

MEDICATION

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

SAFETY IN SECONDS

Helping to achieve safe medication use

DIRECT ORAL ANTICOAGULANTS (DOACS) IN OBESITY

Submitted by Lisa Longo, Pharm. D., BCPS

The PBM Direct Oral Anticoagulant (DOAC) Criteria for Use (CFU) documents have been updated to include information on the use of DOACs in obesity, recognizing the recent guidance from the International Society on Thrombosis and Haemostasis (ISTH) [link: <http://onlinelibrary.wiley.com/doi/10.1111/jth.13323/epdf>] and the Anticoagulation Forum VTE Treatment Guidance (2016) advises limiting DOAC use to situations where warfarin is not an option in patients at extremes of weight (e.g., >120 kg or BMI ≥ 35 kg/m²). VA PBM recommends that when a DOAC is being considered in such patients, a shared decision making approach should be utilized with information provided on the limited data regarding the efficacy and safety of these agents in extremes of body weight and recommendations of some groups against use in this situation.

Under *Issues for Consideration*, the following has been added:

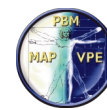
Obesity: *Very limited data are available on the use of DOACs in extremes of body weights. Some pharmacokinetic and pharmacodynamic data have found modest effects of body weight extremes on DOAC exposure, but the clinical relevance is unknown. Subgroup analysis of obese patients from the pivotal phase 3 DOAC trials suggests that DOACs generally appear to be safe and effective; however, data are limited. The ISTH guidance*

on the use of DOACs in obese patients (2016) suggests not using DOACs in patients with a body mass index (BMI) >40 kg/m² or weight of >120 kg. Similarly, the Anticoagulation Forum VTE Treatment Guidance (2016) advises limiting DOAC use to situations where warfarin is not an option in patients at extremes of weight (e.g., >120 kg or BMI ≥ 35 kg/m²). VA PBM recommends that when a DOAC is being considered in such patients, a shared decision making approach should be utilized with information provided on the limited data regarding the efficacy and safety of these agents in extremes of body weight and recommendations of some groups against use in this situation.

For more information about Direct Oral Anticoagulants, please visit the internal VA PBM Website (<https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx/>) under the Clinical Guidance section and the Criteria for Use subsection.

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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

- LMA Mucosal Atomization Devices – Recall Due to Inadequate Delivery of Drug – 11/21/2016 - National PBM Patient Level Recall Communication (TARGETED TO AFFECTED SITES ONLY)

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from the fda

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SMOKING CESSATION

[FDA revises description of mental health side effects of the stop-smoking medicines Chantix \(varenicline\) and Zyban \(bupropion\) to reflect clinical trial findings](#)

12/16/2016

FDA required the manufacturers of varenicline and bupropion to conduct a clinical trial to evaluate the safety of these agents for smoking cessation in patients without and with a history of psychiatric disorders. Out of 8,144 enrolled patients at 140 centers in 16 countries (including the U.S.), 8,058 patients (of which 4,074 had a history of mental health illnesses) were randomized to either varenicline (n=2,016), bupropion (n=2,006), NRT (n=2,022), or placebo (n=2,014). Safety results show:

- Clinically significant neuropsychiatric adverse effects occurred at a similar frequency of about 3 percent across treatment groups in patients without psychiatric diagnoses.
- There was a higher incidence across groups in the cohort of patients with psychiatric diagnoses, and an increased risk associated with varenicline and with bupropion (approximately 12 percent), compared to placebo (approximately 10 percent).
- There was no meaningful difference in risk between varenicline and bupropion.

As such, FDA determined the risk of serious side effects on mood, behavior, or thinking with varenicline and bupropion is lower than previously suspected. The risk of neuropsychiatric adverse events still exists, especially in those with prior or current mental illness, or who have a history of treatment for mental illnesses. However, most people who had these side effects did not have serious consequences such as hospitalization.

Based on these findings, FDA will make the following changes to product labeling:

- Removal of the Boxed Warning for serious mental health side effects in the varenicline label.
- Removal of the language describing the serious mental health side effects seen in patients quitting smoking from the Boxed Warning in the bupropion label.
- Updating the existing warning section in both labels that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial.
- The patient Medication Guide that explains the risks associated with the use of the medicines will continue to be provided with every patient prescription; however, the risk evaluation and mitigation strategy (REMS) that formally required the Medication Guide will be removed.

