Brand Name: Edarbi

Generic Name: azilsartan

Manufacturer[1]: Takeda Pharmaceutical Company

Drug Class[1,2,3,4,5]: Anti-hypertensive, Angiotensin II receptor blocker

Uses:

Labeled Uses[1,2,3,4,5]: Hypertension, alone or as adjunctive therapy with other antihypertensives
Unlabeled Uses:

Mechanism of Action[1,2,3,4,5]: Azilsartan inhibits the binding of angiotensin II to AT_1 receptor. This blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II.

Pharmacokinetics[1,2,3,4,5]:

Absorption:

T_{max}	1.5-3 hours
V_d	16 L
$t_{1/2}$	11 hours
Clearance	2.3 mL/min
Protein binding	>99%
Bioavailability	60%

Metabolism: Azilsartan is metabolized via O-dealkylation and decarboxylation into two primary metabolites. CYP2C9 is the major enzyme responsible for azilsartan metabolism.

Elimination: Azilsartan is eliminated through the feces (55%) and the urine (42%). Only 15% is eliminated as the unchanged drug.

Efficacy:

Bakris GL, Sica D, Weber M, White WB, Roberts A, Perez A, Cao C, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. Journal of Clinical Hypertension. 2001;13(2):81-88.

Study Design: Randomized, double-blind, multicenter, parallel group, placebo-controlled study design

Description of Study: *Methods:* One thousand two hundred seventy-five patients meeting the criteria of primary hypertension were randomized to receive either placebo, 40mg of olmesartan, or 20mg, 40mg, or 80mg of azilsartan for six weeks. The primary end point, change in 24 hour mean systolic blood pressure at week six, was assessed by ambulatory blood pressure monitoring performed at baseline and the final visit. The key secondary endpoint was change in trough sitting clinic systolic blood pressure at week six. Safety was assessed by adverse event

reports. *Outcome Results:* The change in 24-hour systolic blood pressure was significantly greater when comparing 80mg of azilsartan to 40mg of olmesartan with a treatment difference of -2.1mm Hg(95% CI, -4.0 to -0.1; p=0.038). There were no significant differences between 40mg azilsartan and 40mg olmesartan. All strengths of azilsartan were more effective than placebo at reducing systolic blood pressure (p<0.001). The only significant differences in trough sitting clinic systolic blood pressure was observed in 80mg azilsartan versus 40mg olmesartan with a treatment difference of -2.7mm Hg(95% CI, -5.3 to -0.1;p=0.043). The adverse events reported were similar among the groups.

Limitations: This study was sponsored by Takeda Global Research and Development Center, the manufacturer of Edarbi. In addition, all of the authors are either employees of Takeda or have served as consultants of Takeda, suggesting a potential conflict of interest. The primary endpoint was measured using ambulatory blood pressure monitoring. It is difficult to compare this result to other studies as most trials use office blood pressure measurements. The variability of the outcomes were reported as a standard error of the mean, rather than standard deviation. Furthermore, the actual values of variability were not provided. This may have affected the clinical significance of the results.

Conclusion: At a dose of 80mg, azilsartan is superior to the maximum approved dose of olmesartan, 40mg, in reducing systolic blood pressure. The authors observed a 2.1mm Hg difference in systolic blood pressure, which they consider to be clinically significant as differences of 2 to 3mm Hg or more have been associated with cardiovascular risk reduction. In practice however, this difference is not clinically significant. Based on the adverse effects reported, azilsartan appears to have similar side effects to olmesartan. However, further safety studies are needed as the significance of the adverse effects was not apparent (i.e., no p-values were reported) and the duration of the study was not long enough to assess long term adverse effects.

White WB, Weber MA, Sica D, Bakris GL, Perez A, Cao C, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension. 2011;57(3):413-420.

Study Design: Randomized, double-blind, multicenter, parallel group, placebo- and active-controlled trial study design

Description of Study: *Methods:* 1285 patients with stage 1 or stage 2 hypertension were randomized to receive one of the following: 40mg azilsartan, 80mg azilsartan, 320mg valsartan, 40mg olmesartan, or placebo. Patients received half of the intended dose for the first two weeks and were then force-titrated to the aforementioned doses for the remaining four weeks. The primary end point was the change from baseline in the 24-hour mean systolic blood pressure after six weeks of treatment. The secondary end points were change from baseline in trough, seated, clinic systolic blood pressure and change from baseline in the 24-hour mean and clinic diastolic blood pressures. Safety evaluations were performed at every clinic visit. *Outcome Results:* The mean difference in 24-hour systolic blood pressure between 80mg azilsartan and olmesartan was -2.5mmHg (95% CI, -4.4 to -0.6; p=0.009) and between 80mg azilsartan and valsartan was -4.3mm Hg (95% CI, -6.3 to -2.4; p<0.001). 40mg azilsartan was noninferior to valsartan and olmesartan. In the secondary outcome measure for change from baseline in the clinic systolic blood pressure, both 40mg and 80mg azilsartan had significantly larger reductions

compared to valsartan and olmesartan at the end of the study. Changes in both 24-hour and clinic diastolic blood pressures were significantly greater for 80mg azilsartan than both valsartan and olmesartanHowever, 40mg azilsartan was only significantly greater than valsartan. No significant differences in adverse effects were noted between the five treatment groups.

