



**Indian Health Service  
National Pharmacy and Therapeutics Committee**

**Aliskiren Monograph  
Date: April 2012**



**Introduction:**

The purpose of this review is to support the IHS National P&T Committee in making recommendations for the IHS National Core Formulary (NCF) regarding the place in clinical practice of aliskiren (Tekturna®). Aliskiren is used for the treatment of hypertension.

Hypertension is a major risk factor for stroke, myocardial infarction, heart failure, aneurysms of the arteries, peripheral arterial disease, and is a main contributor of chronic kidney disease. Sometimes hypertension is referred to as the “silent killer,” because it usually has no symptoms. However, even moderate elevations in arterial blood pressure, is associated with a shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications. If these measures do not improve blood pressure control, or are not sufficient alone, drug treatment may become necessary. Essential/primary hypertension accounts for approximately 95% of reported cases. Intervention guidelines for the treatment of essential/primary hypertension and those with concomitant disease states, are contained in the JNC 7 document produced by the National Institutes of Health.<sup>1</sup>

Hypertension is widely prevalent among the general population in the United States. There is a 31.3 percent prevalence among this group and a 30 percent prevalence among American Indian and Alaska Natives (AI/AN).<sup>2,3</sup> According to the IHS Fact Sheet, “disparities of the heart” are one of the five leading causes of death among AI/AN (2004 – 2006).<sup>4</sup> Also, rates of death from cardiovascular disease among AI/AN patients is 206.2 per 100,000. This is almost five times the rate of mortality caused by stroke in AI/AN patients.<sup>4</sup>

**Pharmacology/Pharmacokinetics:**

Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to angiotensin I. Whether aliskiren affects other renin-angiotensin-aldosterone system (RAAS) components (ie, angiotensin converting enzyme inhibitor (ACEI) or non-ACEI pathways) is not known.

**Table 1. Pharmacokinetic Properties<sup>5,6</sup>**

Absorption	Distribution	Metabolism	Excretion
Bioavailability: Poorly absorbed ~2.5% of oral dose  Food: Avoid high fat meals AUC decreases 71% and Cmax decreases 85%	Cmax: 1 – 3 hours  Half-life( $t^{1/2}$ ): 24 hours  Steady state blood levels are reached in 7 – 8 days.	CYP 3A4	~25% of absorbed dose found unchanged in urine

**FDA Approved Indications:<sup>5,6</sup>**

- Approved by the FDA for treatment of hypertension on March 5, 2007
- May be used as monotherapy or in conjunction with other anti-hypertensive medications

**Current National Core Formulary Alternatives:**<sup>7</sup>

- Currently there are no other renin inhibitors currently approved by the FDA
- Calcium Channel Blockers: amlodipine; nifedipine; diltiazem; verapamil
- Angiotensin Receptor Blockers: “any product”
- Beta-Blockers: atenolol; carvedilol; metoprolol
- Angiotensin Converting Enzyme Inhibitors: lisinopril
- Diuretic: hydrochlorothiazide

**Dosage and Administration:**

**Table 2. Dosage and Administration**<sup>5</sup>

Agent	Indication	Dosage	Comments
aliskiren	Hypertension	<i>Initial:</i> 150 mg once daily <i>Titration:</i> May increase to 300 mg once daily after 2 weeks <i>Max:</i> 300 mg once daily*	Pregnancy Cat D  No dosage adjustment necessary for renal or hepatic impairment and elderly; caution in severe renal disease due to limited data

