USE OF COMBINATION RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKADE

The clinical benefit of combination therapy with an angiotensin – converting enzyme inhibitor (ACEI) and an angiotensin receptor blocker (ARB) compared to monotherapy in patients with chronic kidney disease remains controversial.1-5 A recent National PBM Bulletin described the considerations of risks versus benefits of dual therapy with agents that block the renin-angiotensin aldosterone system, especially for patients prescribed combination therapy for a potential benefit on kidney outcomes, referencing evidence in the literature (specifically the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial [ONTARGET] trial6,7; and the Altiskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints [ALTITUDE] trial8,9). These clinical trials demonstrated an increase in adverse events (including, but not limited to, impaired kidney function and hyperkalemia) with combination therapy compared to monotherapy, without a benefit in long-term outcomes.6-9 Pertinent VA PBM recommendations included:

- Because of the potential for harm and the lack of proven long-term outcome benefits, combination therapy with an ACEI and ARB should not be initiated in patients with: diabetic nephropathy; diabetes and CKD; or nondiabetic kidney disease, if being used for kidney outcomes. Similarly, an ACEI or ARB should not be used concomitantly with aliskiren.
- For patients already taking an ACEI and an ARB for the potential benefit on kidney outcomes, providers should review treatment for potential discontinuation of either ACEI or ARB, as applicable. If combination therapy is continued, it should be documented that the patient has benefited from combination therapy and that there are no current safety concerns.
- For patients who are receiving combination ACEI and ARB for management of systolic heart failure, combination therapy with an ACEI and ARB may be considered in patients with persistent symptoms despite maximized standard therapy (if it is determined that the benefit outweighs the potential risk for adverse events); however, use of combination (continued on page 2)
**NEWS YOU CAN USE**

**FROM THE FOOD AND DRUG ADMINISTRATION (FDA)**

**CENTRAL NERVOUS SYSTEM**

Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)

01/10/2013

FDA mandates making label changes to lower doses of immediate and extended-release zolpidem products (Ambien®, Ambien CR®, Edluar®, Zolpimist®) at bedtime due to impaired mental alertness the following morning. Pharmacokinetic and driving simulation studies show that blood levels of zolpidem above 50ng/mL may cause impairment while operating a vehicle and increase the risk of accidents. Extended-release formulations impart greater next-morning impairment than immediate-release formulations. Women are more susceptible to next-morning impairment due to a slower rate of elimination for zolpidem than men. Studies have detected blood levels of zolpidem over 50ng/mL as much as 8 hours post-dose. Trials involving 10 mg Ambien (or bioequivalent zolpidem products) resulted in 15% of women and 3% of men with zolpidem concentrations that exceeded 50 ng/mL approximately 8 hours post-dosing. FDA recommends that healthcare practitioners should: 1) Prescribe the lowest dose capable of treating patients’ insomnia symptoms; and 2) Caution patients regarding possible impairment in driving and activities that require alertness the next morning, despite feeling fully awake.

**NOTE:** The VA Psychopharmacology Field Advisory Committee recommends zolpidem doses should not exceed FDA dosing recommendations in new patients.

### Helping to achieve safe medication use

**USE OF COMBINATION RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKADE**

(continued from page 1)

with an aldosterone antagonist and conventional therapy for heart failure that includes an ACEI may be preferable to an ACEI and ARB. Combination therapy in patients with heart failure/evidence of systolic dysfunction after acute MI is not routinely recommended due to an increased risk for adverse events without a survival benefit.

- A brief assessment of combined therapy in fiscal year 2012 showed that a large number of patients in the VA system-wide were receiving a combination of an ACEI and ARB. Based on the aforementioned safety considerations, VISN PBM(s)/P&T Committee(s) should discuss these recommendations for considering discontinuation of either an ACEI or ARB in patients with chronic kidney disease who are receiving combination therapy with both agents, with facilities implementing them upon direction from their VISN Chief Medical Officer and VISN Pharmacist Executive. Additionally, VA Patient and Provider Letters are available on the PBM INTRANet at: [https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx](https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx).