Limitations: This study was funded by Takeda, manufacturer of Edarbi. It was written by the authors who are employees and/or consultants for Takeda. Thus, a potential conflict of interest exists. At baseline, there were statistically significant differences between the groups that may have affected the clinical significance of the results. Because this study only lasted for six weeks, it is unclear how azilsartan's efficacy and safety compares to valsartan and olmesartan over a long duration. The authors reported standard error of the mean, instead of standard deviation. The large variability of the study results may limit the clinical significance. The statistical significance of adverse effects was not apparent as no p-values were provided.

Conclusion: Azilsartan demonstrated superior efficacy at a dose of 80mg to the maximum doses of olmesartan and valsartan. At a lower dose of 40mg, azilsartan was more efficacious than the maximum dose of valsartan. This supports the effectiveness of azilsartan in treating patients with stage 1 and 2 hypertension. It appears that the significant reductions in blood pressure using azilsartan were not associated with an increase in adverse effects. However, more safety studies are needed to address the significance of the adverse effects.

Sica D, White DB, Weber MA, Bakris GL, Perez A, Cao C, et al. New angiotensin II receptor blocker azilsartan medoxomil: comparison to valsartan [abstract PP.16.88]. Journal of Hypertension. 2010;28(e suppl A):e276.

Study Design: Multicenter, randomized, double-blind, parallel-group, active-controlled study design

Description of Study: *Methods:* 982 patients with primary hypertension were randomized to receive 40 mg of azilsartan, 80mg of azilsartan, or 320mg of valsartan per day for twenty-four weeks. For the first two weeks, patients received half of the intended dose and were then force-titrated to the higher final dose for the duration of the study. The primary outcome measure was the change from baseline to twenty-four weeks in 24-hour mean systolic blood pressure measured by ambulatory blood pressure monitoring. The key secondary outcome measure was the change from baseline to twenty-four weeks in sitting trough clinic systolic blood pressure. In addition to efficacy, safety and tolerability were also assessed. *Outcome Results:* 80mg of azilsartan showed superior efficacy over valsartan in the primary outcome. The mean change from baseline in 24-hour mean systolic blood pressure versus valsartan was -4.0 (95% CI, -6.0 to -2.1; $p<0.001$). The lower dose, 40mg, of azilsartan also showed superior efficacy versus valsartan with a mean change from baseline in 24-hour mean systolic blood pressure of -3.6 (95% CI, -5.6 to -1.7; $p<0.001$). Both doses of azilsartan also showed a significantly greater decrease in clinic systolic blood pressure versus valsartan. Adverse events were generally similar between the groups.

Limitations: This study was only published as an abstract, not as a peer-reviewed article. Multiple authors were consultants and/or employees of Takeda and this is a potential conflict of interest. Patients with diabetes were excluded from this study and this is a prime group who could potentially benefit from azilsartan. The statistical variability is presented as standard error

of the mean rather than standard deviation. This makes the results appear more clinically significant than they actually are.

Conclusion: While azilsartan demonstrated superior efficacy over valsartan in this study, the data would be more substantial if the results were published fully in a peer reviewed format. It is difficult to assess the results with the limited information provided from the manufacturer.

Contraindications[1,2,3,4,5]: No known contraindications at this time.

Precautions[1,2,3,4,5]:

Fetal/Neonatal Morbidity and Mortality (Black Box Warning): Drugs that interfere with the renin-angiotensin system can cause morbidity and death of the fetus when given to a pregnant woman during the second or third trimester. Azilsartan is a category C drug during the first trimester and category D in the second and third trimesters. Azilsartan should be discontinued as soon as possible when pregnancy is detected. Using azilsartan during breastfeeding is not recommended as it is unknown if azilsartan is excreted in breast milk.

Hypotension in Volume – or Salt-Depleted Patients: After starting azilsartan, symptomatic hypotension may occur in these patients. Before initiating azilsartan, correct volume or salt depletion or start azilsartan at 40mg. If hypotension does occur, place the patient in supine position and given an infusion of normal saline, if necessary. Once the blood pressure has stabilized, treatment with azilsartan can be continued.

