Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Effectiveness Review Project – Literature Scan Summary

Month/Year of Review: January 2015
PDL Classes: Renin Angiotensin System Drugs and Combinations

Date of Last Review: January 2014
Source Document: OSU College of Pharmacy, Drug Effectiveness Review Project

Current Status of PDL Class:

Current Preferred Drugs	Current Non-Preferred Drugs
Angiotensin Converting Enzyme Inhibitors	
Benazepril (*Lotensin*) Enalapril (*Vasotec*) Lisinopril (*Prinivil*; *Zestril*) Ramipril (*Altace*)	Captopril (*generic*) Enalapril oral susp (*Epaned*) Fosinopril (*generic*) Moexipril (*Univasc*) Quinapril (*Accupril*) Trandolapril (*Mavik*) Perindopril (*Aceon*)
Angiotensin II Receptor Antagonists	
Olmesartan (*Benicar*) Losartan (*Cozaar*) Telmisartan (*Micardis*)	Azilsartan (*Edarbi*) Candesartan (*Atacand*) Eprosartan (*Teveten*) Irbesartan (*Avapro*) Valsartan (*Diovan*)
Direct Renin Inhibitors	
	Aliskiren (*Tekturna*)
Fixed Combination HCTZ Products	
Benazepril/HCTZ (*Lotensin HCT*) Enalapril/HCTZ (*Vaseretic*) Lisinopril/HCTZ (*Prinzide*; *Zestoretic*) Losartan/HCTZ (*Hyzaar*) Olmesartan/HCTZ (*Benicar HCT*) Telmisartan/HCTZ (*Micardis HCT*)	Captopril/HCTZ (*generic*) Fosinopril/HCTZ (*generic*) MoexiprilHCTZ (*Uniretic*) Quinapril/HCTZ (*Accuretic*) Candesartan/HCTZ (*Atacand HCT*) Eprosartan/HCTZ (*Teveten HCT*) Irbesartan/HCTZ (*Avalide*) Valsartan/HCTZ (*Diovan HCT*) Aliskiren/HCTZ (*Tekturna HCT*)

Abbreviations: HCTZ = hydrochlorothiazide; susp = suspension

Previous Conclusions and Recommendations:

- There is moderate quality evidence that dual blockade of the renin-angiotensin system (RAS) does not provide any benefit in all-cause mortality and cardiovascular (CV) mortality compared with monotherapy. There is also an increased risk of hyperkalemia, hypotension, renal failure and withdrawal due to adverse events with dual therapy compared to monotherapy.
- There is moderate quality evidence of no difference between ACE-inhibitors (ACEI) and angiotensin II receptor antagonists (AIIRA) in mortality, CV mortality, hospitalizations, and stroke.

- The JNC8 guideline recommends ACEIs, AIIRAs, thiazide diuretics or calcium channel blockers as options for initial treatment of hypertension (HTN) in the general non-black population based on comparable efficacy on overall mortality, CV, and cerebrovascular outcomes.
- There is insufficient evidence evaluating azilsartan/chlorthalidone combination therapy on long term clinical outcomes; maintain as non-preferred.
- There is no new comparative efficacy or safety evidence for preference of one agent over another within each class; no further review or research is needed.

Research Questions:
- For adults diagnosed with coronary heart disease, hypertension, left ventricular dysfunction, heart failure, non-diabetic chronic kidney disease, or diabetic nephropathy, what are the inter-class differences in effectiveness and harms between ACEIs, AIIRAs and DRIs?
- Are there subgroups based on demographics (age, racial groups, gender), other medications, or co-morbidities for which there are inter-class differences between ACEIs, AIIRAs and DRIs?
- Do fixed combination drug formulations containing an ACEI, ARB or DRI offer benefit in clinically relevant outcomes compared to the respective free drug combination?

Conclusions and Recommendations:
- There is moderate quality evidence of no difference between ACEIs and AIIRAs in regards to reduction in mortality, CV mortality, hospitalizations or stroke, or progression to chronic kidney disease. There is insufficient evidence at this time to suggest DRIs offer any benefit in these clinically relevant outcomes.
- There is moderate quality evidence that risk of dry cough and angioedema associated with ACEIs is higher than with AIIRAs or DRIs. Incidence of angioedema is also more common in heart failure patients than other populations. However, angioedema remains a very rare adverse effect of ACEIs.
- There is moderate quality evidence that dual blockade of the RAS does not provide additional benefit in clinically relevant outcomes compared with monotherapy and increases risk of harm, specifically the risk of hyperkalemia, hypotension, renal failure and withdrawal due to adverse events.
- There is insufficient evidence that fixed combination drug formulations containing an ACEI, AIIRA or DRI offer additional benefit in clinically relevant outcomes compared to the respective free drug combination.
- No further research is needed at this time. Evaluate comparative costs in the executive session.

Methods:
The DERP scan was used to identify any new comparative research on ACEIs, AIIRAs and DRIs since the last P&T review in January 2014.[1] An OVID MEDLINE search was also conducted to identify direct comparative studies of fixed combination drug formulations containing an ACEI, AIIRA or DRI with the respective free drug combination on clinically relevant outcomes such as mortality or morbidity.

Summary:
The DERP scan identified 18 direct comparative studies and 13 systematic reviews across all three drug classes since the previous DERP scan was performed in 2012. No studies evaluating clinically relevant outcomes were identified with the OVID MEDLINE search directly comparing fixed combination drug formulations containing an ACEI, AIIRA or DRI with the free drug combination.

Reference:

1. Holmes R. Drug Class Review on Angiotensin Converting Enzyme Inhibitors, Angiotensin II Receptor Antagonists and Direct Renin Inhibitors, Preliminary Update Scan 3, August 2014. Drug Effectiveness Review Project. Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University.

Author: A Gibler, Pharm.D. Date: January 2015