Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Angiotensin II Receptor Blockers***
-August 2014-

Background:
In August 2014, the IHS National Pharmacy and Therapeutic Committee (NPTC) convened to review antihypertensive medications available for IHS providers relevant to the recently released 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)[1]. One class of medications reviewed were the angiotensin II receptor blockers (ARBs) that include losartan (listed on National Core Formulary), candesartan, eprosartan, irbesartan, olmesartan, telmisartan, azilsartan and valsartan.

Discussion:
Angiotensin II receptor blockers are an effective and overall safe class of antihypertensive medications. All of the ARBs have an FDA indication for the treatment of hypertension and none appear to be significantly more effective than the others in blood pressure control[2]. In the JNC 8 guidelines, ARBs are listed among the choices for initial treatment of hypertension in the general non-black population along with thiazide diuretics, calcium channel blockers, and angiotensin converting enzyme inhibitors (ACEI). ACEI and ARBs are known to be less effective in the black population and are thus not recommended for initial therapy choices for these patients. In addition, in patients >18 years old with chronic kidney disease, an ACEI or ARB is recommended to be included in the treatment of hypertension to improve renal outcomes.

The ARB's also have FDA indications for Type 2 diabetic nephropathy (losartan, irbesartan), cardiovascular event reduction in patients unable to take an ACEI (telmisartan), post MI left ventricular dysfunction or failure to prevent CV mortality (valsartan), hypertension with left ventricular hypertrophy to prevent stroke (losartan), and in the treatment of heart failure (candesartan and valsartan). Though losartan does not have an FDA indication for heart failure, studies suggest that losartan 50 mg daily is at least equivalent to captopril 50 mg three times daily in reduction in all-cause mortality in patients with heart failure[3-4], and may have a greater effect at doses of losartan 150 mg daily as compared to losartan 50 mg daily[5]. ARBs appear to have similar though not superior long term effects on blood pressure control as compared to ACEI. It is recognized that ARBs are better tolerated than ACEIs, primarily due to ACEI induced cough[6]. However, in a recent meta-analysis among diabetic patients, unlike ACEIs, ARBs did not demonstrate a reduction in all-cause mortality, cardiovascular mortality, or major cardiovascular events[7]. Therefore, it is suggested that ARB's be primarily used for patients who are intolerant of ACEIs. ARBs have proven to be a beneficial alternative in patients who develop an ACEI induced cough[8], however caution should be exercised in the use of ARBs in patients who develop angioedema[9], and it is generally not recommended to use ARBs in patients who develop hyperkalemia, oliguria or renal failure while taking an ACEI[10].

It is recognized that hypertension will not likely be controlled with a single agent. The JNC 8 guidelines list any of the choices for initial therapy (thiazide diuretics, calcium channel blockers, ACEIs or ARBs) as acceptable choices for add-on therapy. It has also been shown that fixed dose combination drugs can potentially improve compliance and adherence. Azilsartan is available in fixed combination with chlorthalidone, while all the other ARBs are available in combination with hydrochlorothiazide. Also, olmesartan, telmisartan and valsartan are available in fixed dose combination with the calcium channel blocker amlodipine. Of special note, the combination of an ACEI and ARB is not recommended for the treatment of hypertension as well as their other indications due to an increase in adverse events without recognized improvement in clinical outcomes[11].

ARBs should not be used during pregnancy (Class D) and have a Black Box Warning regarding drugs that act directly on the renin-angiotensin system. These classes of medications can potentially cause injury or death to the developing fetus if used during the second or third trimesters. Renin-angiotensin inhibiting drugs are known to interfere with fetal kidney development causing oligohydramnios, pulmonary hypoplasia and skeletal deformities. Service units are encouraged to develop and maintain procedures to

prevent prescribing and dispensing of these medications to pregnant patients and for prompt discontinuation at the onset of pregnancy.

Findings:
ARBs are an effective and guideline-recommended class of medications in the treatment of hypertension (as well as for other indications including heart failure and for their reno-protective effects in treating hypertension in chronic kidney disease). ARBs should be primarily used in patients who develop cough when taking an ACEI. Due to its present low cost and overall common use of losartan throughout the agency, no changes were made and losartan was continued as the named product on the National Core Formulary (NCF). Discussions were held regarding the compliance and adherence advantages as well as the dosing titration and cost disadvantages with fixed dose combination medications. Though no fixed dose combination medications were approved for the NCF, plans were made to evaluate this issue in greater detail in a future meeting.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

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