With respect to use in heart failure, combination therapy with an ARB and an ACEI may be considered to decrease heart failure hospitalizations.10-13 The results of the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial11 support the recommendation that the combination of an ARB with an ACEI may reduce cardiovascular death and heart failure hospitalizations. Candesartan received FDA approval for the treatment of New York Heart Association (NYHA) class II to IV heart failure and LVEF < 40% to reduce the risk of death from cardiovascular causes and to reduce heart failure hospitalizations. Candesartan is also approved for use in combination with an ACEI. FDA approval for valsartan is for treatment of NYHA class II to IV heart failure, and valsartan significantly reduced hospitalizations for heart failure; however, the product information also includes a statement that there is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACEI. In the Valsartan Heart Failure Treatment (Val-HeFT)12 trial, valsartan reduced the combined primary endpoint of mortality and morbidity compared to placebo in patients with NYHA class II to IV heart failure on standard therapy. According to a subgroup analysis, there was an increased risk of mortality and a trend toward an increased risk of combined morbidity and mortality in patients receiving valsartan in conjunction with an ACEI and beta-adrenergic blocker.12

Two meta-analyses comparing data with an ARB in combination with an ACEI versus an ACEI alone in patients with heart failure reported that there was not a statistically significant difference in all-cause mortality between the two treatment groups, but there was a statistically significant reduction in heart failure hospitalizations.14,15 According to a more recent meta-analysis evaluating the use of dual blockade of the renin-angiotensin aldosterone system with an ACEI, ARB, or direct renin inhibitor, compared to monotherapy on long-term efficacy or safety, there was no significant difference in all-cause or cardiovascular mortality with combination therapy compared to monotherapy. There was, however, an increase in the

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### ATTENTION HEALTHCARE PROFESSIONALS!

As a patient safety measure, USP has changed the labeling standard for Heparin Sodium Injection USP and Heparin Lock Flush Solution USP. As manufacturers transition labels to the new USP standard, products with both the old and new labels will be available for use. This transition period presents potential for confusion and errors. To assist in communicating this change to pertinent staff, USP is in the process of conducting a number of WebEx meetings to explain the change more fully, discuss ways to help mitigate the potential for errors until the label transition is completed, and answer questions you might have. The remaining session is scheduled for:

- **Thursday, February 28, 2013** 4:00 – 5:00 p.m. EST
Getting the most from our safety surveillance

VA PBM WARFARIN INR REPORTS

VA PBM developed Warfarin INR reports to assist facilities in monitoring Warfarin management practices and to identify areas for improvements. These reports, updated by VA PBM on a monthly basis, rely on prescription and INR data extracted from sites and generated by VA PBM. Prior to this, no national INR reports existed since some sites had the ability to conduct INR monitoring while others did not. The standardized approach to tracking and trending anticoagulation management based on prescription and INR data provides consistent reports for all facilities. Facilities may use these reports to review data across the nation and identify a strong practice for networking, review trends over time to quickly identify a negative trend, and to identify a starting point for drilling down to patient level data.

Four distinct metrics for INR values are stratified at the National, VISN, and Facility level to provide twelve reports.

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<tr>
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*Each available at the Facility, VISN, and National level.

COMMON QUESTIONS:
Are non-VA labs captured in the lab review?
No. Non-VA labs are not captured with the exception of non-VA labs that have been transcribed into the VA lab package. Lab values contained in external systems or progress notes are not able to be queried for these reports.

My facility has developed local reports with similar metrics for evaluating anticoagulation. Which report should be used?
Locally and/or regionally developed reports may be used instead of the VA PBM Warfarin INR Reports. The reports may differ as locally or regionally developed reports may not use the same parameters or criteria when evaluating patients receiving anticoagulation. Facilities without a local report may utilize the VA PBM Warfarin INR Reports. The VA PBM Warfarin INR Reports were developed so all facilities would have access to a monitoring report and be able to monitor trends and benchmark their data.

