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News & Noteworthy:

Formulary Drugs Requiring REMS Programs

by *Chloe Haber, PharmD Candidate*

Risk **E**valuation and **M**itigation **S**trategy (REMS) programs were developed as part of the Food and Drug Administration (FDA) Amendments Act in 2007 to enhance drug safety. This act provided the FDA authority to require manufacturers to develop a REMS program to ensure the benefits of specific drugs outweigh the risks. A REMS program is a safety strategy to manage a known or potential serious risk associated with a medication without hindering the treatment process.

REMS programs include any combination of five elements:

1. A medication guide or patient package insert warning patients about concerns
2. A communication plan to support implementation of the REMS and education of health-care providers regarding the risks of the drug (e.g., letters to providers)
3. Elements to Assure Safe Use (ETASU) or required medical interventions that health-care professionals need to execute prior to prescribing or dispensing the drug (e.g., required laboratory tests)
4. An implementation system that requires the drug's sponsor to monitor and evaluate health-care systems responsible for implementing ETASU measures
5. A timetable for assessing the effectiveness of safety measures

In April 2017, the FDA eliminated the requirement for the REMS program for erythropoiesis-stimulating agents (ESAs), namely epoetin alfa (Procrit[®], Epogen[®]) and darbepoetin alfa (Aranesp[®]), for patients with anemia secondary to myelosuppressive chemotherapy. Originally approved in 2010, the APPRISE Oncology Program had required prescribers of ESAs for cancer patients to be

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Pharmacy & Therapeutics Committee Updates

by *Yanmen Yang, PharmD, Pharmacy Practice Resident*

Meeting Months: February 2017 through May 2017

Policies and Protocols:

- ◆ (Updated) Policy "Pyxis[®] User Override Access"
- ◆ (Updated) Policy "Procedure and Sedation in Emergency Room"
- ◆ (Updated) Policy "Diagnosis and Management of Malignant Hyperthermia"
- ◆ (Updated) Policy "CT and MRI Imaging Studies with Contrast"
- ◆ (Updated) Policy "Management of Pain, Agitation, and Delirium in Adult ICU Patients"
- ◆ (Updated) Policy "Moderate Sedation and Analgesia by Non-Anesthesiologist"
- ◆ (Updated) Protocol for "Dilution of Oral Omnipaque[®] for CT Studies"

Formulary Changes:

- ◆ Addition of new antiretrovirals with tenofovir alafenamide (See page 3)
- ◆ Change of tranexamic acid status from non-formulary to formulary
- ◆ Removal of eptifibatide (Integrilin[®]), a glycoprotein IIb/IIIa inhibitor, leaving tirofiban (Aggrastat[®]) as the sole glycoprotein IIb/IIIa inhibitor on formulary
- ◆ Removal of PediaSure[®] Peptide from the Food and Nutrition Services (Dietary) formulary

Research Corner: Immunologic and Virologic Responses to Antiretroviral Therapy in Treatment-Naïve, HIV-Infected Elderly Patients

by Eric Ocheretyaner, PharmD, Infectious Diseases Pharmacy Practice Resident

Presented at the American Society of Microbiology Microbe 2017 Meeting, June 2017. New Orleans, LA

Background: Currently available data on immunologic and virologic responses to antiretroviral therapy (ART) in elderly patients are conflicting. The primary objective of this study was to assess immunologic and virologic responses to ART in treatment-naïve, HIV-infected elderly patients compared to younger patients. The secondary objectives were to evaluate the association of baseline CD4 cell count and ART regimens with immunologic and virologic responses and analyze the time until virologic suppression.

Method: This was a single center, retrospective, descriptive study including treatment-naïve, HIV-infected adults initiated on ART between January 1st, 2005 and April 30th, 2015. Exclusion criteria were discontinuation and/or change of ART within 12 months and no baseline or follow-up CD4 cell count and/or viral load (VL) within 12 months of ART initiation. Immunologic response to ART was defined as an increase of CD4 cell count by 50 to 150 cells/ μ L from baseline within 14 months of ART initiation. Virologic response to ART was defined as achieving an undetectable VL within 24 weeks of ART initiation. Immunologic and virologic responses were compared between the age groups of ≥ 50 years and < 50 years of age. For those ≥ 50 years old, immunologic and virologic responses were analyzed for their association with baseline CD4 cell count (≤ 200 or > 200 cells/ μ L) and ART regimens. Time until VL suppression was compared between patients ≥ 50 versus < 50 years old.