\*Increased incidence of diarrhea with higher doses, without improved BP control

**Efficacy:**

**Monotherapy:**

Although JNC 7 was released prior to aliskiren approval by the FDA, an expert consensus from the American Heart Association released in 2011 states that aliskiren, “appears as effective as ARBs and ACEIs for BP management...”<sup>8</sup> The consensus does not list it as a first line option in their treatment algorithm. However, three randomized controlled trails compared aliskiren to placebo with primary end points of lowering diastolic blood pressure (DBP) by greater than 10 mmHg and/or to less than 90 mmHg significantly reduced DBP ( P < 0.0001 ). The trials used both currently approved doses (150mg and 300mg); unapproved daily doses were also tested (75mg and 600mg). The trials included men and women over 18 years of age with essential mild to moderate hypertension at a baseline of DBP of between 95 mmHg to 110 mmHg. Secondary end points of lowering mean systolic blood pressure (SBP) from baseline were also statistically significant (P < 0.0001).<sup>9-11</sup> One of these trials also compared aliskiren to irbesartan and found similar blood pressure lowering effects with 150 mg daily of aliskiren and 150 mg daily of irbesartan.<sup>10</sup>

**Table 3. Monotherapy Study Results**<sup>12</sup>

Trial	N	Aliskiren 150mg	Aliskiren 300mg	Placebo	Comparator <sup>#</sup>
Oh BH et al. <sup>8</sup>	662	-10.3 + 0.63	-11.1+0.64	-4.9+0.64	NA
Kushiro et al. <sup>10</sup>	455	-7.75 + 0.76	-10.72+0.75	-3.26+0.75	NA
Gradman AH <sup>9</sup> et al.	652	-9.28 + 0.76	-11.77+0.75	-6.34+0.75	-8.88+0.74 (irbesartan 150 mg)

Note: Information within this document is current as of this writing and should not replace clinical judgment.

# - change in diastolic blood pressure (DBP)

### **Combination Therapy:**

There are multiple studies that examined the relationship between aliskiren alone, a comparator, and combination of aliskiren and the comparator.

Oparil et al. published results from an 8-week, randomized, double-blind trial that evaluated patients with hypertension receiving aliskiren 150 mg and valsartan 160 mg, both titrated over four weeks to max doses of 300 mg and 320 mg, respectively. These were then compared to the combination product; where it was shown the combination product was more effective in decreasing blood pressure than either agent alone.<sup>13</sup>

Pool et al. published results from an 8-week, randomized, placebo controlled trial that assessed the effectiveness of aliskiren monotherapy (75,150,300mg), valsartan monotherapy (80,160,320mg), combination aliskiren and valsartan (75/80,150/160,300/320mg), combination valsartan/HCTZ (160/12.5mg), and compared these all versus placebo. It is important to note, that this was the first study to examine the comparison between monotherapies and combination therapy with an angiotensin receptor blocker. The study was not built with enough statistical power to provide conclusive evidence. Only the aliskiren 300mg dose was statistically significant against placebo in DBP reduction. The combination aliskiren and valsartan provided additional, but largely nonsignificant reductions in BP compared with the respective monotherapy. This study provides support for further studies into the potential for aliskiren combo products.<sup>14</sup>

In 2007, Vilamil et al. published results from an 8-week, double-blind, placebo-controlled trial in 2752 hypertensive patients. The primary endpoint was change in mean sitting diastolic blood pressure (MSDBP) from baseline to week eight, and were treated with aliskiren (75, 150, or 300 mg), hydrochlorothiazide (HCTZ) (6.25, 12.5, or 25 mg), the combination of aliskiren and HCTZ, or placebo. The study showed that both doses of aliskiren (150mg & 300mg) were superior to placebo, and all three doses of HCTZ were superior. All combination therapies were superior to placebo, and most were superior to both monotherapies except for aliskiren/HCTZ 150/6.25mg versus either monotherapy and aliskiren/HCTZ 75/12.5mg versus HCTZ monotherapy.<sup>15</sup>

There were two other 8 week randomized controlled studies reviewed that compared aliskiren/valsartan combination therapies at maximum daily therapeutic doses (300mg/320mg) to valsartan or aliskiren at maximum dose monotherapy in stage 2 hypertension. The larger study found a statistically significant decrease in the mean SBP/DBP.<sup>16</sup> The smaller study did not find a significant difference.<sup>17</sup> The larger study saw a mean lowering of approximately 7 mmHg with the combination aliskiren/valsartan (300mg/320mg) therapy versus valsartan 320mg alone. The question of clinical significance is debatable.

