

## Tekturna HCT®

**(alsikiren and hydrochlorothiazide)**

#### Tablets

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use Tekturna HCT safely and effectively. See full prescribing information for Tekturna HCT.**

**Tekturna HCT (alsikiren and hydrochlorothiazide) Tablets**
Initial U.S. Approval: 2008

<b>WARNING: AVOID USE IN PREGNANCY</b>
<b><i>See full prescribing information for complete boxed warning.</i></b>
<b>When pregnancy is detected, discontinue Tekturna HCT as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. (5.1)</b>
<b>INDICATIONS AND USAGE</b>
Tekturna HCT is a combination of alsikiren, a direct renin inhibitor, and hydrochlorothiazide (HCTZ), a thiazide diuretic, indicated for the treatment of hypertension. (1) <p>Limitation of use: This fixed dose combination is not indicated for initial therapy. (1)</p>
<b>DOSAGE AND ADMINISTRATION</b>
• One tablet daily, with a routine pattern with regard to meals. (2) <ul style="list-style-type: none"><li>Order of increasing mean effect: 150/12.5 mg, 150/25 mg or 300/12.5 mg, and 300/25 mg (2.1)</li> <li>If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, titrate up to a maximum of 300/25. (2.2)</li> <li>May be administered with other antihypertensive agents; additive effects with maximal doses of ACE inhibitors and beta blockers have not been demonstrated. (2.3)</li></ul>
<b>DOSAGE FORMS AND STRENGTHS</b>
Tablets (mg alsikiren/mg HCTZ): 150/12.5, 150/25, 300/12.5, 300/25 (3)
<b>CONTRAINDICATIONS</b>
Anuria (4) <p>Hypersensitivity to sulfonamide-derived drugs (4)</p>

#### WARNINGS AND PRECAUTIONS

- Head and Neck Angioedema: Discontinue Tekturna HCT and monitor until signs and symptoms resolve. (5.2)
- Hypotension in Volume- and/or Salt-Depleted Patients: Correct imbalances before initiating therapy with Tekturna HCT. (5.3)
- Patients with Severe Renal Impairment: Use not recommended if GFR <30 mL/min. (5.4)
- Patients with Hepatic Impairment: Use with caution. (5.5)
- Hypersensitivity Reactions: May occur from HCTZ component (5.6)

#### ADVERSE REACTIONS

The most common adverse reactions (incidence ≥1.5% and more common than with placebo) are:

dizziness and diarrhea. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

<b>DRUG INTERACTIONS</b>
<b>Alsikiren:</b> <ul style="list-style-type: none"><li>Cyclosporine: Concomitant use is not recommended.</li></ul>
<b>Hydrochlorothiazide:</b> <ul style="list-style-type: none"><li>Alcohol, Barbiturates, Narcotics: Potentiation of orthostatic hypotension</li> <li>Antidiabetic Drugs: Dosage adjustment of antidiabetic may be required</li> <li>Cholestyramine and Colestipol: Reduced absorption of thiazides</li> <li>Corticosteroids, ACTH: Hypokalemia, electrolyte depletion</li> <li>Lithium: Reduced renal clearance and high risk of lithium toxicity when used with diuretics. Should not be given with diuretics.</li> <li>NSAIDs: Can reduce diuretic, natriuretic, and antihypertensive effects of diuretics. Observe patient closely.</li></ul>
<b>USE IN SPECIFIC POPULATIONS</b>
<b>Nursing Mothers:</b> Adverse reactions may occur in nursing infants. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and **FDA-approved patient labeling**.

Revised: 1/2008

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<b>WARNING: AVOID USE IN PREGNANCY</b>
<b>When pregnancy is detected, discontinue Tekturna HCT as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. [See <i>Warnings and Precautions</i> (5.1)]</b>

<b>1 INDICATIONS AND USAGE</b>
Tekturna HCT is indicated for the treatment of hypertension.

Both alsikiren and hydrochlorothiazide are associated with dose-dependent and dose-independent adverse effects. Patients treated with Tekturna HCT may experience any or all of these adverse effects. For dose-dependent adverse effects, using a strength of Tekturna HCT with a lower dose of the component suspected of causing the adverse effect may produce better tolerability.

#### Ad-On Therapy

A patient whose blood pressure is not adequately controlled with alsikiren alone or hydrochlorothiazide alone may be switched to combination therapy with Tekturna HCT.

A patient whose blood pressure is controlled with hydrochlorothiazide alone but who experiences hypokalemia may be switched to combination therapy with Tekturna HCT.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to Tekturna HCT containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions.

#### Replacement Therapy

Tekturna HCT may be substituted for the titrated components.

#### Limitation of Use

This fixed dose combination is not indicated for initial therapy.

