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Class Update: Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Blockers (ARBs), and Direct Renin Inhibitors (DRIs)

EXECUTIVE SUMMARY:

Month/Year of Review: January 2012
New Product for review: azilsartan (Edarbi)
Manufacturer: Takeda Pharmaceuticals
Last Oregon Review: Feb 2010

Dossier received: Yes

Source Document: DERP

Available Alternatives

Current Preferred Agents:

ACEIs
benazepril
captopril
enalapril
fosinopril
lisinopril
moexipril
quinapril
ramipril
trandolapril

Thiazide Combo:
benazepril-Hydrochlorothiazide
Benicar HCT (olmesartan-hydrochlorothiazide)
captopril/hydrochlorothiazide
enalapril-Hydrochlorothiazide
fosinopril-Hydrochlorothiazide
lisinopril-Hydrochlorothiazide
losartan-Hydrochlorothiazide
Micardis HCT (telmisartan-hydrochlorothiazide)
moexipril-Hydrochlorothiazide
quinapril-Hydrochlorothiazide

ARBs
Benicar (olmesartan)
losartan
Micardis (telmisartan)

Current Non-Preferred Agents:

ACEIs
Aceon (perindopril)

ARBs
Atacand (candesartan)
Teveten (eprosartan)
Avapro (irbesartan)
Diovan (valsartan)

DRIs
Tekturna (aliskiren)

Combo Products:
Azor (amlodipine/olmesartan)
Exforge (amlodipine/valsartan)
Twynsta (telmisartan/amlodipine)
Valturna (aliskiren/valsartan)
Amturnide (aliskiren/amlodipine/hctz)
Tekamlo (aliskiren/amlodipine)
Lotrel (amlodipine/benazepril)
Tarka (trandolapril/verapamil)
Tekturna HCT

Previous Conclusions by HRC:

1. There are no clinically significant differences among ACE-Is or ARBs.
2. Combination therapy with an ACE-I and an ARB produces a reduction in proteinuria in nondiabetic proteinuria or chronic kidney disease but produced no clinically significant difference in other measures of renal function.
3. Rates of cough were lower with ARBs than ACE-Is however overall rates of withdrawal were the same.
4. There were no included studies that evaluated comparative effectiveness/ efficacy and harms between aliskirin as monotherapy or for combination therapy with ACE-I and ARB.
5. There was no significant difference found between ARBS and ACEIs for subgroups based on age, ejection fraction, or NYHA functional class

Reason for Review:

Since the last OR review in 2010 a high quality systematic review was performed for the Agency for Healthcare Research and Quality (AHRQ) to update their previous comparative effectiveness review to evaluate the long-term benefits and harms of ACEIs, ARBs, and DRIs for treating essential hypertension in adults[1]. This review looked at available comparative effectiveness research of DRIs while the previous DERP review only had placebo-controlled studies for the DRIs. Since this systematic review, a new ARB was added to the market. Azilsartan was approved by the FDA in February 2011 for treatment of hypertension[2]. There is also new evidence showing no advantage of combination therapy with an ACEI and ARB on clinical outcomes and more adverse effects associated with the combination.[3] In December, the ALTITUDE study with aliskiren was terminated due to the unlikely benefit from treatment and the higher incidence of adverse events identified in this study. In the treatment arm there was an increased incidence of non-fatal stroke, renal complications, hyperkalemia and hypotension. This was the first trial that evaluated the DRI aliskiren for longer than one year in high risk cardiovascular and renal patients.

Issues:

- Is there any new evidence that there is a meaningful difference in ACEIs, ARBS, and DRIs in long term clinical outcomes or safety that would precipitate changes to previous recommendations?
- Is there any evidence that azilsartan is more effective than currently available medications in the PDL drug class?
- Should azilsartan be added as a preferred agent on the OHA PDL class?

Conclusions:

The AHRQ systematic review concluded that the strength of evidence remains high for equivalence between ACEIs and ARBs for blood pressure lowering and use of a single antihypertensive agent, and a meaningful difference between ARBs and ACEIs only for short-term adverse events due to cough. The overall incidence of cough varies widely in clinical trials and has been reported to be in the range of 5 to 35% and a much lower incidence has been described in studies of patients presenting for the evaluation of chronic cough[4]. The evidence looked at since the initial review did not change any conclusions made regarding long term cardiovascular outcomes, quality of life, progression of renal disease, medication adherence, or persistence rates of angioedema, or differences in key patient subgroups and the strength of evidence remains low to moderate. There was insufficient evidence to reach conclusion for the DRIs for any outcomes of interest.

