Tekturna®

T2007-90/T2007-06

(aliskiren)
Tablets
150 mg and 300 mg

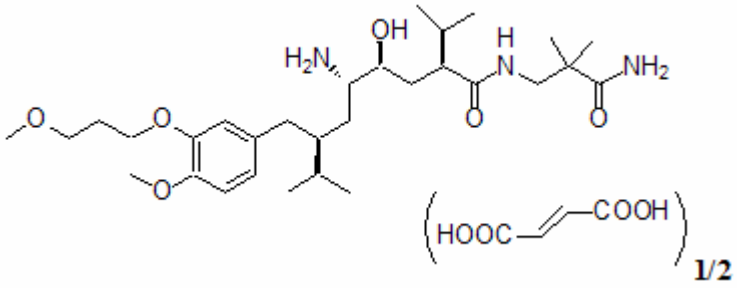
Rx only

Prescribing Information

USE IN PREGNANCY: When used in pregnancy drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Tekturna should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

DESCRIPTION

Aliskiren, the active component of Tekturna® Tablets, is an orally active, nonpeptide, potent renin inhibitor. Aliskiren is present in Tekturna Tablets as its hemifumarate salt. Aliskiren hemifumarate is chemically described as (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate and its structural formula is



Molecular formula: $C_{30}H_{53}N_3O_6 \bullet 0.5\ C_4H_4O_4$

Aliskiren hemifumarate is a white to slightly yellowish crystalline powder with a molecular weight of 609.8 (free base- 551.8). It is soluble in phosphate buffer, n-Octanol, and highly soluble in water.

Tekturna is available for oral administration as film-coated tablets containing 150 mg, and 300 mg of aliskiren base and the following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Ang II also inhibits renin release, thus providing a negative feedback to the system. This cycle, from renin through angiotensin to aldosterone and its associated negative feedback loop, is known as the renin-angiotensin-aldosterone system (RAAS). Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to Ang I. Whether aliskiren affects other RAAS components, e.g., ACE or non-ACE pathways, is not known.

All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE inhibitors and ARBs, the result is increased levels of PRA. During treatment with aliskiren, however, the effect of increased renin levels is blocked, so that PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents. PRA reductions in clinical trials ranged from approximately 50%-80%, were not dose-related and did not correlate with blood pressure reductions. The clinical implications of the differences in effect on PRA are not known.

Pharmacokinetics

Aliskiren is a poorly absorbed (bioavailability about 2.5%) drug with an approximate accumulation half life of 24 hours. Steady-state blood levels are reached in about 7-8 days.

Absorption and Distribution

Following oral administration, peak plasma concentrations of aliskiren are reached within 1 to 3 hours. When taken with a high fat meal, mean AUC and C_{max} of aliskiren are decreased by 71% and 85%, respectively. In the clinical trials of aliskiren, it was administered without requiring a fixed relation of administration to meals.

Metabolism and Elimination

About one-fourth of the absorbed dose appears in the urine as parent drug. How much of the absorbed dose is metabolized is unknown. Based on the in vitro studies, the major enzyme responsible for aliskiren metabolism appears to be CYP 3A4.

Special Populations

Pediatric

The pharmacokinetics of aliskiren have not been investigated in patients <18 years of age.

Geriatric

The pharmacokinetics of aliskiren were studied in the elderly (≥65 years). Exposure (measured by AUC) is increased in elderly patients. Adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).

Race
The pharmacokinetic differences between Blacks, Caucasians and the Japanese are minimal.
Renal Insufficiency

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Rate and extent of exposure (AUC and C_{max}) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment. Adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).
Hepatic Insufficiency

The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to-severe liver disease. Consequently, adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION**)**.
Cardiac Electrophysiology
Aliskiren's effects on ECG intervals were 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.

Drug Interactions

Effects of Other Drugs on Aliskiren

Based on in-vitro studies, aliskiren is metabolized by CYP 3A4.

Co-administration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.

Co-administration of irbesartan reduced aliskiren C_{max} up to 50% after multiple dosing.

Co-administration of atorvastatin resulted in about a 50% increase in aliskiren C_{max} and AUC after multiple dosing.
Ketoconazole

Co-administration of 200 mg twice-daily ketoconazole with aliskiren resulted in an approximate 80% increase in plasma levels of aliskiren. A 400 mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.

