

MEDICATION

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

SAFETY IN SECONDS

Helping to achieve safe medication use

ISMP TARGETED MEDICATION SAFETY BEST PRACTICES FOR HOSPITALS

The Institute for Safe Medication Practices (ISMP) launches consensus-based medication safety best practices focusing on identifying and addressing repetitive error-related issues that continue to cause harm to patients. These strategies were reviewed by an external expert advisory panel and approved by ISMP's Board of Trustees. ISMP encourages adoption of these practices in all hospitals in the United States and will conduct baseline and follow-up surveys (www.surveymonkey.com/s/ISMPTargets) to assess the effectiveness of these efforts and barriers to implementation. ISMP's targeted medication safety best practices for hospitals consist of:

- Dispense vinCRISTine (and other vinca alkaloids) in a minibag of a compatible solution and not in a syringe.
- Use a weekly dosage regimen default for oral methotrexate.
 - ◊ If override to daily, require a hard stop verification of an appropriate

oncologic indication.

◊ Provide patient education by a pharmacist for all weekly oral methotrexate discharge orders.

- Measure and express patient weights in metric units only. Ensure that scales used for weighing patients are set and measure only in metric units.
- Ensure that all oral liquids that are not commercially available as unit dose are dispensed by the pharmacy in an oral syringe.
- Purchase oral liquid dosing devices (oral syringes/cups/droppers) that only display the metric scale.
- Eliminate glacial acetic acid from all areas of the hospital.

For more information, visit ISMP's website at: www.ismp.org/tools/bestpractices/.

REFERENCES:

Institute for Safe Medication Practices (ISMP). 2014-15 Targeted Medication Safety Best Practices for Hospitals. *ISMP Medication Safety Alert! Acute Care* January 2014; 19 (1): 1,4.

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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

- Saxagliptin and Cardiovascular Safety – 02/18/14 - [National PBM Bulletin](#)
- Testosterone Products and Cardiovascular Safety – 02/07/14 - [National PBM Bulletin](#)
- ADDENDUM: Additional Lots Identified for Abbott FreeStyle Glucose Test Strips Recall – 12/04/13 - [National PBM Communication](#)

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from the fda

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UROLOGY

[FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products](#)

1/31/2014

Two recent studies identify a possible risk of increased cardiovascular events in men receiving testosterone therapy. FDA continues to evaluate this association between testosterone treatment and increased risk of stroke, heart attack, or death, but has not yet reached a firm conclusion. FDA recommends that:

- Providers should consider whether the benefits of FDA-approved testosterone treatment will outweigh the potential risks of treatment.
- Providers should comply with the prescribing information in the product labeling.
- Patients should not stop their testosterone treatment without prior discussion with their health care providers.

For more information, visit: [National PBM Bulletin - Testosterone Products and Cardiovascular Safety](#).

OVER-THE-COUNTER PRODUCTS

[FDA warns of possible harm from exceeding recommended dose of over-the-counter sodium phosphate products to treat constipation](#)

1/8/2014

Severe dehydration and electrolyte abnormalities leading to acute kidney injury, arrhythmias, and death have occurred in adults and children who received a larger than recommended single dose or more than one dose in a day of oral or rectal over-the-counter (OTC) sodium phosphate solutions to treat constipation. FDA reviewed reports of serious adverse events associated with sodium phosphate drug products in the FDA Adverse Event Reporting System (FAERS) database as well as in the medical literature from as far back as 1957 and found 54 cases (25 adults and 29 children). All reports of serious outcomes involved dehydration and/or electrolyte disturbances (hyperphosphatemia, hypocalcemia, and hypernatremia), acute kidney injury, and/or death (48% [12/25] of adult cases and 3% [1/29] of pediatric cases). Route of administration (oral or rectal) did not affect the severity of adverse events. Risk factors for developing adverse events include:

- age over 55 years;
- hypovolemia or decreased intravascular volume;
- kidney disease;
- bowel obstruction or inflammation, or decreased bowel transit time;
- use of diuretics, ACEIs, ARBs, or NSAIDs.

FDA recommends:

- Providers should not prescribe OTC sodium phosphate products for more than one dose per 24 hours and for no more than 3 days when used for constipation.
- Providers should instruct patients on adequate hydration when using OTC sodium phosphate products.
- Providers should evaluate serum electrolytes and kidney function in patients at risk for adverse events, as well as in patients who have retained a rectal dose for more than 30 minutes, are vomiting, or have signs of dehydration.

For more information, see discussion published in last month's newsletter: [Issue 1; Volume 4; January 2014](#).

Getting the most from our safety surveillance

TSOACs AND RENAL FUNCTION: INFORMATION ON DOSING AND CALCULATING CREATININE CLEARANCE FROM THE PIVOTAL TRIALS

Three target specific oral anticoagulants (TSOACs) (dabigatran, rivaroxaban, and apixaban) are currently approved by the Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). Rivaroxaban carries additional FDA approved indications for the treatment of patients with venous thromboembolism (VTE) and prevention of recurrent events and for the prophylaxis of VTE in patients undergoing hip or knee replacement surgery. The TSOACs undergo varying degrees of renal elimination, and dosage adjustments are recommended in patients with significant renal impairment

based on the patient's creatinine clearance (CrCl). Several methods may be used to estimate CrCl that may produce different results. In certain scenarios, the estimated CrCl using one or another method may ultimately affect the recommended TSOAC dose.