For more information about varenicline use within the VA, please visit the internal VA PBM Website (<https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx/>) under the Clinical Guidance section and the Criteria for Use subsection.

CENTRAL NERVOUS SYSTEM

[FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women](#)

12/14/2016

Animal and human studies suggest that repeated or prolonged use of general anesthetic and sedation drugs may negatively affect the developing brain. Fetuses of women in their third trimester of pregnancy and children younger than 3 years are most prone to this effect. On the other hand, a single, short exposure to general anesthetic and sedation drugs in infants or toddlers may not likely impact behavior or learning. While most anesthetic drugs have demonstrated adverse effects on brain development in different species of animals, no specific medications have been shown to be safer than any other. Further research can help to fully characterize how early life anesthetic exposure might affect children's brain development, particularly for more lengthy or repeated exposures and in more vulnerable children. For greater awareness regarding this risk, FDA requires warnings to be added to the labels of the general anesthetic and sedation drugs in Table 1. FDA recommends that health care professionals discuss with parents, caregivers, and pregnant women the benefits, risks, and appropriate timing and duration of surgery or procedures requiring anesthetic and sedation drugs as well as the health risks of not treating certain conditions.

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from the fda

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Generic Name	Brand Name
desflurane	Suprane
etomidate	Amidate
halothane	Only generic is available
isoflurane	Forane
ketamine	Ketalar
lorazepam injection	Ativan
methohexital	Brevital
midazolam injection, syrup	Only generic is available
pentobarbital	Nembutal
propofol	Diprivan
sevoflurane	Ultane, Sojourn

Table 1. List of General Anesthetic and Sedation Drugs Affected by this Label Change .

ENDOCRINOLOGY

[Updated FDA review concludes that use of type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer](#)

12/12/2016

FDA reviewed published epidemiological studies evaluating the risk of bladder cancer with pioglitazone use. Although results were inconsistent, the overall data suggest that pioglitazone use may be linked to an increased risk of bladder cancer. Furthermore, findings of these and other reviewed studies conflicted about whether the duration of use and/or total dose over time of pioglitazone influenced the risk of bladder cancer. FDA has updated the drug labels to include information about these additional studies. FDA recommends that health care professionals should:

- Not use pioglitazone in patients with active bladder cancer;
- Consider the benefits and risks before using pioglitazone in patients with a history of bladder cancer;
- Educate patients on the following signs or symptoms associated with bladder cancer after starting pioglitazone, and to contact their providers if they experience:
 - Blood or a red color in the urine;
 - New or worsening urge to urinate;
 - Pain when urinating .

Getting the most from our safety surveillance

NAN ALERT—OBSERVE FOR POSSIBLE FLUID LEAKAGE WHEN PREPARING PARENTERAL SYRINGES

Submitted by Jessica Zacher, Pharm. D., PGY-2 Medication Use Safety Pharmacy Resident

The national alert network (NAN) issued a warning recently about the potential for certain parenteral syringes to leak fluid beyond the plunger while being prepared. Reports have come through to the Institute for Safe Medication Practices (ISMP) from three different hospitals experiencing this issue. The syringes, which have most frequently been identified as 10mL syringes manufactured by BD, have been reported to leak fluid beyond the black stopper and up to the first and second rib on the side of the barrel that is exposed to air. Assessments that have been made by BD have shown that leakage between the first and second ribs of the stopper does not alter the sterility of the product, and does not affect the accuracy of the volume delivered. Leakage beyond the second rib, however, could potentially be contaminated and should not be used. BD currently has a corrective action project underway to address the issue with the 10mL syringes. There are a few recommendations provided by the NAN alert that will be useful until the issue is resolved:

- Always use proper technique when preparing syringes, and **be sure to maintain vertical alignment of the plunger rod with the syringe barrel** when drawing up a solution using an inverted vial technique.
- If leakage is observed beyond the second rib of the stopper and into the area exposed to air, discard that syringe.
- Utilize additional precautions if leaking syringes contain hazardous drugs.
- Share this information with sterile syringe production personnel, and clinical personnel who prepare medications in parenteral syringes.
- Report the lot number of all leaking syringes identified to FDA Medwatch, the ISMP National Medication Errors Reporting Program (MERP), and the syringe manufacturer.

REFERENCES:

NAN ALERT. Observe for possible fluid leakage when preparing parenteral syringes. National Coordinating Council on Medication Error Reporting and Prevention (NCCMERP); September 15, 2016. ■