Effects of Aliskiren on Other Drugs

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.

Co-administration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.

Warfarin

The effects of aliskiren on warfarin pharmacokinetics have not been evaluated in a well-controlled clinical trial.

Furosemide

When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively.

CLINICAL TRIALS

Aliskiren Monotherapy

The antihypertensive effects of Tekturna® (aliskiren) have been demonstrated in six randomized, double-blind, placebo-controlled 8-week clinical trials in patients with mild-to-moderate hypertension. The placebo response and placebo-subtracted changes from baseline in seated trough cuff blood pressure are shown in Table 1.

Table 1: Reductions in Seated Trough Cuff Blood Pressure in the Placebo-Controlled Studies

		Aliskiren daily dose, mg			
Study	Placebo	75	150	300	600
	Mean change	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
1	2.9/3.3	5.7/4*	5.9/4.5*	11.2/7.5*	--
2	5.3/6.3	--	6.1/2.9*	10.5/5.4*	10.4/5.2*
3	10/8.6	2.2/1.7	2.1/1.7	5.1/3.7*	--
4	7.5/6.9	1.9/1.8	4.8/2*	8.3/3.3*	--
5	3.8/4.9	--	9.3/5.4*	10.9/6.2*	12.1/7.6*
6	4.6/4.1	--	--	8.4/4.9†	--

*$p<0.05$ vs. placebo by ANCOVA with Dunnett's procedure for multiple comparisons.

†$p<0.05$ vs. placebo by ANCOVA for the pairwise comparison.

The studies included approximately 2,730 patients given doses of 75-600 mg of aliskiren and 1,231 patients given placebo. As shown in Table 1, there is some increase in response with administered dose in all studies, with reasonable effects seen at 150-300 mg, and no clear further increase at 600 mg. A substantial proportion (85%-90%) of the blood pressure lowering effect was observed within 2 weeks of treatment. Studies with ambulatory blood pressure monitoring showed reasonable control throughout the interdosing interval; the ratios of mean daytime to mean nighttime ambulatory BP ranged from 0.6 to 0.9.

Patients in the placebo-controlled trials continued open-label aliskiren for up to one year. A persistent blood pressure lowering effect was demonstrated by a randomized withdrawal study (patients randomized to continued drug or placebo), which showed a statistically significant difference between patients kept on aliskiren and those randomized to placebo. With cessation of treatment, blood pressure gradually returned toward baseline levels over a period of several weeks. There was no evidence of rebound hypertension after abrupt cessation of therapy.

Aliskiren lowered blood pressure in all demographic subgroups, although Black patients tended to have smaller reductions than Caucasians and Asians, as has been seen with ACE inhibitors and ARBs.

Aliskiren in Combination with Other Antihypertensives

Diuretics

Aliskiren 75, 150, and 300 mg and hydrochlorothiazide 6.25, 12.5, and 25 mg were studied alone and in combination in an 8-week, 2,776-patient, randomized, double-blind, placebo-controlled, parallel-group, 15-arm factorial study. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 2.

Table 2: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Hydrochlorothiazide

		Hydrochlorothiazide, mg			
Aliskiren, mg	Placebo mean change	0	6.25	12.5	25
		Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
0	7.5/6.9	--	3.5/2.1	6.4/3.2	6.8/2.4
75	--	1.9/1.8	6.8/3.8	8.2/4.2	9.8/4.5
150	--	4.8/2	7.8/3.4	10.1/5	12/5.7
300	--	8.3/3.3	--	12.3/7	13.7/7.3

Valsartan

Aliskiren 150 and 300 mg and valsartan 160 and 320 mg were studied alone and in combination in an 8-week, 1,797-patient, randomized, double-blind, placebo-controlled, parallel-group, 4-arm, dose-escalation study. The dosages of aliskiren and valsartan were started at 150 and 160 mg, respectively, and increased at four weeks to 300 mg and 320 mg, respectively. Seated trough cuff blood pressure was measured at baseline, 4, and 8 weeks. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 3.