**Table 4. Combination Therapy Study Results<sup>12</sup>**

Trial	N	Aliskiren 150mg	Aliskiren 300mg	Placebo	Comparator <sup>#</sup>
Oparil et al. <sup>12</sup>	1176	N/A	-9.0	-4.1	-9.7 (valsartan 320 mg)
Pool et al. <sup>13</sup>	1123	-10.3 ± 0.62	-12.3 ± 0.62	-8.6 ± 0.62	-10.5+1.07; -11.0+1.07; -11.3+1.05 (valsartan 80 mg; 160 mg; 320 mg)
Vilamil et al. <sup>14</sup>	2752	-0.89 ± 0.59	-10.3 ± 0.60	-6.9	-9.1+0.58; -10.1+0.59; -9.4+0.61 (hydrochlorothiazide 6.25 mg; 12.5 mg; 25 mg)

Note: Information within this document is current as of this writing and should not replace clinical judgment.

# - change in diastolic blood pressure (DBP)

### **Systematic Reviews:**

#### *Cochrane:*

Musini et al. performed a literature search on renin inhibitors using three popular databases and references from retrieved articles. The main objective was to quantify the dose-related blood pressure lowering efficacy of renin inhibitors versus placebo in the treatment of primary hypertension. The trials had to meet certain criteria: double-blinded, placebo-controlled, random allocation to specific doses of renin inhibitor group and parallel placebo group, and duration of follow up of at least three weeks. This resulted in six trials with 3694 total patients. The meta-analysis showed a dose-related response in systolic/diastolic blood pressure lowering effect as compared with placebo for aliskiren. The article also concluded that the blood pressure lowering effects are similar to those seen with ACE inhibitors and ARBs.<sup>18</sup>

#### *NICE:*

In August 2011, NICE's guideline development group (GDG) released its newest guidelines on hypertension. They're recommendation was to not support aliskirens use for treatment of resistant hypertension due to insufficient evidence of its effectiveness.<sup>19</sup>

### **Adverse Events:**<sup>5,12</sup>

- Angioedema with an increased risk with history of any etiology or airway surgery, less than 1 % in clinical trials
- Peripheral edema
- Hyperkalemia (1%) which was similar to placebo, with an increased risk in patients with renal dysfunction
- Hypotension with an increased risk in volume or salt depleted patients
- Teratogenicity (Category D)
- GI with diarrhea being the highest incidence at 2.3%, also dyspepsia, abdominal pain, esophageal reflux
- Headache, nasopharyngitis, dizziness, fatigue, URI, and back pain all with similar instance to placebo
- Cough although rates were one half to one third of the ACEI arm in clinical trials (lisinopril and ramipril)
- Two seizures reported in clinical trials, one had pre-existing seizure history.
- Minor lab abnormalities although not clinically relevant: serum potassium; creatine kinase; blood urea nitrogen (BUN); hematocrit (HCT) and hemoglobin (HGB); serum uric acid

### **Precautions/Contraindications:**<sup>5,12,20,21</sup>

#### **Boxed Warning**

- **Use in pregnancy: Drugs that act directly on the renin-angiotensin can cause injury and even death to the developing fetus**
- **When pregnancy is detected, discontinue aliskiren immediately**
- None

- Special note that in Canada, aliskiren is contraindicated for concomitant use with an ACEI or ARB in type two diabetes mellitus patients at high risk for fatal and non-fatal cardiovascular and renal events. This led to early termination of the ALTITUDE clinical trial.<sup>20</sup> This trial investigated whether aliskiren 300mg in combination with optimal ACEI or ARB treatment would reduce morbidity and mortality in patients with type 2 diabetes, pre-existing disease of the heart and the circulatory system, and/or the kidney. The trial was stopped early because the monitoring group concluded that study patients were not likely to benefit from aliskiren treatment. In addition, there was a greater incidence of adverse events related to nonfatal stroke, renal complications (ESRD), hyperkalemia, and hypotension in this high-risk population.

