for 120 events worldwide, with 44 occurring in the US or

Canada. Each of these wrong route vincristine errors share one thing in common: the preparation and administration of the vinca alkaloid in a syringe. Other factors have also contributed to the incorrect route of administration, including inability to differentiate intravenous vincristine from another intrathecal medication (i.e., methotrexate, cytarabine, or hydrocortisone); error in labeling of syringes; simultaneous presence of both intravenous and intrathecal medications in a treatment area; administration of vinca alkaloids in a non-oncology unit without experienced staff; chemotherapy administration beyond normal hours; lack of drug verification prior to intrathecal administration;

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VA PHARMACY BENEFITS MANAGEMENT SERVICES (PBM)

PBM maintains VA's national drug formulary, as well as promotes, optimizes, and assists VA practitioners with the safe and appropriate use of all medications.

VA CENTER FOR MEDICATION SAFETY (VA MedSAFE)

VA MedSAFE performs pharmacovigilance activities; tracks adverse drug events (ADEs) using spontaneous and integrated databases; enhances education and communication of ADEs to the field; and promotes medication safety on a national level.

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NEWSWORTHY... from the pbm

- Abbott FreeStyle Glucose Test Strips Recall - 11/29/2013 - [National PBM Communication](#)
- Regadenoson (Lexiscan) and Adenosine (Adenoscan): Risk of Heart Attack and Death - 11/29/2013 - [National PBM Bulletin](#)
- Imitrex STATdose System and Sumatriptan Succinate Injection Refill 6mg Recall - 11/22/2013 - [National PBM Communication](#)
- LMWHs and Increased Risk of Spinal Column Bleeding and Paralysis - 11/15/2013 - [National PBM Bulletin](#)
- Tigecycline (Tygacil) and Increased Risk of Death - 10/01/2013 - [National PBM Bulletin](#)

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from the fda

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ENDOCRINOLOGY

[FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines](#)

11/25/2013

Previous meta-analyses associate rosiglitazone treatment with an increased risk of adverse cardiovascular events, including heart attack. However, limitations in the data prompted the FDA to order a re-evaluation of results from a large, long-term clinical trial conducted after market approval of rosiglitazone, entitled **Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD)**, which looked at the cardiovascular safety of rosiglitazone monotherapy compared with rosiglitazone used in combination with metformin and sulfunylurea. The readjudicated results suggested that rosiglitazone does not show a statistically significant increase in risk of heart attack compared to standard-of-care drugs metformin and sulfonylurea. Based on this data, FDA is requiring modifications to the rosiglitazone Risk Evaluation and Mitigation Strategy (REMS) program to remove both the requirements for restricted distribution and enrollment to be able to prescribe, dispense, or receive rosiglitazone medicines.

CARDIOLOGY

[FDA warns of rare but serious risk of heart attack and death with cardiac nuclear stress test drugs Lexiscan \(regadenoson\) and Adenoscan \(adenosine\)](#)

11/20/2013

Previous product labeling for regadenoson (Lexiscan) and adenosine (Adenoscan) already documents the known risk of heart attack and death with use of these drugs. However, accounts of myocardial infarction (MI) and death associated with regadenoson (Lexiscan) and adenosine (Adenoscan) continue to be reported in the FDA Adverse Event Reporting System (FAERS) database as well as in the medical literature. As such, FDA approved changes to the drug labels of these agents to reflect these serious events and updated recommendations for use, including:

- *Screen all nuclear stress test candidates for their suitability to receive regadenoson (Lexiscan) and adenosine (Adenoscan).*
- *Avoid using these drugs in patients with symptoms or signs of acute myocardial ischemia such as unstable angina or cardiovascular instability; these patients may be at greater risk of serious cardiovascular reactions to regadenoson (Lexiscan) and adenosine (Adenoscan).*
- *Cardiac resuscitation equipment and trained staff should be readily available before administering regadenoson (Lexiscan) and adenosine (Adenoscan).*

OVER-THE-COUNTER (OTC) MEDICATIONS

[FDA requests label changes and single-use packaging for over-the-counter topical antiseptic products to decrease risk of infection](#)

