

# FDA Drug Safety Communication: New Warning and Contraindication for blood pressure medicines containing aliskiren (Tekturna)

## Safety Announcement

[4-20-2012] The U.S. Food and Drug Administration (FDA) is warning of possible risks when using blood pressure medicines containing aliskiren with other drugs called angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with diabetes or kidney (renal) impairment. These drug combinations should not be used (are contraindicated) in patients with diabetes. In addition, a new warning is being added to avoid use of these drug combinations in patients with kidney impairment. The labels for the aliskiren drugs are being updated based on preliminary data from a clinical trial, "[Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints \(ALTITUDE\)](#)".<sup>1</sup>

In ALTITUDE, the risks of kidney (renal) impairment, low blood pressure (hypotension), and high potassium blood levels (hyperkalemia) in a group of patients taking aliskiren plus an ARB or ACEI increased relative to a group of patients taking placebo plus an ARB or ACEI. The preliminary data from ALTITUDE also demonstrated a slight excess of cardiovascular events (death or stroke) in the aliskiren group [[see Data Summary](#)]; however, FDA has reached no definite conclusion regarding an actual link between these drugs and death or stroke. FDA will evaluate the final trial results as well as results from other aliskiren trials and will communicate any new information when it becomes available.

The following recommendations are being added to the drug labels for aliskiren-containing products as of 4/20/12:

- A new contraindication against the use of aliskiren with ARBs or ACEIs in patients with diabetes because of the risk of renal impairment, hypotension, and hyperkalemia.
- A warning to avoid use of aliskiren with ARBs or ACEIs in patients with moderate to severe renal impairment (i.e., where glomerular filtration rate [GFR] < 60 mL/min).

## Additional Information for Patients

- Do not stop taking aliskiren without talking to your healthcare professional. Stopping aliskiren suddenly can cause problems if your high blood pressure (hypertension) is not treated.
- Tell your healthcare professional if you are taking an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB). (See Tables 2 and 3)
- Tell your healthcare professional if you have been diagnosed with diabetes or kidney problems.
- Discuss any questions you have about aliskiren with your healthcare professional.
- Report any side effects you experience to the FDA MedWatch program using the information in the "Contact FDA" box at the bottom of the page.

## Additional Information for Healthcare Professionals

- Concomitant use of aliskiren with ARBs or ACEIs in patients with diabetes is contraindicated because of the risk of renal impairment, hypotension, and hyperkalemia.
- Avoid use of aliskiren with ARBs or ACEIs in patients with renal impairment where GFR < 60 mL/min.
- Valtorna (a combination drug containing aliskiren and valsartan) should not be used in patients with diabetes.
- Valtorna will no longer be marketed after July 2012. See [Novartis's website](#)<sup>4</sup>  for more information.
- Be aware of the preliminary findings from the ALTITUDE trial for death and stroke; FDA has not concluded that there is a link between these drugs and death or stroke [[see Data Summary](#)]
- Report adverse events involving aliskiren to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

## Facts about aliskiren-containing products

- Aliskiren is a renin inhibitor used to treat high blood pressure (hypertension) by lowering blood pressure.
- Aliskiren is found in the following medications:
  - Amturnide (aliskiren hemifumarate, amlodipine besylate, and hydrochlorothiazide)
  - Tekturna (aliskiren hemifumarate)
  - Tekturna HCT (aliskiren hemifumarate and hydrochlorothiazide)
  - Tekamlo (aliskiren hemifumarate and amlodipine besylate)
  - Valtorna (aliskiren hemifumarate and valsartan)\*
- In 2011, a total of approximately 2.4 million prescriptions for aliskiren-containing products were dispensed to 451,000 patients from U.S. outpatient retail pharmacies.<sup>1</sup>

\*Novartis (the manufacturer of aliskiren-containing products) decided to stop marketing Valtorna, a combination drug product containing aliskiren and the ARB drug valsartan, but will ensure that Valtorna is available until July 2012 so that healthcare professionals can transition patients to other therapy. More information can be found in [Novartis's Dear Healthcare Professional letter \(PDF - 762KB\)](#)<sup>2</sup> .

## Data Summary

FDA has evaluated preliminary data from ALTITUDE ([Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints](#))<sup>6</sup>, a clinical trial conducted post-approval. ALTITUDE was terminated early for lack of efficacy and because risks of renal impairment, hypotension, and hyperkalemia were observed to be greater in diabetic patients treated with aliskiren than in patients treated with placebo. The information below describes the ALTITUDE interim trial results.

### Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE)

The purpose of ALTITUDE was to determine whether aliskiren (compared to placebo), on top of conventional treatment, reduces death and disease caused by the heart, the circulatory system and the kidney. Patients with type 2 diabetes with renal disease (defined either by the presence of albuminuria or reduced GFR) were randomized to aliskiren 300 mg daily (n=4283) or placebo (n=4296). All patients were receiving concomitant therapy with an ARB or ACEI. The primary efficacy outcome was the time to the first event of the primary composite endpoint, which consisted of cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, onset of end-stage renal disease, renal death, and doubling of serum creatinine concentration from baseline sustained for at least one month.

After a median patient follow up of about 27 months, the trial was terminated early for lack of efficacy. Greater risks of renal impairment, hypotension and hyperkalemia were observed in aliskiren- compared to placebo-treated patients, as shown in the Table 1 below.

**Table 1. Incidence of Selected Adverse Reactions in ALTITUDE<sup>1</sup>**

	Aliskiren N=4283		Placebo N=4296	
	Serious Adverse Event* (%)	Adverse Event (%)	Serious Adverse Event* (%)	Adverse Event (%)
Renal	4.7	12.4†	3.3	10.4†
Hypotension	2.0	18.6††	1.7	14.8††
Hyperkalemia	1.1	36.9	0.3	27.1

<sup>1</sup> as reported by the investigator

†renal failure, renal failure acute, renal failure chronic, renal impairment

††dizziness, dizziness postural, hypotension, orthostatic hypotension, presyncope, syncope

\*A Serious Adverse Event (SAE) is defined as an event that: is fatal or life-threatening, results in persistent or significant disability/incapacity; constitutes a congenital anomaly/birth defect; requires inpatient hospitalization or prolongation of existing hospitalization; or is medically significant (i.e., an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes previously listed).

The risks of stroke (2.7% aliskiren vs. 2.0% placebo) and death (6.9% aliskiren vs. 6.4% placebo) were numerically higher in aliskiren-treated patients. At this time, however, the significance of these findings is unknown; FDA has reached no conclusion regarding a link between aliskiren treatment and these cardiovascular-related events.

In an FDA analysis of data from U.S. outpatient retail pharmacies in 2011, it was found that approximately 22% of patients on aliskiren products (Tekturna, Tekturna HCT, Tekamlo, and Amturnide) had concurrent use with ACEIs/ARBs **and** diabetic medications and approximately 30.5% of Valturna patients received concurrent therapy with diabetic medications.<sup>2</sup>

FDA will review the final study data (including follow-up information on patients who discontinued aliskiren in ALTITUDE) and data from other ongoing trials with aliskiren when they become available.

## References

1. IMS, Vector One®: National (VONA) and Total Patient Tracker (TPT). Year 2011. Extracted April 2012.
2. Wolters Kluwer Concurrent Product Analyzer (WKCP). Year 2011. Extracted February 2012.
3. <http://www.fda.gov/Drugs/DrugSafety/ucm300889.htm>