Results: A total of 158 patients were included. By 14 months of ART, 85.9% ($n = 67/78$) of the patients ≥ 50 years old and 92.5% ($n = 74/80$) of those < 50 years old achieved immunologic response ($p = 0.0207$). By 24 weeks of ART, 64.1% ($n = 50/78$) of the patients ≥ 50 years old and 65% ($n = 52/80$) of those < 50 years old achieved virologic response ($p = 1$). In patients with ≥ 50 years of age, baseline CD4 cell count was not significantly associated with either immunologic (≤ 200 cells/ μ L, 85.3% [$n = 29/34$] vs. > 200 cells/ μ L, 86.4% [$n = 38/44$], $p = 1$) or virologic (≤ 200 cells/ μ L, 64.7% [$n = 22/34$] vs. > 200 cells/ μ L, 63.6% [$n = 28/44$], $p = 1$) response. Also, immunologic ($p = 0.179$) and virologic ($p = 0.13$) responses were not significantly different among ART regimens in the elderly patients. The amount of time it took elderly patients to achieve virologic suppression was not significantly different compared to the younger patients ($p = 0.459$).

Conclusion: Treatment-naïve, HIV-infected elderly patients achieved virologic response to ART that was comparable to younger patients although their immunologic response to ART was significantly lower.

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Formulary Drugs Requiring REMS Programs

certified in the safe use of ESAs after post-marketing data identified increased mortality and/or poorer tumor outcomes in patients with certain types of cancers. Following labeling and regulatory changes over several years, as well as changes in evidence-based clinical hematology/oncology guidelines, the requirement for additional prescriber credentialing through the APPRISE program was deemed no longer necessary.

In conclusion, REMS programs vary in complexity. See the table below for examples of hospital formulary drugs with REMS programs and their associated risks. Among patient care providers, compliance with these measures will help ensure patients receive the necessary medications while preventing associated risks.

Examples of Medications with REMS Requirements		
Medication	Associated Risks	REMS Program Requirements
Bupropion Sustained Release (Zyban [®])	Neuropsychiatric adverse events (such as risk of changes in thinking and behavior, depression and suicidal behaviors)	<ul style="list-style-type: none"> Medication Guide for patients from outpatient pharmacy
Clozapine (Clozaril [®])	Severe neutropenia	<ul style="list-style-type: none"> Prescriber, pharmacy, and patient enrollment Ongoing reassessment of white blood cell count
Mycophenolate (Myfortic [®] , CellCept [®])	Embryo-fetal toxicity/Birth defects Higher risks of miscarriage	<ul style="list-style-type: none"> Educating healthcare providers Medication Guide informing female patients of reproductive age the importance of pregnancy prevention and planning
Thalidomide (Thalomid [®])	Embryo-fetal toxicity/Birth defects Increased risk of venous thromboembolism	<ul style="list-style-type: none"> Prescriber, pharmacy, and patient enrollment Medication Guide for patients from outpatient pharmacy Pregnancy test initially and periodically during treatment Mandatory confidential survey

Formulary Updates: Look-Alike-Sound-Alike HIV Medications

by Yanmen Yang, PharmD, Pharmacy Practice Resident, and Eric Ocheretyaner, PharmD, ID Pharmacy Practice Resident

New HIV medications containing tenofovir alafenamide (TAF), a nucleoside reverse transcriptase inhibitor (NRTI) and novel prodrug of tenofovir, were recently added to the SUNY Downstate Medical Center formulary. These medications are similar to the available products containing tenofovir disoproxil fumarate (TDF), with reduced risk of bone toxicity and nephrotoxicity. It is prudent to clarify with the patient and the Infectious Diseases (ID) service which medication(s) should be ordered for ID approval and dispensed for the patient.

