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MEDICATION SAFETYINSECONDS

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

Helping to achieve safe medication use

FDA'S NEW CLOZAPINE REMS PROGRAM AND ASSOCIATED CHANGES IN REQUIREMENTS FOR MONITORING, PRESCRIBING, AND DISPENSING

Note: VA providers and pharmacies should continue to follow the process outlined by the current Handbook and should not enroll in the new registry until additional guidance is sent to the field from the National Clozapine Coordinating Center (NCCC) via a PBM Communication.

FDA is implementing a Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program as well as new changes required for the monitoring, prescribing, and dispensing of clozapine, an atypical antipsychotic medication indicated for treatment-resistant schizophrenia because of the life-threatening risk of severe neutropenia associated with its use. Starting on October 12, 2015, all clozapine products will be available only through the use of the Clozapine REMS Program, which will replace the current six individual registries established by the manufacturers of the drug. Under this new REMS program, prescribers, pharmacies, and patients will enroll in one centralized clozapine registry which will maintain all relevant clinical information necessary for managing the safe and appropriate use of clozapine therapy. In order to prescribe and dispense clozapine, prescribers and pharmacies will be required to become certified in the Clozapine REMS Program according to a specific transition schedule starting on October 12, 2015. Starting December 14, 2015, in order to dispense clozapine, outpatient pharmacies are required to obtain a pre-dispense authorization (PDA) from the Clozapine REMS Program before clozapine can be dispensed. Inpatient pharmacies do not need to obtain a PDA. Patients currently treated with clozapine and enrolled in the separate registries as

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NEWSWORTHY...

from the pbm

- BD Syringes and Loss of Drug Potency: FDA Expands Warning – UPDATE – 09/23/2015 - National PBM Bulletin
- OmniPod Insulin Management System Recall – 09/15/2015 – National PBM Patient Level Recall Communication
- Allergan Ophthalmic Product Recall Due to Particulate Matter: ADDENDUM – 09/04/2015 - National PBM Patient Level Recall Communication
- Allergan Ophthalmic Product Recall Due to Particulate Matter – 09/02/2015 - National PBM Patient Level Recall Communication

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IN THIS ISSUE:

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.

EDITOR-IN-CHIEF

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NEWSWORTHY...

from the fda

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INFECTIOUS DISEASE

FDA cautions about dose confusion and medication error with antibacterial drug Avycaz (ceftazidime and avibactam)

9/22/2015

FDA has received reports of three medication errors related to confusion on how the strength appears on the vial and carton labels of the intravenous antibacterial drug Avycaz (ceftazidime and avibactam) since its approval in February 2015. Each vial contains 2.5 grams of Avycaz (ceftazidime 2 grams and avibactam 0.5 grams). However, the vial and carton labels of Avycaz (ceftazidime and avibactam) expressed the strength to reflect the individual active ingredients which led to mix-ups:

- 2/3 cases stated that the errors occurred during preparation of the dose in the pharmacy which was based on the ceftazidime portion alone (an adjusted dose of 1.25 grams due to renal impairment) rather than the intended 1 gram of ceftazidime and 250 milligrams of avibactam. This resulted in a higher-than-intended dose in 1 of the 2 cases.
- 1/3 cases described concern about the potential for confusion because the strength displayed for Avycaz (ceftazidime and avibactam) differs from the usual listing on labels for other beta-lactam/beta-lactamase antibacterial drugs.
- No adverse events were reported.

To prevent medication errors, FDA has revised the labels to indicate that each vial contains Avycaz 2.5 grams, equivalent to ceftazidime 2 grams and avibactam 0.5 grams.

PAIN MANAGEMENT

FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger

9/21/2015

FDA is investigating the use of tramadol in children aged 17 years and younger due to the rare but serious risk of slowed or difficult breathing. This risk may increase in children treated with tramadol for pain after surgery to remove their tonsils and/or adenoids. In addition, those who have genetic variations that make them "ultra-metabolizers" may convert tramadol to the active form of the opioid faster and more completely than usual. This was the case in a 5-year-old child in France who experienced severely slowed and difficult breathing requiring emergency intervention and hospitalization after taking a single prescribed dose of tramadol oral solution for pain relief following surgery to remove his tonsils and adenoids. Of note, tramadol is not FDA-approved for use in children, but off-label use occurs. FDA continues to evaluate all available information and will issue final conclusions and recommendations after completing their review.