11/13/2013

Contamination of topical antiseptic products has led to infections ranging from localized events at the site of injection to systemic outbreaks and fatal outcomes as reported in the medical literature as well as submitted to the Centers for Disease Control (CDC) and the FDA. Impurities may originate during the manufacturing process or from the user when diluting the product with contaminated water, not using appropriate aseptic techniques during handling, or storing antiseptic solutions under non-sterile conditions. To minimize contamination of these products and risk of infection, FDA requests that manufacturers:

- Package antiseptics indicated for preoperative or preinjection skin preparation in single-use containers;
- Voluntarily revise the product labels for topical antiseptics to indicate whether the drug is manufactured as a sterile or nonsterile product.

FDA also recommends that health care professionals:

- Apply antiseptics in single-use containers only one time to one patient.
- Not dilute antiseptic products after opening them.
- Discard applicators and any unused solution after the single application.

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from the fda

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ANTICOAGULANTS

[Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on low molecular weight heparins](#)

11/6/2013

All anticoagulants may cause spinal bleeding when used in conjunction with epidural/spinal anesthesia or spinal puncture. Enoxaparin carries a known risk for epidural or spinal hematomas when used with spinal procedures as highlighted in the *Boxed Warning* and the *Warnings and Precautions* sections of current brand and generic product labeling. However, due to continued reports of these serious adverse events, FDA requires that manufacturers update the *Warnings and Precautions* section of the brand and generic enoxaparin product labels, as well as product information for other low molecular weight heparin (LMWH) products, with timing recommendations for anticoagulant dosing in the setting of catheter placement or removal in spinal anesthesia in order to reduce the risk. See [National PBM Bulletin](#) addressing LMWHs and Increased Risk of Spinal Column Bleeding and Paralysis for details.

NEUROLOGY

[FDA approves label changes for anti-seizure drug Potiga \(ezogabine\) describing risk of retinal abnormalities, potential vision loss, and skin discoloration](#)

10/31/2013 *** UPDATE FROM 04/26/2013***

FDA approved changes to the drug label of the anti-seizure drug ezogabine (Potiga) that highlights risks of potentially permanent abnormalities to the retina, vision loss, as well as discoloration of the skin, nail, mucous membrane, and sclera. FDA recommends that providers:

- Reserve use of ezogabine (Potiga) for patients that:
 - Demonstrate inadequate response to alternative anti-epileptic therapies and whose benefits outweigh risks.
 - Comply with eye exams before therapy and every six months during treatment (visual acuity and dilated fundus photography, with additional vision testing as necessary).
- Discontinue treatment if:
 - Retinal pigment abnormalities or vision changes occur, unless benefits outweigh the risk of vision loss.
 - Patients do not show substantial clinical benefit after adequate dose titration.
 - Skin discoloration develops (alternative agents should be considered).

Risk for retinal abnormalities, detection time, progression rate, or reversibility after discontinuation remain unknown.

ONCOLOGY

[FDA requires multiple new safety measures for leukemia drug Iclusig; company expected to resume marketing](#)

12/20/2013 UPDATED

Ponatinib (Iclusig) awaits re-marketing pending new safety measures required by the FDA, including a targeted indication for treatment of adult patients with:

- *T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).*
- *Chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.*

Other FDA stipulations consist of additional warnings on the risk of developing blood clots and vascular occlusion (approximately 1 out of every 4 patients treated); revised recommendations on dosage and administration (optimal dose not yet identified); an updated Medication Guide consistent with new safety information; requirement for a risk evaluation and mitigation strategy (REMS); and more postmarket investigations by the manufacturer to assess safety.

[FDA Drug Safety Communication: FDA asks manufacturer of the leukemia drug Iclusig \(ponatinib\) to suspend marketing and sales](#)

11/5/2013 UPDATED

FDA instructs providers of patients stabilized and benefitting from ponatinib (Iclusig) to continue as clinically appropriate under an emergency Investigational New Drug (IND) application. Treatment may continue as long as patients demonstrate optimal response and benefit. Providers should immediately discontinue and consider alternative agents in patients with an inadequate response. New patients should not initiate treatment with ponatinib (Iclusig) unless other treatment options do not exist or have resulted in suboptimal outcomes.