Azilsartan is the eighth ARB indicated for the treatment of hypertension to lower blood pressure either alone or in combination with other agents. Although recent studies have demonstrated that azilsartan is more effective than olmesartan, valsartan, and ramipril at lowering systolic BP[5-8], there is no evidence showing an impact in clinical cardiovascular outcomes, preventing mortality, or showing reduction in cardiovascular risk in patients with hypertension. In addition, other established ARBs have evidence for multiple indications including CHF, diabetic nephropathy, stroke prevention, and treatment of hypertension in pediatric patients while azilsartan is only indicated for blood pressure lowering. In short term studies, azilsartan seems to be well tolerated with the most common side effects being diarrhea and headache. Still, long term safety is unclear as a very limited number of patients have received the drug for at least one year. Losartan is currently the only ARB available in generic form.

Use of azilsartan in Specific Subpopulations:

Pediatric Use: Safety and effectiveness in patients under 18 years of age have not been established.

Geriatrics: No dose adjustment necessary. Abnormally high serum creatinine values were more likely to be reported for patients age 75 or older.

Gender, race, and ethnicity: Azilsartan was effective in reducing blood pressure regardless of the age, gender, or race of patients, but the effect was smaller in black patients, approximately half, who tend to have lower renin levels. This is similar to other drugs in this class.

Place in therapy:
The value of azilsartan remains unclear until longer term studies evaluating clinical outcomes and additional indications are conducted.

Recommendations:
1. Due to lack of comparative effectiveness research for any clinical outcomes, recommend maintaining all DRI's and products containing a DRI as non-preferred on the current PDL.
2. Due to lack of long term studies demonstrating reduction of cardiovascular events and mortality or long-term safety data compared to multiple alternatives, recommended making azilsartan a nonpreferred ARB.
3. No significant evidence exists since last OHA class review that would mandate changes to PDL medications based on comparative effectiveness research. Recommend comparing costs of agents for any further additions or eliminations to preferred products.

I. Background

An estimated 80 million Americans have cardiovascular disease and 73.6 million of these people have hypertension.[9] The renin-angiotensin-aldosterone system (RAAS) has long been considered a significant contributor to CVD through increases in blood volume, arterial pressure, and vascular lesions. Agents used to modulate the RAAS include ACEIs, ARBS, and DRIs.[8] The strength of the evidence in support of renin-angiotensin system blockade has led to incorporation of ACE-Is and ARBs into important clinical guidelines in the treatment of several medical conditions including hypertension, congestive heart failure, and renal disease. The recently updated guidelines published by the National Institute for Health and Clinical Excellence (NICE) recommend treating hypertension with an ACE or a low cost ARB if an ACE is not tolerated as step 1 treatment in patients under 55 years old secondary to evidence showing no meaningful difference between ACEIs and ARBs on major clinical outcomes including death, cardiovascular events, stroke, and diabetes. They also recommend not combining an ACE and an ARB for treatment of hypertension due to evidence showing no advantage on clinical outcomes and more associated adverse effects when using the combination[3]. Although outdated, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) recommends an ACEI or ARB for patients with hypertension who have heart failure, diabetes, or chronic kidney disease.[10] The Kidney Disease Outcome Quality Initiative guidelines recommend ACEIs or ARBs for patients with diabetic or non-diabetic proteinuric renal disease[11]. ACEIs are also recommended in all patients with symptoms of heart failure and reduced ejection fraction and ARB's are recommended as alternatives[12].

Hypertension is a highly prevalent disease that is a major risk factor for cardiovascular disease. There is growing evidence for increased CV complications and mortality associated with hypertension and higher BP levels, including an increased rate of death due to stroke and ischemic heart disease. The Framingham Heart Study found an association between BP category and incidence of CV disease and data from the National, Heart, Lung, and Blood Institute indicate that hypertension is associated with a shorter overall life expectancy. Therapies aimed at the RAAS are frequently used for the lowering of blood pressure as well as in other indications such as heart failure, myocardial infarction, diabetes, and renal disease.