Original Formulations	NEW Formulations
Tenofovir Disoproxil Fumarate (TDF)	Tenofovir Alafenamide (TAF)
tenofovir disoproxil fumarate (Viread [®])	tenofovir alafenamide (Vemlidy [®])
emtricitabine and tenofovir disoproxil fumarate (Truvada [®])	emtricitabine and tenofovir alafenamide (Descovy [®])
emtricitabine, rilpivirine, and tenofovir disoproxil fumarate (Complera [®])	emtricitabine, rilpivirine, and tenofovir alafenamide (Odefsey [®])
elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (Stribild [®])	elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (Genvoya [®])
efavirenz, emtricitabine and tenofovir disoproxil fumarate (Atripla [®])	----

Featured patient-care question

Nurses Want To Know ...

by Alquon Hailstock, PharmD Candidate

Q: What happens when patients cannot swallow oral medications? Can I crush or open them?

A: In institutional settings, patients with problems swallowing or who require a feeding tube may be unable to receive solid oral medications. While many tablets can be crushed or capsules opened and contents mixed with food or water, certain medications cannot be crushed due to their formulation. The general rule of thumb is that any medication with a special release mechanism – extended release, delayed release, sustained release (e.g., metoprolol XL) – should not be crushed, as crushing destroys the release mechanism and can cause harm by releasing a large dose all at once. For other formulations, crushing sublingual tablets (e.g., nitroglycerin) can enhance or reduce a drug’s efficacy. Or, enteric-coated drugs may cause irritation of the stomach lining if crushed (e.g., aspirin). If medications with a special release mechanism or enteric coating are ordered for a patient who cannot swallow, prescribers should be contacted to consider immediate-release tablets, oral suspensions/solutions, or orally disintegrating tablets. For more information, see <http://www.ismp.org/tools/donotcrush.pdf>.

Spotlight on Safety: Not Worth the “Weight”

by LilyAnn Jeu, PharmD, Medication Safety/Internal Medicine Clinical Pharmacist

For a variety of medications and patient populations (e.g., pediatric and neonatal patients), weight-based dosing is the primary means to determine the appropriate dose of medication. Drug classes include antibiotics (e.g., vancomycin), anticoagulants (e.g., treatment doses of heparin drip or enoxaparin), and chemotherapeutic agents. Inaccurate weights used for dosing place patients at risk for overdose and acute toxicity or subtherapeutic doses and therapeutic failure.

For patient VW, during a 10-day admission earlier this month, the weight was documented 8 times in the electronic health record (See table below). Of these, 2 outliers in data entry suggest weights were recorded incorrectly: A patient weight of 114 lbs was recorded as 114 kg (and electronically converted to 251.3 kg) on June 8th and then a weight of 49.7 kg was recorded as 49.7lbs (and electronically converted to 22.54 kg) on June 14th. Both errors introduced the potential for harm.

Observations	Column Date/Time	Height: feet(1,3)	Height: inches(2,3)	Height: cm(3,3)	How Height Obtained	How Height Ob	Weight: lbs(5,3)	Weight: kg(6,3)	How Weight Obtained	How Weight O	Weight Method Scale(8,3)
	06-16-2017 15:00	5	1	154.9	Stated		105	47.62	Stated		
	06-15-2017 22:00				Stated				Actual		
	06-15-2017 11:30						105.8	47.99	Actual		
	06-15-2017 11:00						0	0			
	06-14-2017 10:05						49.7	22.54	Actual		standing scale
	06-09-2017 15:53	5	1	154.9			110	49.89			
	06-09-2017 04:00						110.9	50.3	Actual		bed
	06-08-2017 01:00		5	1	Stated		251.3	114	Actual		bed
	06-07-2017 09:10						105.8	48	Actual		bed
	06-07-2017 06:00	5	9	175.2	Stated		106	48.08	Actual		

Although it may be difficult to identify the “true” patient weight upon initial assessment, clinicians updating weight information in the health record should review previous entries and investigate discrepancies for potential typographical errors.