**Precautions:**<sup>20</sup>

- Pregnancy Category D
- Head and Neck Angioedema
- Hypotension
- Impaired renal function: Consider periodic serum electrolytes to determine imbalances in patients with greater than moderate renal dysfunction
- Hyperkalemia
- Renal Artery Stenosis
- Cyclosporine or itraconazole usage

**Look-alike/Sound-alike Error Risk Potential:**<sup>12,20</sup>

- Tekturna® may be confused with: Valturna ; Ketek; Sanctura; Tarceva; Taztia; Tetrex
- Aliskiren may be confused with: Aspirin; Alkeran; Eskalith; Visken

**FDA Risk Evaluation and Mitigation Strategy (REMS):**<sup>22</sup>

- None

**Drug Interactions:**<sup>5,20,21</sup>

Avoid concomitant use of Aliskiren with P-Glycoprotein inhibitors like cyclosporine and itraconazole; ACE or ARB if patient has type 2 diabetes mellitus; NSAIDS as they may lead to increased risk of renal impairment or loss of anti-hypertensive effect.

Aliskiren may increase levels or effects of: amifostine; antihypertensives; hypotensive agents; rituximab.

Levels of aliskiren can be increased by: alfuzosin; atorvastatin; conivaptan; cyclosporine; itraconazole; ketoconazole; MAO inhibitors; NSAIDS; pentoxifylline; P-glycoprotein/ABCB1 inhibitors; PDE 5 inhibitors; prostacyclin analogues; verapamil; diazoxide; herbal products with hypotensive properties.

Aliskiren may decrease furosemide effects.

Aliskiren effects can be decreased by grapefruit juice as aliskiren is a CYP3A4 substrate; herbal products with hypertensive properties; methylphenidate; NSAIDS; P-glycoprotein inducers; tocilizumab; yohimbine; high fat meals decrease absorption.

## **Conclusions:**

After a review of multiple studies, aliskiren is a potential option for patients with hypertension. Studies have shown a statistically significant decrease in both DBP and SBP from baseline in patients with mild to moderate hypertension when compared with placebo. Aliskiren caused decreases in BP with monotherapy and combination therapy with ACEI's, ARB's, and HCTZ. Also, when compared with valsartan and ramipril, aliskiren showed similar decreases in blood pressure.<sup>23</sup>

This medication would benefit some members of our patient population, but a large proportion would be unable to utilize it due to risks associated with diabetic patients. Aliskiren would most likely only be able to be used in our patients with uncontrolled hypertension without DM.

Throughout the studies, aliskiren was generally well tolerated in the populations studied. The most common adverse effects were gastrointestinal, dizziness, hyperkalemia, angioedema, and nasopharyngitis, but incidence was similar to placebo. However, the incidence of cough and angioedema were not greater than those seen with ACEIs.

## **Recommendations:**

While there are theoretical advantages of inhibition of the RAAS system further up the cascade compared to current therapies, such as ACEI/ARB, clear data showing superiority is lacking. Aliskiren is a viable option for monotherapy or combination therapy for patients who cannot tolerate ACEI/ARB treatment for any reason. However, given that they have shown only similar outcomes to standard of care medications that inhibit the RAAS system and aliskiren's severe risk in diabetic patients when combined with ACE/ARB therapy, it is not recommended to be added to the national formulary at this time.