Current guidelines recommend a step-wise approach from lifestyle modifications to monotherapy or combination therapy, as many patients cannot reach goal on one drug and will require two or more antihypertensive agents selected from different classes. The target BP for patients with hypertension is < 140/90 mm Hg and <130/80 for whose with diabetes mellitus, heart disease, or renal disease. Despite the availability of a wide selection of antihypertensive agents, optimal BP control remains a challenge. Although ACEIs, ARBS, and DRIs all target the renin system, they all do so in a slightly different way, targeting the pathway at different points and questions still arise whether there are any differences in these classes are in fact equivalent and how they compare in effecting clinical outcomes

II. Systematic Reviews:

AHRQ Review[1] :

Published in June 2011
Compared the ACEIs, ARBs, and DRIs in both efficacy and safety in adult patients with hypertension. Clinical outcomes of interest were blood pressure control, mortality, morbidity, safety, persistence/adherence, cardiovascular risk reduction, and quality of life. They also assessed if there was any evidence showing that different subgroups of patients tolerated the different agents better.

The review included only relevant head to head comparator studies that had a minimum of 12 weeks follow-up.

Did not include studies comparing the newest ARB, azilsartan.

Conclusions:

1. There is high quality evidence that ACEIs and ARBs appear to have similar long-term effects on blood pressure. There is low quality evidence regarding the effects of DRIs on blood pressure and is only based on three studies.
2. There is low quality evidence that shows no difference exists between ACEIs and ARBs regarding mortality and major cardiovascular events due to extremely low numbers of the outcomes that were reported. There is insufficient evidence comparing DRIs to detect a difference in these outcomes.
3. There is low quality evidence that there are differences between ACEIs and ARBs in quality of life and insufficient evidence comparing DRIs.
4. There is high quality evidence that there is a difference in withdrawals due to adverse events between ACEIs and ARBs and this can be contributed to an increased risk of cough associated with the ACEIs than ARBs. Cough is the only adverse event shown to have evidence of difference across treatment rates.
5. There is low quality evidence showing no significant difference comparing DRIs and ACEIs in withdrawals due to adverse events.
6. Evidence does not support any conclusions regarding comparative effectiveness or safety in patient subgroups based on age, race, ethnicity, sex, comorbidities, and concurrent use of other medications.

Remaining Issues:
There is still little comparative evidence for long-term benefits or harms of ACEIs and ARBs, and DRIs in particular about death or major cardiovascular events. There is very limited comparative effectiveness research for the DRIs versus ACEIs or ARBS with only 3 studies meeting the authors' inclusion criteria for evaluation and reporting.

Further comparative studies are needed to emphasize:

- Subgroups of importance
- Outcomes over several years to compare cardiovascular and cerebrovascular events
- Cancer-related outcomes
- Broader representation of groups to include the elderly and ethnic minorities
- Long-term comparisons of DRIs with ACEIs and ARBs
- Evaluation of differential effects of specific medications that are different than other agents within the class

Although this recent AHRQ systematic review only evaluated outcomes in patients with hypertension the most recent DERP report found similar results when comparing ACEIs and ARBs in clinical outcomes including cardiovascular events, mortality, quality of life, renal function, and symptoms in patients with heart disease, diabetic proteinuria, nondiabetic proteinuria and chronic kidney disease. This report also concluded that ARBs are not different from, nor inferior to, ACEIs.[12]

III. New ARB: Azilsartan

Clinical Findings –

Azilsartan is an ARB indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents. Azilsartan was approved based on the results of seven double-blind, randomized studies involving a total of 5,941 patients with hypertension ranging from 6 weeks to 6 months in duration; two of which have been published and peer reviewed. These studies only evaluated azilsartan's effects on the intermediate biomarker of blood pressure. There is no evidence with long term clinical outcomes assessed. Azilsartan has been compared head to head with the other ARBS olmesartan and valsartan as well as with the ACEI ramipril.[2] The details of the 2 published full-text head to head trials are shown in the evidence table found in Appendix 1.

