

NATIONAL PBM BULLETIN

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DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

ALISKIREN ADVERSE EVENTS IN COMBINATION WITH AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR ANGIOTENSIN II RECEPTOR ANTAGONIST IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

I. ISSUE

Novartis, the manufacturer of aliskiren (TEKTURNA), announced the discontinuation of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) based on interim analysis that patients in the aliskiren treatment group experienced an increase in adverse events including nonfatal stroke, renal complications, hyperkalemia and hypotension, compared to placebo. The manufacturer is recommending that aliskiren be discontinued in patients with diabetes mellitus (DM) on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonist (ARB).¹

II. BACKGROUND

The ALTITUDE study was conducted in over 8600 patients with type 2 DM and additional cardiovascular (CV) or renal complications to evaluate the addition of aliskiren to standard therapy that included treatment with an ACEI or ARB. The primary endpoint of the trial was the first occurrence of CV death, resuscitated sudden death, nonfatal myocardial infarction, nonfatal stroke, unplanned hospitalization for heart failure (HF), doubling of baseline serum creatinine concentration to above the upper limit of normal, and onset of end stage renal disease (ESRD) or renal death. The trial was discontinued after the Data Monitoring Committee noted an increase in adverse events in the treatment group after 18 to 24 months (planned 4 year trial).^{1,2}

Outcome	Aliskiren (N=4283)	Placebo (N=4296)	HR (95% CI)	P value
Primary Endpoint	581 (13.6%)	542 (12.6%)	1.09 (0.97 to 1.22)	0.1663
Secondary Endpoint (Composite CV)	444 (10.4%)	396 (9.2%)	1.14(0.99 to 1.30)	0.0664
Secondary Endpoint (Composite Renal)	166 (3.9%)	180 (4.2%)	0.93 (0.76 to 1.15)	0.5178
CV death	179 (4.2%)	162 (3.8%)	1.12 (0.90 to 1.38)	0.3110
Nonfatal stroke	112 (2.6%)	85 (2.0%)	1.34 (1.01 to 1.77)	0.0439
Onset ESRD/death	72 (1.7%)	60 (1.4%)	1.22 (0.87 to 1.72)	0.2518
All cause death	297 (6.9%)	277 (6.4%)	1.08 (0.92 to 1.27)	0.3661

Based on review of the data, the Data Monitoring Committee concluded that treatment with aliskiren did not offer benefit for the patients enrolled in the trial, and resulted in adverse clinical outcomes; therefore, the trial was discontinued. Further analysis of the data is ongoing. As a precautionary measure, the manufacturer has made specific recommendations for the discontinuation of aliskiren as outlined in the Recommendations section below.¹

Aliskiren containing products available in the U.S. include: TEKTURNA (aliskiren), TEKTURNA HCT (aliskiren and hydrochlorothiazide), VALTURNA (aliskiren and valsartan), TEKAMLO (aliskiren and amlodipine), and AMTURNIDE (aliskiren, amlodipine and hydrochlorothiazide). Aliskiren, and the aliskiren containing fixed-dose combination products, are not listed on the VA National Formulary and are restricted to VA National Criteria for Use.⁴

III. DISCUSSION

Aliskiren is FDA approved for the treatment of hypertension, to lower blood pressure. Long-term outcome data are not available in patients with HTN, or with other conditions, that demonstrate a reduction in morbidity or mortality with aliskiren. Based on review of interim results of ALTITUDE, it was concluded that aliskiren does not provide benefit, and may cause harm (nonfatal stroke, renal complications, hyperkalemia and hypertension), in patients with DM being treated with an ACEI or ARB. The manufacturer has recommended that aliskiren be discontinued in patients with DM who are also receiving an ACEI or ARB.