Impaired Renal Function: In patients whose renal function may depend on the activity of the renin-angiotensin system, treatment with angiotensin receptor blockers and angiotensin-converting enzyme inhibitors has been associated with oliguria or progressive azotemia and rarely with acute renal failure and death.

Anaphylactic Reactions and Angioedema: Use caution when prescribing azilsartan for patients with a history of angioedema related to ACE inhibitor therapy. Although angiotensin II receptor blockers do cause an accumulation of kinins, angioedema has been reported rarely in patients taking an angiotensin II receptor blocker.

Pediatric Use: Safe use has not been evaluated in children under the age of 18.

Geriatric Use: No dosage adjustment is needed. Significant increases in serum creatinine were seen more often in adults greater than 75 years of age.

Adverse Effects[1,2,3,4,5]:

Occurring in > 1% and < 10% of patients

Gastrointestinal

Diarrhea (2%)

Other

Fatigue (1.1-2.5%)

Occurring in < 1%

Cardiovascular

Hypotension/Orthostatic hypotension (0.4%)

Gastrointestinal

Nausea (0.3%)

Hematologic

Low hemoglobin (0.2%)

Low hematocrit (0.4%)

Low red blood cell count (0.3%)

Neurologic

Asthenia (0.3%)

Dizziness (0.3%)

Postural dizziness (0.3%)

Renal

Oliguria

Progressive azotemia

Respiratory

Cough (0.3%)

Drug Interactions[1,2,3,4,5]:

Non-steroidal anti-inflammatory agents including selective cyclooxygenase-2 inhibitors

Co-administration of NSAIDs with azilsartan in patients who are elderly, volume-depleted, or who have compromised renal function may result in deterioration of renal function. The antihypertensive effects of azilsartan may be lessened by NSAIDs.

Co-administration with drugs that cause hyperkalemia

Eplerenone, potassium salts, postassium-sparing diuretics, tolvaptan, trimethoprim

Co-administration with drugs that cause hypotension

Other antihypertensives, amifostine, diazoxide, ethanol, MAO inhibitors, pentoxyifylline, phosphodiesterase 5 inhibitors, prostacyclin analogues

Co-administration with drugs that diminish the antihypertensive effect of antihypertensives

Methylphenidate, yohimbine

Lithium

Azilsartan may increase the serum concentration of lithium.

Rifamycin derivatives

Rifamycin derivatives may increase the metabolism of azilsartan.

Rituximab

Azilsartan may enhance the hypotensive effect of rituximab.

Sodium phosphates

Azilsartan may enhance the nephrotoxic effects of sodium phosphates.

Dosing/Administration[1,2,3,4,5]:

Adult Dosing

Initial dose: 80mg/day as a single dose in otherwise healthy patients; consider 40mg/day as a single dose in patients with volume depletion

Maintenance dose: 80mg/day as a single dose

Pediatrics (<18 years old)

Due to lack of study, use of azilsartan in pediatric patients should be avoided.

Elderly

No dose adjustment for azilsartan is needed for elderly patients.

Renal Impairment

No dose adjustment is required in patients with mild-to-severe renal impairment or end-stage renal disease. Monitor serum creatinine, especially following initiation of azilsartan.

Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. Azilsartan has not been studied in patients with severe hepatic impairment.

Use in special circumstances:

Overdosage[1,5]: Limited data is available in regards to overdosage in humans. If an overdose occurs, supportive therapy should be instituted as needed per the patient's clinical status. Azilsartan is not dialyzable.

Conclusion:

Azilsartan is an effective therapy for patients with stage 1 or stage 2 hypertension. While it has been proven to be statistically superior to both olmesartan and valsartan, studies are needed that compare it to the other angiotensin II receptor blockers in order to determine its place in therapy for that class of drugs. Cost considerations may be important with the availability of current and soon-to-be available generic angiotensin II receptor blockers. The side effects and adverse events appear to be minimal and are similar to other angiotensin II receptor blockers. However, it is difficult to assess the significance of the adverse events compared to other drugs within the same class as previous studies have not provided the p-values for this information. Based on its effectiveness and tolerability, azilsartan appears to be another clinically useful antihypertensive agent.

Recommended References:

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5. Azilsartan Medoxomil Oral. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: June 11, 2011.
6. Bakris GL, Sica D, Weber M, White WB, Roberts A, Perez A, Cao C, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. The Journal of Clinical Hypertension. 2001;13(2):81-88.
7. White WB, Weber MA, Sica D, Bakris GL, Perez A, Cao C, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension. 2011;57(3):413-420.
8. Sica D, White DB, Weber MA, Bakris GL, Perez A, Cao C, et al. New angiotensin II receptor blocker azilsartan medoxomil: comparison to valsartan [abstract PP.16.88]. Journal of Hypertension. 2010;28(e suppl A):e276.

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