One double-blind, placebo-controlled, randomized trial compared azilsartan 40mg and 80mg to valsartan 320mg, or olmesartan 40mg daily for 6 weeks. The primary efficacy end point was the change from baseline in 24-hour mean SBP. Azilsartan 80mg showed a statistically significant greater change in baseline in mean difference compared to both valsartan and olmesartan (-4.3 and -2.5 respectively) while azilsartan 40mg had a statistically significant mean difference in BP compared to valsartan only -3.2) and was noninferior to olmesartan. Safety and tolerability were similar among the placebo and all active treatments[6].

In another double-blind, randomized, placebo-controlled trial, patients were randomized to placebo, azilsartan 20mg, 40mg, or 80mg or olmesartan 40mg daily for 6 weeks. The change in 24-hour SBP was significantly greater with azilsartan 80mg compared to olmesartan 40mg (mean difference -2.1), while azilsartan 40mg was found to be noninferior[8].

Both of these studies uses similar inclusion and exclusion criteria and were rated as fair quality. They both had extensive exclusion criteria and had unclear information regarding their randomization methods. In subgroup analysis, both studies saw differences only in the black population which is consistent with previous findings.

There are additional comparative effectiveness studies conducted evaluating blood pressure that have not been published. The abstracts for these were presented at the 2010 European Meeting on Hypertension and can be found in the Journal of Hypertension. Preliminary results from a randomized, double blind study showed that azilsartan 40mg and 80mg reduced both clinic and mean 24-hour systolic BP significantly more than did ramipril 10mg and there were less discontinuations due to adverse events and cough with both doses of azilsartan. [14] In another trial, azilsartan was combined with the diuretic chlorthalidone and provided further SBP reduction from baseline and appeared to be superior to the combination of olmesartan and hydrochlorothiazide[15]. Additive effects on blood pressure of amlodipine combined with azilsartan have also been demonstrated.[16]

The short duration of these studies remains an important limitation making it difficult to evaluate the long-term benefit and side effects of azilsartan. There is no evidence on the possible role of azilsartan in preventing mortality and CV morbidity.

Clinical pharmacology [17]

Azilsartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues. Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Drug safety [17]

Black Box Warning: Avoid use in pregnancy. If pregnancy is detected, azilsartan should be discontinued as soon as possible to avoid serious injury or even death to the developing fetus.

Pregnancy/Lactation rating: Pregnancy Category C (first trimester) and D (second and third trimesters).

Dose Index (efficacy/toxic): Limited data are available related to overdosage in humans. During controlled clinical trials in healthy subjects, once daily doses up to 320 mg of azilsartan were administered for 7 days and were well tolerated.

Common Drug-Related Adverse Events[17]**:**

Treatment with azilsartan was well-tolerated with an overall incidence of adverse reactions similar to placebo. The most common adverse effect was diarrhea with an incident of 2%.The rate of withdrawals due to adverse events in placebo-controlled monotherapy and combination therapy trials was 2.4 % for placebo, 2.2% for azilsartan 40 mg, and 2.7% for azilsartan 80 mg. The most common adverse event leading to discontinuation, hypotension/orthostatic hypotension, was reported by 0.4% (8/2146) patients randomized to azilsartan 40 mg or 80 mg compared to 0% (0/801) patients randomized to placebo. Generally, adverse reactions were mild, not dose related and similar regardless of age, gender and race.

Other adverse reactions that have been reported with an incidence of >0.3% and greater than placebo are:
Gastrointestinal Disorders: nausea
General Disorders and Administration Site Conditions: asthenia, fatigue
Musculoskeletal and Connective Tissue Disorders: muscle spasm
Nervous System Disorders: dizziness, dizziness postural
Respiratory, Thoracic and Mediastinal Disorders: cough

Appendix 1:
COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Cardiovascular Mortality
3) Cardiovascular Hospitalizations
5) Withdrawals due to adverse events

Primary Study Endpoint: 1) Change from baseline in 24-hour mean SBP by ambulatory blood pressure monitoring.

