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# Aliskiren Tablets (Tekturna)

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## Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Data described below reflect the evaluation of the safety of Tekturna in more than 6,460 patients, including over 1,740 treated for longer than 6 months, and more than 1,250 patients for longer than 1 year. In placebo controlled clinical trials, discontinuation of therapy due to a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with Tekturna vs. 3.5% of patients given placebo. These data do not include information from the ALTITUDE study ].**Clinical Studies** , and**WARNINGS AND PRECAUTIONS** ,**CONTRAINDICATIONS**which evaluated the use of aliskiren in combination with ARBs or ACEIs [see

Two cases of angioedema with respiratory symptoms were reported with Tekturna use in the clinical studies. Two other cases of periorbital edema **: *Angioedema*** without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%. In addition, 26 other cases of edema involving the face, hands, or whole body were reported with Tekturna use including 4 leading to discontinuation. In the placebo controlled studies, however, the incidence of edema involving the face, hands or whole body was 0.4% with Tekturna compared with 0.5% with placebo. In a long term active control study with Tekturna and HCTZ arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms ].**WARNINGS AND PRECAUTIONS**[see

Tekturna produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% **:*Gastrointestinal*** in placebo patients. In women and the elderly (age ? 65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg comparable to those seen at 300 mg for men or younger patients (all rates about 2.0-2.3%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

-Tekturna was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any Tekturna use vs. 0.6% for placebo). In active-**:*Cough*** ontrolled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the Tekturna arms were about one-third to one-half the rates in the ACE inhibitor arms.

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with Tekturna in the clinical trials. One of these **:*Seizures*** patients did have predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures (for the other patient EEG and imaging results were not reported). Tekturna was discontinued and there was no re-challenge.

Other adverse effects with increased rates for Tekturna compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%) and renal stones (0.2% vs. 0%).

-Aliskiren's effect on ECG intervals was studied in a randomized, double-blind, placebo and active-controlled (moxifloxacin), 7-day repeat dosing study with Holter monitoring and 12 lead ECGs throughout the interdosing interval. No effect of aliskiren on QT interval was seen.

### Clinical Laboratory Findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of Tekturna in patients with hypertension not concomitantly treated with an ARB or ACEI. In multiple-dose studies in hypertensive patients, Tekturna had no clinically important effects on total cholesterol, HDL, fasting triglycerides, or fasting glucose.

In patients with hypertension not concomitantly treated with an ARB or ACEI, minor increases in blood urea nitrogen (BUN) or **:*Blood Urea Nitrogen, Creatinine*** ].**WARNINGS AND PRECAUTIONS** serum creatinine were observed in less than 7% of patients treated with Tekturna alone vs. 6% on placebo [see

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.08 g/dL and 0.16 volume percent, respectively, **: *Hemoglobin and Hematocrit*** for all aliskiren monotherapy) were observed. The decreases were dose-related and were 0.24 g/dL and 0.79 volume percent for 600 mg daily. This effect is also seen with other agents acting on the renin angiotensin system, such as angiotensin inhibitors and angiotensin receptor blockers and may be mediated by reduction of angiotensin II which stimulates erythropoietin production via the AT1 receptor. These decreases led to slight increases in rates of anemia with aliskiren compared to placebo were observed (0.1% for any aliskiren use, 0.3% for aliskiren 600 mg daily, vs 0% for placebo). No patients discontinued therapy due to anemia.

In patients with hypertension not concomitantly treated with an ARB or ACEI, increases in serum potassium > 5.5 mEq/L were infrequent (0.9% **:*Serum Potassium***

].**WARNINGS AND PRECAUTIONS** and **CONTRAINDICATIONS** compared to 0.6% with placebo) [See

Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 ?mol/L) while HCTZ produced larger increases (about **:*Serum Uric Acid*** 30 ?mol/L). The combination of aliskiren with HCTZ appears to be additive (about 40 ?mol/L increase). The increases in uric acid appear to lead to slight increases in uric acid-related AEs: elevated uric acid (0.4% vs 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs 0%).

Increases in creatine kinase of > 300% were recorded in about 1% of aliskiren monotherapy patients vs. 0.5% of placebo patients. Five cases of **:*Creatine Kinase*** creatine kinase rises, three leading to discontinuation and one diagnosed as subclinical rhabdomyolysis, and another as myositis, were reported as adverse events with aliskiren use in the clinical trials. No cases were associated with renal dysfunction.

## Postmarketing Experience

The following adverse reactions have been reported in aliskiren post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

*Hypersensitivity: anaphylactic reactions and angioedema requiring airway management and hospitalization*
*Urticaria*
*Peripheral edema*
*Hepatic enzyme increase with clinical symptoms of hepatic dysfunction*
*Severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis*
*Pruritus*
*Erythema*