MENTAL HEALTH

FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines

9/15/2015

New Clozapine REMS program changes requirements for clozapine monitoring, prescribing, and dispensing. VA providers and pharmacies should continue to follow the process outlined by the current Handbook and should not enroll in the new registry until additional guidance is sent to the field from the National Clozapine Coordinating Center (NCCC) via a PBM Communication. For more details, see article on page 1 of this issue or click on the above link.

ENDOCRINOLOGY

FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density

9/10/2015

FDA has revised the canagliflozin (Invokana and Invokamet) drug labels to include strengthened warnings and

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NEWSWORTHY...

from the fda

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new information on the following safety concerns observed with use of this agent in clinical trials:

- An increased risk of bone fracture (as demonstrated in nine pooled clinical trials with a mean duration of exposure to canagliflozin of 85 weeks):
  - occurring as early as 12 weeks after treatment initiation;
  - more likely to be low trauma (e.g., arising after falls from no more than standing height); and
  - affecting the upper extremities.
- Decreases in bone mineral density at the hip and lumbar spine according to a clinical trial that the manufacturer of canagliflozin conducted at the request of the FDA to evaluate changes to bone mineral density over two years in 714 elderly individuals.

FDA continues to evaluate the risk of bone fractures with other drugs in the SGLT2 inhibitor class, including dapagliflozin (Farxiga, Xigduo XR) and empagliflozin (Jardiance, Glyxambi, Synjardy), to determine any need for additional label changes or studies. In the meantime, FDA recommends that healthcare professionals:

- Consider factors that contribute to fracture risk prior to initiating canagliflozin.
- Counsel patients about factors that may contribute to bone fracture risk.

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well as the National Non-Rechallenge Master File (NNRMF) will be automatically transferred into the new centralized program.

Along with the new Clozapine REMS Program, other changes enable treatment with clozapine for a greater number of patients where benefits may outweigh risk. These changes include:

- Patients with benign ethnic neutropenia (BEN) now can be treated with clozapine.
- Neutropenia will be monitored by the absolute neutrophil count (ANC) only:
  - **For general population patients**, i.e., those without benign ethnic neutropenia (BEN), interrupt treatment if neutropenia is suspected to be clozapine-induced for ANC less than 1,000 cells per microliter.
  - **For patients with BEN**, interrupt treatment if neutropenia is suspected to be clozapine-induced for ANC less than 500 cells per microliter.
- Although re-challenging patients that have had severe neutropenia with clozapine use is not recommended, the revised prescribing allows prescribers to exercise clinical judgement where the benefit of therapy outweighs the risk of recurrent severe neutropenia.

Currently, VA's National Clozapine Coordinating Center (NCCC) approves and monitors all clozapine therapy in VA medical centers across the system. The unique structure of the Veterans Health Information Systems and Technology Architecture allows data on each clozapine patient to be gathered and evaluated when a clozapine prescription is written and subsequently at weekly intervals to ensure appropriate use according to FDA guidelines. Abnormal blood results will trigger a warning for physician re-evaluation or will block dispensing according to the severity or absence of required laboratory data. To date, VA, led by the NCCC, continues to work with the FDA and manufacturers of clozapine on methods to remain in compliance with the new REMS system when initiated.

As previously stated, VA providers and pharmacies should continue to follow the process outlined by the current Handbook and should not enroll in the new registry until additional guidance is sent to the field from the NCCC via a PBM Communication.

For more information, visit:

- The FDA website: FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines ;
- the Clozapine REMS Program website: www.clozapinerems.com ; or
- Call the Clozapine REMS Program at 844-267-8678.

REFERENCE:

Food and Drug Administration. Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. http://www.fda.gov/Drugs/DrugSafety/ucm461853.htm . Accessed 9/15/2015 .