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population/ Duration	N	Efficacy Results[2]	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
1.White et al RCT, DB[6] 491-019	1. azilsartan (AZ) 40mg 2. Azilsartan (AZ) 80mg 3. Valsartan (VAL 320mg 4. Olmesartan (OLM) 40mg 5. placebo	Adults whose SBI was between 150 and 180 and whose mean 24-hour SBP was between 130 and 180 Mean age 56 54% men Duration = 6 weeks	1. 280 2. 285 3. 254 4. 290 5. 154	<u>Change in 24 h mean baseline SBP (mean treatment difference in mm Hg)</u> <u>*Vs. Placebo*</u> AZ 40mg -13.2 P<0.001 AZ 80mg -14.3 P<0.001 VAL 320mg -9.9 P<0.001 OLM 40mg -11.7 P<0.001 <u>*Vs. Olmesartan*</u> AZ 40mg -1.4 95% CI (-3.3,-0.5) P=0.136 AZ 80mg -2.5 95% CI (-4.4,-0.6) P= 0.009 <u>*Vs. Valsartan*</u> AZ 40mg -3.2 P=0.001 AZ 80mg -4.3 95% CI (-6.3,-2.4) P<0.001	 N/A N/A N/A N/A NS N/A N/A N/A	<u>Discontinued due to adverse events:</u> 1. 7 (2.5%) 2. 9 (3.2%) 3. 8 (2.8%) 4. 6 (2.1%) 5. 4 (2.6%)	 NS	Fair: Significant cardiovascular exclusion criteria making it hard to generalize to population Eligible patients underwent a 3 to 4 weeks washout period before randomization Among all randomized patients, 96 % were included in the data analysis Unclear if allocation concealment or appropriate randomization took place There was a marginally statistically significant treatment difference between black and white patients *Clinical outcomes of Mortality, Cardiovascular Mortality, and Cardiovascular Hospitalizations not reported

2.Bakris, et al[8] RCT, DB 491-008	1. azilsartan (AZ)20mg 2. Azilsartan (AZ) 40mg 3. Azilsartan(AZ) 80mg 4. Olmesartan (OLM) 40mg 5. placebo	Adults whose SBI was between 150 and 180 and Whose 24 hr mean SBP was between 130 and 170 Mean age 58 Duration = 6 weeks	1. 283 2. 283 3. 285 4. 282 5. 142	<u>Change in 24 h mean baseline SBP (mean treatment difference in mm Hg)</u> *<u>Vs. Placebo</u>* AZ 20mg -10.8 95%CI (-13.2,-8.3) P<0.001 AZ 40mg -12.1 95%CI (-14.5,-9.7) P<0.001 AZ 80mg -13.2 95%CI (-15.6,-10.8) P<0.001 OLM -11.2 95%CI (-13.6,-8.8) P<0.001 *<u>Vs. Olmesartan</u>* AZ 20mg -0.4 95%CI (-1.6,-2.4) P=0.687 AZ 40mg -0.92 95%CI (-2.9,1.0) P=0.352 AZ 80mg -2.1 95%CI (-4.0.-0.1) P=0.038	 N/A N/A N/A N/A NS NS N/A	Discontinued due to adverse events: 1. 11(3.9%) 2. 3(1.1%) 3. 6(2.1%) 4. 4(1.4%) 5. 6(4.2%)	 NS	Fair; Significant cardiovascular exclusion criteria making it hard to generalize to population Unclear if allocation concealment or appropriate randomization took place Black population subgroup demonstrated a trend for less BP reduction in all active treatment groups compared with Caucasians, but a trend of greater efficacy with azilsartan 80mg compared with olmesartan 40mg Low rates of attrition. *Clinical outcomes of Mortality, Cardiovascular Mortality, and Cardiovascular Hospitalizations not reported

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, STEMI – ST-segment elevation myocardial infarction, NSTEMI – non-ST-segment elevation myocardial infarction

Appendix 2 : Specific Drug Information

DOSE & AVAILABILITY:

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
40mg	Tab	PO	Daily	None	None	Not Established	None	Caution in patients with Volume or Salt-depleted Patients. Consider starting with lower 40mg dose for those on high dose diuretics.
80mg	Tab	PO	Daily	None	None	Not Established	None	

Pharmacokinetics

Parameter	Result
Oral Bioavailability	60%
Cmax	1.5-3 hours
Protein Binding	>99%
Elimination	Feces 55% Urine 42% Metabolite 15%
Half-Life	11 hours
Metabolism	O-dealkylation decarboylation

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