IV. MANUFACTURER, PBM AND VA MEDSAFE RECOMMENDATIONS

The manufacturer has made the following recommendations:¹

For patients with DM taking medications containing aliskiren, providers should review treatment at the next routine (non-urgent) visit at which the following is recommended:

Aliskiren or aliskiren-containing fixed-dose combination products should not be used in combination with ACEIs or ARBs in patients with DM, therefore:

- Healthcare professionals should stop aliskiren-containing treatment in patients with DM who are also taking an ACEI or an ARB. Alternative antihypertensive treatment should be considered as necessary.³
- Healthcare professionals should stop the use of the fixed-dose combination of aliskiren and valsartan (VALTURNA) in patients with DM, as this product contains aliskiren and an ARB. Alternative antihypertensive treatment should be considered as necessary.³
- Aliskiren-containing products should not be initiated in patients with DM who are also taking either an ACEI or an ARB. Likewise, products with an ACEI or ARB should not be initiated in patients with DM who are also taking aliskiren.
- Patients should NOT stop any treatment before discussing with a healthcare professional.

In accordance with the VA National Criteria for Use,⁴ PBM and VA MedSAFE recommend:

- Aliskiren should be restricted to treatment of HTN^a in patients who have documented inadequate response or contraindication to, or inability to tolerate at least three antihypertensive agents on the VA National Formulary, one from each of the following drug classes: thiazide-type diuretic, ACEI (or ARB if an ACEI is indicated and the patient is ACEI intolerant^b), long-acting calcium channel blocker. Since most patients will require more than one antihypertensive agent to control their blood pressure, if the patient's blood pressure is not at goal despite therapy as recommended above, a trial of at least two additional antihypertensive agents listed on the VA National Formulary (e.g., reserpine, beta-adrenergic blocker, centrally acting agent, vasodilator, aldosterone antagonist, alpha-blocker) as supplemental therapy should be attempted prior to considering aliskiren.
- The long-term efficacy and safety of combination therapy with aliskiren and an ACEI or ARB in the treatment of HTN compared to combination with an antihypertensive agent with a different mechanism of action is unknown; therefore, combination therapy with aliskiren and an ACEI or ARB is not advised at this time.
- Upon direction of the VISN Pharmacist Executives, facilities are to determine the most appropriate method for implementation of the recommendations to discontinue aliskiren in patients with DM who are also on an ACEI or ARB. A VA Provider Letter is available on the PBM INTRAnet at [Aliskiren, Provider Letter](#) that may be modified as needed based on recommendations for implementation at the facility level.

^a The role of aliskiren as monotherapy or combination therapy with either an ACEI or ARB in influencing long-term outcomes for HTN or for other indications (e.g., chronic kidney disease, heart failure) has not been established.

^b Unable to tolerate an ACEI due to cough or other non life-threatening reason. It is unknown if an ARB can be safely used as an alternative in patients who develop significant kidney dysfunction, hyperkalemia, or angioedema with an ACEI, as these adverse events have also occurred with the use of an ARB.

V. REFERENCES

1. Direct Healthcare Professional Communication on potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes and renal impairment and/or cardiovascular disease treated with aliskiren (Tekturna®) tablets and aliskiren-containing combination products. January 2012. Novartis Pharmaceuticals Corporation; East Hanover NJ. http://www.pharma.us.novartis.com/assets/pdf/TKT-1118923%20Dear_HCP_Letter_email_with%20Tek-Val%20PIs_vf.pdf.
2. Parving HH, Brenner BM, McMurray JJ, et al. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant* 2009;24:1663-71.
3. VA/DoD Clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. Washington DC: The Management of Hypertension in the Primary Care Setting Workgroup. Department of Veteran Affairs and Department of Defense; Update version 2.0b-2004. http://www.healthquality.va.gov/hypertension/htn04_pdf1.pdf.
4. Aliskiren, Criteria for Use. VA Pharmacy Benefits Management Services and Medical Advisory Panel. December 2007 (update in progress). <http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Forms/AllItems.aspx?RootFolder=%2fPBM%2fClinical%20Guidance%2fCriteria%20For%20Use&FolderCTID=&View=%7b786029AE%2d74D9%2d40BC%2dBCC7%2dBECF18B1B7FD%7d>.

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe these medications (e.g., cardiologists, endocrinologists, nephrologists, primary care providers, subject matter experts and clinic staff, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).