Table 3: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Valsartan

Aliskiren, mg	Placebo mean change	Valsartan, mg		
		0	160	320
0	4.6/4.1*	--	5.6/3.9	8.2/5.6
150	--	5.4/2.7	10.0/5.7	--
300	--	8.4/4.9	--	12.6/8.1

* The placebo change is 5.2/4.8 for week 4 endpoint which was used for the dose groups containing Aliskiren 150 mg or Valsartan 160 mg.

ACE inhibitors and Amlodipine

Aliskiren has not been studied when added to maximal doses of ACE inhibitors to determine whether aliskiren produces additional blood pressure reduction with a maximal dose of an ACE inhibitor. Aliskiren 150 mg provided additional blood pressure reduction when co-

administered with amlodipine 5 mg in one study, but the combination was not statistically significantly better than amlodipine 10 mg.

INDICATIONS AND USAGE

Tekturna® (aliskiren) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. Use with maximal doses of ACE inhibitors has not been adequately studied.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Tekturna® (aliskiren) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin system, has been associated with a potential risk of birth defects in retrospective data. Healthcare professionals that prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the potential risks of these agents during pregnancy.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Tekturna should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in-utero exposure to a renin inhibitor should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of Tekturna in pregnant women. Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose (MRHD) of 300 mg/day on a mg/m^2 basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m^2 basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m^2 basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients, but whether angioedema rates are higher in Blacks with aliskiren is not known. Tekturna should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Experience with ACE inhibitors indicates that even in those instances where only swelling of the tongue is seen initially, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Very rarely, fatalities have been reported in patients with angioedema associated with laryngeal edema or tongue edema with ACE inhibitors. Patients with involvement of the tongue, glottis or larynx are more likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and measures necessary to ensure a patent airway should be promptly provided (see ADVERSE REACTIONS).

Hypotension

An excessive fall in blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Tekturna alone. Hypotension was also infrequent during combination therapy with other antihypertensive agents (<1%). In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those receiving high doses of diuretics), symptomatic hypotension could occur after initiation of treatment with Tekturna. This condition should be corrected prior to administration of Tekturna, or the treatment should start under close medical supervision.

If an excessive fall in blood pressure occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline (see DOSAGE AND ADMINISTRATION). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

General

Impaired Renal Function

Patients with greater than moderate renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of Tekturna®

(aliskiren) in hypertension. Caution should be exercised in these patients because of the paucity of safety information with Tekturna in these patients and the potential for other drugs acting on the renin-angiotensin system to increase serum creatinine and blood urea nitrogen.

Hyperkalemia

Increases in serum potassium > 5.5 meq/L were infrequent with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Routine monitoring of electrolytes and renal function is indicated in this population. Concomitant use of Tekturna with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium. If concomitant use is considered necessary, caution should be exercised.

Renal Artery Stenosis

No data are available on the use of Tekturna in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Information for Patients

Pregnancy

Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss other treatment options with female patients planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema

Angioedema, including laryngeal edema, may occur at any time during treatment with Tekturna. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Drug Interactions

Patients should report any medications they take with aliskiren.

Furosemide

When aliskiren was given with furosemide, the blood concentrations of furosemide were reduced significantly. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic (rasH2) mouse study with aliskiren hemifumarate at oral doses of up to 1500 mg aliskiren/kg/day. Although there were no statistically significant increases in tumor incidence associated with exposure to aliskiren, mucosal epithelial hyperplasia (with or without erosion/ulceration) was

observed in the lower gastrointestinal tract at doses of 750 or more mg/kg/day in both species, with a colonic adenoma identified in one rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure ($AUC_{0\text{-}24hr}$) basis, 1500 mg/kg/day in the rat is about 4 times, and is in the mouse about 1.5 times, the maximum recommended human dose (300 mg aliskiren/day). Mucosal hyperplasia in the cecum or colon of rats was also observed at oral doses of 250 mg/kg/day (the lowest tested dose) as well as at higher doses in 4- and 13-week studies.

Aliskiren hemifumarate was devoid of genotoxic potential in the Ames reverse mutation assay with *S. typhimurium* and *E. coli*, the in vitro Chinese hamster ovary cell chromosomal aberration assay, the in vitro Chinese hamster V79 cell gene mutation test and the in vivo mouse bone marrow micronucleus assay.