Who can access the VA PBM Warfarin INR Reports?
Access is granted to individuals who have received approval from the local facility Chief of Pharmacy or if working in a network position the approval may be granted by the VISN Pharmacist Executive (VPE). Individuals with approval from the respective Chief of Pharmacy or VPE will be granted access to the reports. Send an Outlook e-mail message containing the approval to Anthony_Au@va.gov and Von_Moore@va.gov to be granted access.

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risk for hyperkalemia (RR 1.55, 95% CI 1.32 to 1.82; P<0.001), hypotension (RR 1.66, 95% CI 1.38 to 1.98; P<0.001), and renal failure (RR 1.41, 95% CI 1.09 to 1.84; P=0.01) with combination therapy compared to monotherapy in the overall patient population that was also significantly increased in the subgroup of patients with heart failure. In the trials that reported heart failure hospitalizations, there was a reduction in heart failure hospitalizations (RR 0.82, 95% CI 0.74 to 0.92; P=0.0003) in patients receiving combination therapy compared to monotherapy. Heart failure hospitalizations were also reduced when the groups were analyzed according to patients with heart failure (RR 0.77 95% CI 0.68 to 0.99; P<0.001); although, the difference was not significant in the subgroup of patients without heart failure. There was no significant difference in all-cause or cardiovascular mortality with dual therapy versus monotherapy in the subgroup of patients with heart failure.15

Patients with NYHA class II to IV heart failure who are on standard therapy for heart failure should be considered as a candidate for an aldosterone antagonist (provided the patient has preserved kidney function and normal potassium levels), as treatment with an aldosterone antagonist was shown to improve symptoms, decrease hospitalizations for worsening heart failure, and decrease mortality in this patient population.16,17 In a meta-analysis evaluating the addition of an ARB, direct renin inhibitor, or aldosterone antagonist in patients receiving standard therapy for heart failure that included an ACEI, addition of an aldosterone antagonist decreased the rate of death, cardiovascular death, heart failure hospitalizations, and the composite cardiovascular death or heart failure hospitalizations. There was no difference in these outcomes when either an ARB or direct renin inhibitor was added to standard therapy. Regarding safety, addition of an aldosterone antagonist increased the risk for hyperkalemia by 110%; whereas the addition of an ARB increased the risk of hyperkalemia by 138%, renal failure by 126%, and hypotension by 63%, and addition of a direct renin inhibitor increased the risk for hypotension by 98%.18

Guidelines recommend that combination therapy with an ACEI and ARB may be considered in patients with systolic heart failure and persistent symptoms despite maximized standard therapy (i.e., an ACEI and beta-blocker, with diuretics as indicated); however, (continued on page 4)
use of combination with an aldosterone antagonist and conventional therapy for heart failure that includes an ACEI may be preferable to an ACEI and ARB.18,19 Combination therapy in patients with heart failure/evidence of systolic dysfunction after acute MI is not routinely recommended due to an increased risk for adverse events without a survival benefit.20

REFERENCES
8. Direct Healthcare Professional Communication on potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes and renal impairment and/or cardiovascular disease treated with aliskiren (Tekturna®) tablets and aliskiren-containing combination products. January 2012. Novartis Ph-ma c e u t i ca ls Corpo r at ion ; Ea s t Ha n o v e r NJ. h t t p : / / w w w. p h a r ma . u s . n o v ar t is . c o m / a s s e ts / p d f / T K T - 2 0 0 3 8 2 3 % 2 0 D e a r J C P _ L e t t e r _ e m a i l _ w i t h % 2 0 T e k - Va % 2 0 P h s _ y f . p d f

Contributed by: Elaine Furmaga, Pharm. D.