Getting the most from our safety surveillance

ADVERSE DRUG EVENTS (ADES) WITH NEWLY APPROVED MEDICATIONS

Submitted by Von Moore, Pharm.D. and Anthony Au, Pharm.D., BCPS

VA conducts routine safety surveillance on medications and adverse events that may be of interest due to patient safety concerns and potential reduction of adverse outcomes. New medications are reviewed when known ADEs related to the drug can be severe (example: bleeding) or when large numbers of patients may be utilizing the newly approved medication (example: target specific oral anticoagulants [TSOACs], also known as direct oral anticoagulants [DOACs] - dabigatran, apixaban, rivaroxaban). This increased surveillance provides opportunities for clinicians to review the adverse events that are actually occurring in the veteran population. The actual events may differ from what was observed during pre-approval clinical studies.

The ten medications shown in table 1 have been FDA-approved for use after July 1, 2012. Also shown in table 1 are severe ADE reports for each drug from date of approval until October 1, 2015. However, all ADEs (regardless of severity) to these medications should be submitted to the FDA MedWatch program (through VA ADERS) during their first three years of use after approval. For the agents listed in table 1, the three year window for reporting all ADEs to MedWatch would expire after July 1, 2015, with the exact cut-off date for each agent listed below.

Table 2 includes the top reactions that have occurred with apixaban, dimethyl fumarate, and simeprevir from the reports below. The number of reports received may reflect a medication that has high utilization. For that reason, surveillance efforts also evaluate the patients that have been exposed to the drug to aid in understanding the medication's risk in veteran patients. In the case of apixaban, there are other medications (dabigatran, rivaroxaban, and warfarin) that can be reviewed as comparators. While these reactions may not be unexpected and the outcomes may not have been severe, the reported reactions are important in considering the appropriate and safe use of the medication.

The three year reporting to MedWatch is not the only surveillance conducted with VA ADERS reports, but it is an important part of patient and medication safety in the VA. Understanding these safety implications, when using a new medication in the veteran population, aids in appropriate therapy selection and patient medication management. ■

Table 1: Top 10 new medications with reports in VA ADERS

Rank	Generic	Approval Date	3 Year MedWatch Report Date	Reports (severe)
1	APIXABAN	12/28/2012	*12/28/2015*	86 (23)
2	DIMETHYL FUMARATE	3/27/2013	*3/27/2016*	37 (4)
3	SIMEPREVIR	11/22/2013	*11/22/2016*	22 (6)
4	SOFOSBUVIR	12/6/2013	*12/6/2016*	22 (9)
5	IBRUTINIB	11/13/2013	*11/13/2016*	17 (8)
6	REGORAFENIB	9/27/2012	*9/27/2015*	13 (7)
7	POMALIDOMIDE	2/8/2013	*2/8/2016*	12 (6)
8	ENZALUTAMIDE	8/31/2012	*8/31/2015*	8 (1)
8	CARFILZOMIB	7/20/2012	*7/20/2015*	7 (5)
10	PONATINIB	12/14/2012	*12/14/2015*	7 (5)

Table 2: Symptoms of adverse reaction reported in VA ADERS (not all symptoms shown in table)

APIXABAN		DIMETHYL FUMARATE		SIMEPREVIR	
REACTION	**Count**	**REACTION**	**Count**	**REACTION**	**Count**
GASTROINTESTINAL HEMORRHAGE	20	DIARRHEA	9	SUNBURN	6
RASH	13	RASH	8	LIVER FUNCTION TEST ABNORMAL	3
HEMORRHAGE	13	FLUSHING	7	RASH	3
ANEMIA	10	VOMITING	6	ANEMIA	2
EPISTAXIS	6	ABDOMINAL PAIN	5	THROMBOCYTOPENIA	2
VOMITING	5	PRURITUS	4	CONSTIPATION	2
DIZZINESS	5	FATIGUE	2	VOMITING	2
HEMATURIA	4	DYSPNEA	2	BLOOD CREATININE INCREASED	2
PRURITUS	4			MYALGIA	2
HOSPITALIZATION	4			ANGIOEDEMA	2
DIARRHEA	3			SKIN EXFOLIATION	2
DEATH	3			PHOTOSENSITIVITY REACTION	2
HEADACHE	3				