Fertility of male and female rats was unaffected at doses of up to 250 mg aliskiren/kg/day (8 times the maximum recommended human dose of 300 mg Tekturna/60 kg on a mg/m^2 basis.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters) (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Nursing Mothers

It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of aliskiren in pediatric patients have not been established.

Geriatric Use

Of the total number of patients receiving aliskiren in clinical studies, 1,275 (19%) were 65 years or older and 231 (3.4%) were 75 years or older. Blood pressure responses and adverse effects were generally similar to those in younger patients.

ADVERSE REACTIONS

Tekturna® (aliskiren) has been evaluated for safety in more than 6,460 patients, including over 1,740 treated for longer than 6 months, and more than 1,250 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.

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema 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 aliskiren 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 aliskiren compared with 0.5% with placebo. In a long term active control study with aliskiren and HCTZ arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse effects. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% 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.

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

Other adverse effects with increased rates for aliskiren 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%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One of these 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). Aliskiren was discontinued and there was no re-challenge.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.

Clinical Laboratory Findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of Tekturna. In multiple-dose studies in hypertensive patients Tekturna had no clinically important effects on total cholesterol, HDL, fasting triglycerides, fasting glucose, or uric acid.

Blood Urea Nitrogen, Creatinine

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients with essential hypertension treated with Tekturna alone vs 6% on placebo.

Hemoglobin and Hematocrit

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.08 g/dL and 0.16 volume percent, respectively, 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.

Serum Potassium

Increases in serum potassium >5.5 meq/L were infrequent in patients with essential hypertension treated with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an angiotensin-converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%) and routine monitoring of electrolytes and renal function is indicated in this population.

Serum Uric Acid

Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 μmol/L) while HCTZ produced larger increases (about 30 μmol/L). The combination of aliskiren with HCTZ appears to be additive (about a 40 μmol/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%).

Creatine Kinase

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 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.

OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, supportive treatment should be initiated.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of Tekturna® (aliskiren) is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg. Doses above 300 mg did not give an increased blood pressure response but increased the rate of diarrhea. The antihypertensive effect of a given dose is substantially attained (85%-90%) by 2 weeks.

Tekturna may be administered with other antihypertensive agents. Most exposure to date is with diuretics and an angiotensin receptor blocker (valsartan) and the drugs together have a greater effect at their maximum recommended doses than either drug alone. It is not known whether additive effects are present when aliskiren is used with angiotensin-converting enzyme inhibitors or beta blockers.

No initial dosage adjustment is required in elderly patients, for patients with mild-to-severe renal impairment, or for patients with mild-to-severe hepatic insufficiency. Care should be exercised when dosing Tekturna in patients with severe renal impairment, as clinical experience with such patients is limited.

Patients should establish a routine pattern for taking Tekturna with regard to meals. High fat meals decrease absorption substantially (see Absorption and Distribution).

HOW SUPPLIED

Tekturna® (aliskiren) is supplied as a light-pink, biconvex unscored round tablet containing 150 mg of aliskiren, and as a light-red biconvex ovaloid tablet containing 300 mg of aliskiren. Tablets are imprinted with NVR on one side and IL, IU, on the other side of the 150, and 300 mg tablets, respectively.

All strengths are packaged in bottles and unit-dose blister packages (10 strips of 10 tablets) as described below in Table 4.

Table 4: Tekturna Tablets Supply

Tablet	Color	Imprint	Imprint	NDC 0078-XXXX-XX		
		Side 1	Side 2	Bottle of 30	Bottle of 90	Blister Packages of 100
150 mg	Light-pink	NVR	IL	0485-15	0485-34	0485-35
300 mg	Light-red	NVR	IU	0486-15	0486-34	0486-35

Storage

Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature].

Protect from moisture.

Dispense in tight container (USP).

REV: SEPTEMBER 2007

T2007-90

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

PATIENT INFORMATION

T2007-06

Tekturna® (pronounced tek-turn-a)

(aliskiren)

Tablets

Dosing Strengths:
150 mg tablets
300 mg tablets

Available by Prescription Only

Please read all of the available information before you start taking Tekturna. This leaflet does not take the place of talking with your doctor about your condition and treatment. If you have any questions about Tekturna, ask your doctor or pharmacist, visit **www.Tekturna.com**, or call 1-888-Tekturna (1-888-835-8876).