Clinical Pearls: Clinical Significance of PPI and Clopidogrel Drug Interaction

by Jane Ching, PharmD, Pharmacy Practice Resident

Clopidogrel bisulfate (Plavix[®]) is an antiplatelet agent recommended following percutaneous coronary interventions and acute coronary events to decrease the risk of subsequent cardiovascular (CV) events.^{1,2} Its effects on inhibition of platelet aggregation requires metabolism of the prodrug to the active form via hepatic cytochrome P450 isozymes (e.g., CYP2C19, CYP3A4, CYP3A5). While proton pump inhibitors (PPIs) can reduce the risks of gastrointestinal ulceration and bleeding associated with clopidogrel use, PPI inhibition of the CYP2C19 enzyme may prevent prodrug conversion and sufficient levels of active clopidogrel for cardiac benefits.³

Several pharmacodynamics studies reported a significant decrease in clopidogrel efficacy when administered with PPIs.⁴ This led the FDA to issue warnings in 2009 against the concomitant use of these drugs.⁵ The clopidogrel package insert was also updated in 2009 with a Boxed Warning for use of clopidogrel with CYP2C19 inhibitors, such as omeprazole and esomeprazole.⁶

To date, the only randomized controlled trial to evaluate the clinical effect of a PPI (omeprazole) with clopidogrel on CV outcomes found no statistically significant difference among patients receiving dual antiplatelet therapy with aspirin.⁷

However, systematic reviews of the literature drew conflicting findings of increased cardiac risk for some outcome measures, depending on the methodology of the review.^{2,4} Melloni *et al.*² also concluded an increased risk of myocardial infarction and all-cause cardiac mortality in patients taking pantoprazole and rabeprazole. These PPIs have been identified with low inhibition of the CYP2C19 enzyme, suggesting use of a PPI may be a marker of increased baseline CV risk in study patients rather than effects of the drug interaction alone.² Overall, conflicting conclusions may also reflect selection bias or limitations of observational and retrospective studies.

In November 2016, the FDA released a reminder to continue to warn against use of clopidogrel only with omeprazole (rather than all PPIs) and to suggest pantoprazole as an alternative PPI for consideration.⁸ At SUNY Downstate Medical Center, pantoprazole may be an option for patients upon discharge.

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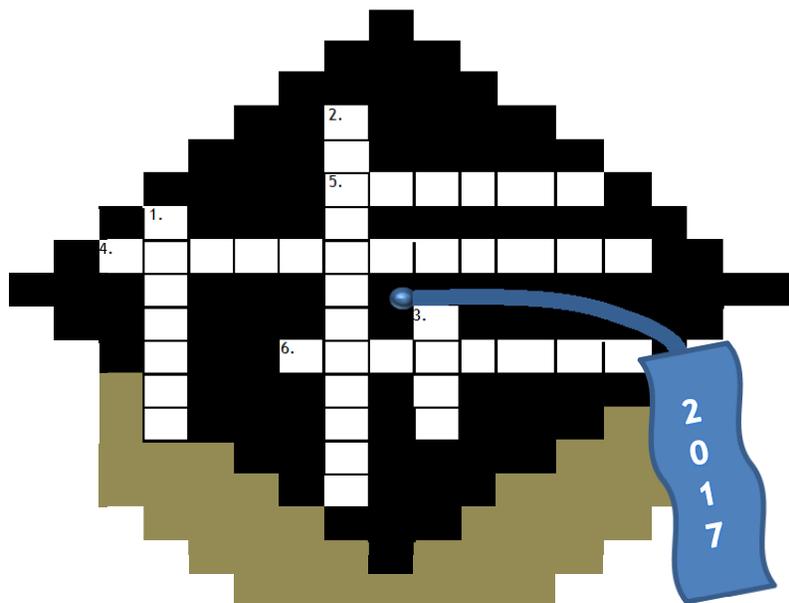
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Answers to Crossword Puzzle:

- Down:** 1. Bruises 2. Constipation 3. COX2
Across: 4. Breakthrough 5. NSAIDs 6. Naloxone

Crossword Puzzle: Congratulations! It Hasn't Been a Painless Journey

by Jane Ching, PharmD, Pharmacy Practice Resident



Down

1. NSAIDs can increase the risk of bleeding and _____.
2. Common gastrointestinal side effect of opioids
3. Celecoxib (Celebrex[®]) is a _____ selective NSAID.

Across

4. Pain superimposed on persistent pain is known as "_____ pain"
5. Class of pain medication that works by inhibiting prostaglandin synthesis
6. Opioid overdose can be reversed with the drug _____ when given right away.



Team Tip of the Day

I II III V IV

Controlled drug symbols are getting a new look.

Always handle controlled drugs according to federal and state requirements.

1 2 3 4