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...NEWSWORTHY

from the fda

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[FDA asks manufacturer of the leukemia drug Iclusig \(ponatinib\) to suspend marketing and sales](#)

10/31/2013

Due to an increased frequency of blood clots and narrowing of blood vessels since the drug was approved in December 2012, FDA has asked the manufacturer of the leukemia chemotherapy drug ponatinib (Iclusig) to suspend its marketing and sales while it continues to evaluate the drug and identify a dose level or exposure duration deemed safe. Approximately 24 percent of patients in the Phase 2 clinical trial (median treatment duration 1.3 years) and approximately 48 percent of patients in the Phase 1 clinical trial (median treatment duration 2.7 years) have experienced adverse events affecting the blood vessels that supply the heart, brain, and extremities. Serious adverse reactions involving the eyes (blindness or blurred vision) have also occurred in ponatinib (Iclusig)-treated patients. The increasing rate and pattern of events suggests a drug-related association. At this time, patients and health care professionals should follow FDA's new recommendations for the use of ponatinib (Iclusig):

- *Patients without a response should immediately stop treatment and discuss alternatives with their providers.*
- *Patients demonstrating a response and whose benefits outweigh the risks should continue treatment under a single-patient Investigational New Drug (IND) application or expanded access registry program while FDA's safety investigation continues. FDA and the manufacturer will coordinate this transition.*
- *Providers should not initiate treatment in new patients unless alternatives do not exist or have been exhausted with suboptimal outcomes. If clinically indicated, these patients can be considered for treatment under an IND or expanded access registry program. For details on how to obtain access under an IND, please visit: [Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use](#).*

[FDA investigating leukemia drug Iclusig \(ponatinib\) after increased reports of serious blood clots in arteries and veins](#)

10/11/2013

Clinical trials and postmarket reports show an increase in frequency in certain serious adverse events associated with use of the chemotherapy agent ponatinib (Iclusig): fatal heart attacks; coronary artery disease exacerbation; stroke; congestive heart failure (CHF); occlusion of large arteries of the brain as well as of blood vessels in the extremities resulting in urgent surgical procedures to restore blood flow; loss of blood flow to extremities leading to tissue death requiring amputation; decreased vision; and clots in blood vessels of the eye. These adverse events occurred in all age groups regardless of cardiovascular risk factors. At the time of approval in 2012, product information (*Boxed Warning* and *Warnings and Precautions* sections) previously warned of serious and life-threatening blood clots and severe narrowing of blood vessels (arteries and veins) in patients taking ponatinib (Iclusig). FDA recommends that patients seek medical attention for any signs/symptoms of heart attack or stroke as investigations continue.

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and missing or incomplete warning labels. Because of the continued risk of administering vincristine or another vinca alkaloid intrathecally instead of intravenously, the following actions have been recommended by ISMP, the Joint Commission, and the World Health Organization (WHO) to prevent tragic and frequently fatal outcomes from occurring:

- *“Dispense intravenous (IV) vincristine in a minibag of a compatible solution (e.g., 25 mL for pediatric patients and 50 mL for adults) and never dispense and/or administer the drug using a syringe.*
- *Prohibit IV vincristine in areas where intrathecal medications are administered and/or stored.*
- *Confirm that any prescribed intrathecal medications have been*

administered before dispensing IV vincristine.”

FDA has also approved revisions to the vincristine product label that reads: *“To reduce the potential for fatal medication errors due to incorrect route of administration, vincristine sulfate injection should be diluted in a flexible plastic container and prominently labeled as indicated for intravenous use only.”* However, although these recommendations have been promoted as early as 2001, results from the most recent ISMP oncology self-assessment survey suggest only partial compliance with these practices.

REFERENCE:

Institute for Safe Medication Practices. Death and neurological devastation from intrathecal vinca alkaloids: Prepared in syringes = 120; Prepared in minibags = 0. *ISMP Medication Safety Alert*. September 2013; 18(18):1-4.