IMPORTANT WARNING: If you get pregnant, stop taking Tekturna and call your doctor right away. Tekturna may harm an unborn baby, causing injury and even death. If you plan to become pregnant, talk to your doctor about other treatment options before taking Tekturna.

What Is High Blood Pressure (Hypertension)?

Blood pressure is the force that pushes the blood through your blood vessels to all the organs of your body. You have high blood pressure when the force of your blood moving through your blood vessels is too great. Renin (pronounced REE-nin) is a chemical in the body that starts a process that makes blood vessels narrow, leading to high blood pressure.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.

What Is Tekturna?

Tekturna is a type of prescription medicine called a direct renin inhibitor that works in the body to help lower blood pressure (hypertension).

How Does Tekturna Work?

Tekturna reduces the effect of renin and the harmful process that narrows blood vessels. Tekturna helps blood vessels relax and widen so blood pressure is lowered.

Who Should Not Take Tekturna?

- **If you get pregnant**, **stop taking Tekturna and call your doctor right away. If you plan to become pregnant, talk to your doctor about other treatment options for your high blood pressure.**
- **Do not take Tekturna if you are allergic to any of its ingredients.**

Aliskiren is the active ingredient in Tekturna. The inactive ingredients (the ingredients that bind the tablet together) are colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide. These inactive ingredients are considered safe and are commonly used in many medications. Talk to your doctor if you have questions.

Tekturna has not been studied in children under 18 years of age.

What Should I Tell My Doctor Before Taking Tekturna?

Tell your doctor about all your medical conditions, including whether you:

- are pregnant or planning to become pregnant.
- are breast-feeding**.** It is not known if Tekturna passes into your breast milk. You should choose either to take Tekturna or breast-feed, but not both.
- have kidney problems.
- are allergic to any of the ingredients in Tekturna.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you are taking:

- other medicines for high blood pressure or a heart problem.
- water pills (also called “diuretics”).
- medicines for treating fungus or fungal infections.

Your doctor or pharmacist will know what medicines are safe to take together.

How Should I Take Tekturna?

- Take Tekturna once a day, at the same time each day. As with any blood pressure medication, it is important to take Tekturna on a regular daily basis exactly as prescribed by your doctor.
- Tekturna can be taken by itself or safely in combination with other medicines to lower high blood pressure. It can also be safely taken in combination with medications for other conditions such as high cholesterol or diabetes**.** Your doctor may change your dose if needed.

- Tekturna can be taken with or without food.

If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at your regular time. If you take too much Tekturna, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What Are Possible Side Effects Of Tekturna?

Tekturna may cause the following serious side effect:

- **Low blood pressure (hypotension).** Your blood pressure may get too low if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down if you feel faint or dizzy. Call your doctor right away.

Side effects were usually mild and brief. Few patients decided to stop taking Tekturna because of side effects. In clinical studies, the most common side effect experienced by more patients taking Tekturna than patients taking a sugar pill (placebo) was diarrhea. Other less common reactions to Tekturna include cough, and rash.

If you develop an allergic reaction involving swelling of the face, lips, throat and/or tongue which may cause difficulty in breathing and swallowing, stop taking Tekturna and contact your doctor immediately.

For a complete list of side effects, ask your doctor or pharmacist. Tell your doctor if you get any side effect that bothers you or will not go away.

How Do I Store Tekturna?

- Store Tekturna tablets at room temperature between 59^{o} to 86^{o}F.
- Keep Tekturna in the original prescription bottle in a dry place. Do not remove the desiccant (drying agent) from the bottle.
- Keep Tekturna and all medicines out of the reach of children.

General Information About Tekturna

Do not give Tekturna to other people, even if they have the same condition or symptoms you have. It may harm them.

This leaflet summarizes the most important information about Tekturna.

For more information about Tekturna, ask your doctor or pharmacist, visit www.Tekturna.com, or call 1-888-Tekturna (1-888-835-8876).

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