

New Drug Bulletin: Aliskiren (Tekturna® - Novartis)

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Aliskiren (Tekturna®) received FDA-approval March 5, 2007, for the treatment of hypertension in adults either as monotherapy or in combination with other antihypertensives. Aliskiren directly inhibits renin activity preventing the conversion of angiotensinogen to angiotensin I.

The oral bioavailability of aliskiren is approximately 2.5%. Peak concentrations occur within 1 to 3 hours of an oral dose. A high-fat meal decreases the mean area under the curve (AUC) and peak concentration (C_{max}) of aliskiren by at least 70%, although during trials aliskiren was administered without regard to meals. Aliskiren's degree of protein binding is unknown and the half-life is 24 hours. The quantity of absorbed drug that is metabolized is unknown. In vitro studies show CYP 3A4 is likely responsible for the metabolism of aliskiren. Approximately 25% of absorbed aliskiren is excreted in the urine unchanged. The route of elimination of metabolites is unknown.

As monotherapy, aliskiren 75 to 600 mg per day decreases seated systolic blood pressure (SBP) 1.9 to 12.1 mm Hg and decreases seated diastolic blood pressure (DBP) 1.7 to 7.6 mm Hg. The combination of aliskiren and hydrochlorothiazide decreases seated SBP 3.5 to 13.7 mm Hg and decreases seated DBP 2.1 to 7.3 mm Hg. The combination of aliskiren and valsartan decreases seated SBP 5.6 to 12.6 and decreases seated DBP 3.9 to 8.1 mm Hg. A combination trial of aliskiren and amlodipine 5 mg found no significant difference between amlodipine 10 mg and the combination. Data are lacking evaluating aliskiren in combination with beta blockers or maximal doses of angiotensin converting enzyme (ACE) inhibitors.

Angioedema is the most serious adverse effect associated with aliskiren and was reported in 4 of 6460 patients. The most common side effect of aliskiren is diarrhea (2.3%) and is more common with doses higher than 300 mg daily. Other possible adverse effects included increased cough (1.1%), rash (1%), increased uric acid (0.4%), gout (0.2%), and renal stones (0.2%).

Aliskiren is likely metabolized by CYP 3A4. The combination of aliskiren and atorvastatin increases the C_{max} and AUC of aliskiren by 50%. Aliskiren has no effect on atorvastatin concentrations. Concomitant administration of ketoconazole increases aliskiren plasma concentrations by 80%. The combination of aliskiren and irbesartan decreases the C_{max} of aliskiren by 50%. Aliskiren in combination with furosemide results in increased furosemide concentrations. Aliskiren in combination with the following agents does not result in clinically significant interactions: amlodipine, atenolol, celecoxib, digoxin, hydrochlorothiazide, lovastatin, metformin, ramipril, valsartan, and warfarin.

The starting dose of aliskiren is 150 mg once daily. Increase the dose to 300 mg once daily for patients requiring further hypertension control. Doses greater than 300 mg daily result in no additional blood pressure-lowering effect and increased adverse effects. Avoid use in patients with moderate renal dysfunction (creatinine 1.7 mg/dL for women or 2 mg/dL for

men). Do not use during the second or third trimester of pregnancy due to potential fetal damage.

Aliskiren is available in 150 mg and 300 mg tablets in bottles of 30 or 90 and unit-dose packages of 100. The wholesale acquisition cost (WAC) is \$1.95 per 150 mg tablet and \$2.46 per 300 mg tablet.

In summary, aliskiren is the first direct renin inhibitor available for the treatment of hypertension. Aliskiren is effective in lowering blood pressure either as monotherapy, or in combination with hydrochlorothiazide or valsartan. Further studies are needed to evaluate combination therapy with other agents including maximum doses of ACE inhibitors, beta blocking agents, or calcium channel blocking agents.

References:

1. Tekturna® (aliskiren) package insert. East Hanover, NJ: Novartis, March 2007.

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