Getting the most from our safety surveillance

MEDICATION USE EVALUATION (MUE) OF PHARMACOLOGICAL TREATMENT OF DEMENTIA

BACKGROUND/RATIONALE:

Cholinesterase inhibitors (Ch-I) are considered standard of care by many who care for patients with Alzheimer's disease (AD), dementia with Lewy bodies, Parkinson's disease dementia, and other forms of dementia. The VHA Pharmacy Benefits Management (PBM), VISN Pharmacist Executives (VPEs), and Medical Advisory Panel (MAP) have published Criteria for Use (CFU) guidance for Ch-I's and memantine to provide a standardized method for appropriate prescribing and monitoring of patients on these medications.² The appropriateness of prescribing and safety of these medications in relation to the CFU needed to be assessed in a large-scale evaluation across VA medical centers.

OBJECTIVES:

The purpose of this MUE was to collect information as a quality assurance and improvement (QA/QI) initiative to describe the current prescribing landscape of Ch-I's in relation to the VHA PBM Criteria for Use guidance.

The specific objectives for this MUE were:

- To describe current prescribing habits of the Ch-I in the management of dementia.
- To evaluate if current practice is in compliance with PBM CFU in relation to appropriateness of indication and monitoring of safety outcomes.
- To determine areas of improvement.

METHODS:

This was a retrospective cohort evaluation consisting of two parts: 1) a prescription database evaluation to identify potentially eligible patients on a Ch-I during July 1 – September 30, 2010; 2) facility level medical record review spanning a minimum 2-year period from July 1, 2010 – September 30, 2012 on a randomly selected subset of patients.

Only select criteria were evaluated:

- Acceptable Diagnosis and Indication per CFU
 - Dementia associated with Alzheimer's disease
 - Dementia associated with Parkinson's disease
 - Lewy body dementia
 - Mixed dementia (AD+vascular dementia)
- Dosing and Frequency of renewal
 - Minimum therapeutic dose
 - 6-month intervals
- Safety outcomes
 - Bradycardia (≤ 50 bpm)
 - Chronic diarrhea
 - Serious Liver Disease
 - Substantial weight loss ($>10\%$)

- Monitoring of efficacy

RESULTS/FINDINGS:

Twenty-four VA medical centers participated in the medical record review. 3962 medical records were reviewed with 3895 records analyzed after excluding 67 patients who were enrolled in a mental health study. Table 1 (on page 6) describes the dementia medication regimens prescribed at the MUE RX Index date and at the most recent follow-up through September 30, 2012. Table 2 (on page 6) provides performance results in relation to the CFU measures selected for review in this MUE.

LIMITATION/DISCUSSION:

Limitations of the MUE include: retrospective chart review, inter-reviewer variability, incomplete documentation in medical record, and the assessment of timeliness limited to the two most recent visits.

The MUE identified several areas for improvement. These, in particular, include specific dementia diagnosis and staging, timely follow-up, and documentation of therapeutic benefit. A recent study at the New England VA Healthcare System revealed that nearly half of individuals with a persistent diagnosis of "Dementia, Not Otherwise Specified (NOS)" met criteria for a specific dementia². One explanation for why 'Dementia, NOS' is frequently selected may be due to the fact that it is one of the top three diagnoses available for selection in the drop-down window within electronic health record when a clinician types "dementia." Moreover, once selected, the same diagnosis will automatically be listed and easily "clicked" at subsequent visits, whereas entering a new code would require additional steps. Another area identified for improvement is in regards to safety; in particular, the prescribing of concomitant anticholinergic drugs and management in patients experiencing bradycardia. Twenty of the 24 sites reported additional local restrictions or less restrictive CFU than the National CFU.

A few participant sites have discussed local improvement actions such as developing an interdisciplinary noon CME program incorporating aspects of diagnosis dementia, concomitant anticholinergic therapy, and co-management of patients outside VA. Since no interaction flags trigger when an anticholinergic medication is prescribed, sites are considering local tools to assist with this process. Another site is considering adding a requirement to document the date cognitive testing was performed into the current order set to prevent the use of outdated cognitive scores for prescription renewal. Consideration is also given to requiring documentation of therapeutic benefit to the order set. A few sites have provided feedback on the potential utility of having separate follow-up and prescription renewal timeframe

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Getting the most from our safety surveillance

MEDICATION USE EVALUATION (MUE) OF PHARMACOLOGICAL TREATMENT OF DEMENTIA

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requirements for stable patients versus newly-initiated patients.