## **References**

1. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. May 21 2003;289(19):2560-2572.
2. Centers for Disease Control (CDC) High Blood Pressure Facts. Centers for Disease Control Website. <http://www.cdc.gov/bloodpressure/facts.htm>. Accessed March 5, 2012.
3. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics--2011 Update: A Report From the American Heart Association. *Circulation*. Feb 1 2011;123(4):e18-e209.
4. Indian Health Service Facts Sheet: Indian Health Disparities. Indian Health Service website. <http://www.ihs.gov/PublicAffairs/IHSBrochure/Disparities.asp>. Accessed March 8, 2012.
5. Tekturna (aliskiren) tablets: package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2012.
6. Aliskiren. Drug Facts and Comparisons. Facts & Comparisons® eAnswers [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed March 5, 2012.
7. IHS National Core Formulary: [http://www.ihs.gov/nptc/index.cfm?module=dsp\\_nptc\\_formulary](http://www.ihs.gov/nptc/index.cfm?module=dsp_nptc_formulary); Accessed March 5, 2012.
8. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*. May 31 2011;123(21):2434-2506.

9. Oh BH, Mitchell J, Herron JR, Chung J, Khan M, Keefe DL. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. *J Am Coll Cardiol*. Mar 20 2007;49(11):1157-1163.
10. Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, Bedigian MP. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation*. Mar 1 2005;111(8):1012-1018.
11. Kushiro T, Itakura H, Abo Y, Gotou H, Terao S, Keefe DL. Aliskiren, a novel oral renin inhibitor, provides dose-dependent efficacy and placebo-like tolerability in Japanese patients with hypertension. *Hypertens Res*. Dec 2006;29(12):997-1005.
12. U.S. Department of Veterans Affairs: Clinical Guidance/Drug Monographs. Veterans Affairs website. <http://www.pbm.va.gov/Clinical%20Guidance/Drug%20Monographs/Aliskiren.doc>. Accessed March 5, 2012.
13. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet*. Jul 21 2007;370(9583):221-229.
14. Pool JL, Schmieder RE, Azizi M, et al. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. *Am J Hypertens*. Jan 2007;20(1):11-20.
15. Villamil A, Chrysant SG, Calhoun D, et al. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens*. Jan 2007;25(1):217-226.
16. Yarows SA, Oparil S, Patel S, Fang H, Zhang J. Aliskiren and valsartan in stage 2 hypertension: subgroup analysis of a randomized, double-blind study. *Advances in therapy*. Dec 2008;25(12):1288-1302.
17. Flack JM, Yadao AM, Purkayastha D, Samuel R, White WB. Comparison of the effects of aliskiren/valsartan in combination versus valsartan alone in patients with Stage 2 hypertension. *Journal of the American Society of Hypertension : JASH*. Mar 2012;6(2):142-151.
18. Musini VM, Fortin PM, Bassett K, Wright JM. Blood pressure lowering efficacy of renin inhibitors for primary hypertension: a Cochrane systematic review. *J Hum Hypertens*. Aug 2009;23(8):495-502.
19. National Clinical Guideline Center. Hypertension: The clinical management of primary hypertension in adults. Update of guidelines 18 and 34. <http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf>. Accessed April 1, 2012.
20. Lexi-Comp, Inc. (Lexi-Drugs™ ). Lexi-Comp, Inc.; March 9, 2012.
21. Journal of renin-angiotensin-aldosterone system. Baseline characteristics in the aliskiren trial in type 2 diabetes using cardio-renal endpoints. Available at: <http://jra.sagepub.com/content/early/2012/02/14/147032031143481>, Accessed March 5, 2012.
22. U.S. Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>. Accessed March 5, 2012.
23. Andersen K, Weinberger MH, Egan B, et al. Comparative efficacy of aliskiren monotherapy and ramipril monotherapy in patients with stage 2 systolic hypertension: subgroup analysis of a double-blind, active comparator trial. *Cardiovascular therapeutics*. Dec 2010;28(6):344-349.

**Authors:** LT Karsten Smith, Pharm D.; LT James Haley, Pharm D.; CDR Michael Lee, PharmD, NCPS, BCPS

**Note:** Information within this document is current as of this writing and should not replace clinical judgment.