How was renal function assessed during the clinical trials? In the pivotal AF trials with dabigatran (RE-LY), rivaroxaban (ROCKET-AF), and apixaban (ARISTOTLE), CrCl was estimated using the Cockcroft-Gault formula including serum creatinine (sCr), age,

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Getting the most from our safety surveillance

TSOACs AND RENAL FUNCTION: INFORMATION ON DOSING AND CALCULATING CREATININE CLEARANCE FROM THE PIVOTAL TRIALS

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gender, and body weight. In the RE-LY and ROCKET-AF trials with dabigatran and rivaroxaban, actual body weight (rather than ideal or adjusted body weight) was used for the CrCl calculation. The ARISTOTLE trial protocol did not further specify which body weight should be used for the CrCl calculation.

The estimated CrCl using the Cockcroft-Gault equation is as follows:

CrCl (ml/min) = $[(140 - \text{age}) \times \text{weight (kg)}] / (72 \times \text{SCr}) \times 0.85$ if female

Tips in considering TSOACs and renal dosing:

- Dabigatran is primarily renally eliminated; rivaroxaban undergoes significant renal elimination (less than dabigatran); and apixaban undergoes minor renal elimination.
- Use of actual body weight rather than ideal or adjusted body weight in the Cockcroft-Gault calculation could potentially affect estimates and recommendations in overweight and obese patients. In RE-LY, 50% of patients had a body mass

index (BMI) of 28 or higher, and 17% of patients weighed 100 kg or more. In ROCKET AF, 14% of patients had a BMI greater than 35, and 2.9% weighed greater than 90 kg. Similar data are not available from ARISTOTLE.

- Clinical judgment should be used in choosing the best TSOAC and dose, considering the stability of the patient's renal function and any underlying conditions that affect renal function (e.g., heart failure).

REFERENCES:

1. Apixaban (Eliquis) prescribing information. Bristol-Myers Squibb, Princeton NJ and Pfizer Inc, New York, NY. January 2014.
2. Dabigatran (Pradaxa) prescribing information. Boehringer Ingelheim. Ridgefield CT. December 2013.
3. Data on file (Pradaxa). Boehringer Ingelheim Pharmaceuticals, Inc. Warminster PA. October 30, 2013.
4. Data on file (Xarelto). Janssen Pharmaceutical Companies of Johnson and Johnson. Titusville NJ. September 18, 2013.
5. Data on file (Eliquis). Bristol-Myers Squibb. January 29, 2014.
6. Rivaroxaban (Xarelto). Prescribing Information. Janssen Pharmaceuticals Inc. 2011. Titusville NJ. January 2014.
7. Target specific oral anticoagulant (TSOAC) Criteria for Use and Algorithm. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs; January 2014.

Contributed by:

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PBM TSOAC Dosing Recommendations in Renal Impairment^{4,*}

	DABIGATRAN	RIVAROXABAN	APIXABAN
Extent of renal elimination	Primarily renal elimination	Significant renal elimination	Minor renal elimination
VA PBM	Avoid if CrCl <30 ml/min (not studied) Avoid if CrCl ≤50 ml/min and if on concomitant dronedarone or systemic ketoconazole	Avoid if CrCl <30 ml/min (not studied) Reduced dose of 15 mg once daily for patients with CrCl 30-50 ml/min (studied and FDA approved)	Avoid if SCr >2.5 mg/dL or CrCl <25 ml/min (not studied) Reduced dose of 2.5 mg BID if ≥2 of the following: <ul style="list-style-type: none"> ▪ SCr ≥1.5 mg/dL ▪ ≥80 yrs ▪ wt ≤60 kg (studied and FDA approved)
Package Labeling	Reduced dose of 75 mg BID if CrCl 15-30 ml/min Reduced dose of 75 mg BID if CrCl 30-50 ml/min AND on concomitant dronedarone or systemic ketoconazole. No recommendations for CrCl <15 ml/min or dialysis	Reduced dose of 15 mg once daily if CrCl 15-50 ml/min Avoid if CrCl <15 ml/min	Reduced dose of 2.5 mg BID if patients have 2 or more: <ul style="list-style-type: none"> ▪ Age ≥80 yrs ▪ Weight ≤60 kg ▪ Serum creatinine ≥1.5 mg/dL ESRD and on stable hemodialysis: <ul style="list-style-type: none"> ▪ 5 mg BID if age <80 yrs and weight >60 kg ▪ 2.5 mg BID if age ≥80 yrs or weight ≤60 kg

*VA PBM has recommended dosing based on what was studied in pivotal clinical trials which differs some from the prescribing information for all 3 agents. For example, rivaroxaban is FDA approved for CrCl as low as 15 ml/min, even though patients were excluded from trials with CrCl <30 ml/min. ■