Recommendation/Conclusion:

VA PBM is awaiting results of a VA Cooperative Study evaluating the use of memantine in combination with donepezil in the treatment dementia. Those results, in conjunction with the findings of the MUE, will be used to update information in the PBM CFU if warranted.

REFERENCES:

1. Pharmacy Benefits Management Services website. <http://www.pbm.va.gov/PBM/clinicalguidance/CriteriaForUse.asp> - Cholinesterase Inhibitors Criteria for Use Updated 7/31/08 (Accessed September 2012 – December 2013).
2. Butler D, Kowall N, Lawler E, et al. Underuse of diagnostic codes for specific dementias in the Veterans Affairs New England healthcare system. *J Am Geriatr Soc* 2012;60:910-915.

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Table 1. Dementia Medication Regimens

Dementia Regimens	Index (N=3895)	Follow—Up (N=3240)
No drug therapy		655 (16.8%)
Ch-I Monotherapy, n (%)	3029 (77.8%)	2087 (64.4%)
Donepezil	1650 (42%)	1337 (41.3%)
Galantamine	1322 (34%)	709 (21.9%)
Rivastigmine	57 (1.5%)	41 (1.3%)
Memantine monotherapy, n (%)	7 (0.2%)	74 (2.3%)
Ch-I combination with memantine, n (%)	832 (21.4%)	845 (26.1%)
Donepezil + Memantine	565 (67.9%)	617 (73%)
Galantamine + Memantine	235 (28.2%)	200 (23.7%)
Rivastigmine + Memantine	32 (3.8%)	28 (3.3%)
Ch-I dual therapy	11 (0.3%)	13 (0.4%)

*NOTE: Donepezil and galantamine are listed on the VA National Formulary (VANF).

Table 2. Compliance with Select PBM Criteria for Use Measures

Compliance with PBM Criteria for Use Measures	n (%)
Diagnosis	
Approved Diagnosis (Dementia associated with Alzheimer’s disease, Parkinson’s Disease, Lewy body dementia, mixed AD + vascular dementia)	1369 (35.1%)
-Dementia NOS	1519 (39.0%)
Dosing	
# Patients prescribed minimum therapeutic dose at any time	3410 (87.5%)
RX Renewal and Clinical Assessment	
RX Renewal ≤ every 6 months	2003 (51.4%)
Clinical Evaluation ≤ every 6 months	1724 (44%)
# Patients w/ documentation of benefit; continuation in line with treatment goals	278 (7%)
Safety	
Concomitant anticholinergic (lower score desired)	863 (22%)
Bradycardia	
• Ch-I discontinued if at least 1 episode HR ≤ 50 bpm (n=446)	159 (35.7%)
• Ch-I discontinue if >1 episode HR ≤ 50 bpm (n=163)	56 (34.4%)
• In new starts (n=438), # patients with at least 1 episode HR ≤ 50 bpm +/- 30 days	8 (1.8%)
(lower score better)	
Chronic diarrhea with follow-up action: discontinuation, adjustment, or treatment	91 (58.7%)
Liver Disease (lower score desired)	56 (1.4%)
Weight Loss (>10%) (lower score desired)	272 (7%)

PBM/VAMedSAFE would like to acknowledge and thank the following participant sites: Hudson Valley HCS; Delaware and Southern New Jersey Healthcare System; Philadelphia VAMC; Carl Vinson VAMC; Charleston VAMC; James A. Haley Veterans’ Hospital; North Florida/South Georgia VAMC; Tennessee Valley HCS; Dayton VAMC; Cleveland VAMC; Ann Arbor VAMC; Fayetteville VAMC; Biloxi VAMC; Tuscaloosa VAMC; Central and North Texas HCS; Albuquerque VAMC; Salt Lake City HCS; Montana HCS; Hilo CBOC; VA Northern CA HCS; Sioux Falls VAMC; VA Sierra Nevada HCS; VA Central Iowa HCS. ■