#### 2 DOSAGE AND ADMINISTRATION

**2.1 Dose Selection**
The recommended once-daily doses of Tekturna HCT in order of increasing mean effect are 150/12.5 mg, 150/25 mg or 300/12.5 mg, and 300/25 mg.

Regardless of the dose of the single agent, patients switched from monotherapy to Tekturna HCT will experience greater blood pressure reductions with use of the combination product.

#### 2.2 Dose Titration

The antihypertensive effect of Tekturna HCT is largely manifested within 1 week, with maximal effects generally seen at around 4 weeks. If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, the dose may be titrated up to a maximum of alsikiren 300 mg/hydrochlorothiazide 25 mg.

#### 2.3 Use with Other Antihypertensive Drugs

Tekturna HCT may be administered with other antihypertensive agents. It is not known whether additive effects are present when Tekturna HCT is used with angiotensin-converting enzyme inhibitors or beta blockers. [See *Clinical Studies* (14)].

#### 2.4 Relationship to Meals

Patients should establish a routine pattern for taking Tekturna HCT with regard to meals. High-fat meals decrease absorption substantially [see *Clinical Pharmacology* (12.3)].

#### 2.5 Dosing in Specific Populations

##### Renal Impairment

The usual regimens of Tekturna HCT may be followed as long as the patient’s creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Tekturna HCT is not recommended.

##### Hepatic Impairment

Adjustment of the starting dose is not necessary with hepatic impairment.

##### Elderly Patients

Adjustment of the starting dose is not required for elderly patients.

#### 3 DOSAGE FORMS AND STRENGTHS

- 150 mg/12.5 mg tablets: white, biconvex ovaloid, film-coated tablets imprinted with NVR/LCI
- 150 mg/25 mg tablets: pale yellow, biconvex ovaloid, film-coated tablets imprinted with NVR/CLL
- 300 mg/12.5 mg tablets: violet white, biconvex ovaloid, film-coated tablets imprinted with NVR/CVI
- 300 mg/25 mg tablets: light yellow, biconvex ovaloid, film-coated tablets imprinted with NVR/CVV

#### 4 CONTRAINDICATIONS

Because of the hydrochlorothiazide component, Tekturna HCT is contraindicated in patients with anuria or hypersensitivity to sulfonamide-derived drugs [see *Warnings and Precautions* (5.6) and *Adverse Reactions* (6.1)]. Hypersensitivity reactions may range from urticaria to anaphylaxis [see *Adverse Reactions* (6.1)].

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 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. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. [See *Use in Specific Populations* (8.1)] In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. In addition, first trimester use of ACE inhibitors has been associated with birth defects in retrospective data. Thiazides cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occurred in adults.

##### 5.2 Head and Neck Angioedema

##### Alsikiren

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with alsikiren. 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 alsikiren is not known. Tekturna HCT 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.

##### 5.3 Hypotension in Volume- and/or Salt-Depleted Patients

An excessive fall in blood pressure (hypotension) was rarely seen (<1% in patients with uncomplicated hypertension treated with Tekturna HCT in controlled trials. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Tekturna HCT, 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. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

##### 5.4 Patients with Severe Renal Impairment

*Tekturna HCT*
In patients with severe renal impairment (GFR <30 mL/min), loop diuretics are preferred to thiazides, so Tekturna HCT is not recommended.

##### Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

##### 5.5 Patients with Hepatic Impairment

##### Hydrochlorothiazide

Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

##### 5.6 Hypersensitivity Reactions

##### Hydrochlorothiazide

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

##### 5.7 Systemic Lupus Erythematosus

##### Hydrochlorothiazide

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

##### 5.8 Lithium Interaction

##### Hydrochlorothiazide

Lithium generally should not be given with thiazides. [See *Drug Interaction* (7)].

##### 5.9 Serum Electrolyte Abnormalities

##### Tekturna HCT

In the short-term controlled trials of various doses of Tekturna HCT the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 2.2%; the incidence of

hyperkalemia (serum potassium >5.5 mEq/L) was 0.8%. No patients discontinued due to increase or decrease of serum potassium.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. The intervals should be based on the history of electrolyte abnormalities in patients with alsikiren or hydrochlorothiazide monotherapy.

**Based on experience with the use of other substances that affect the renin-angiotensin system (RAS),** concomitant use of Tekturna HCT 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.

##### 5.10 Renal Artery Stenosis

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

##### 5.11 Cyclosporine

##### Alsikiren

When alsikiren was given with cyclosporine, the blood concentrations of alsikiren were significantly increased. Concomitant use of alsikiren with cyclosporine is not recommended [see *Drug Interactions* (7)].

#### 6 ADVERSE REACTIONS

##### 6.1 Clinical Studies Experience

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Risk of fetal/neonatal morbidity and mortality [see *Warnings and Precautions* (5.1)]
- Head and neck angioedema [see *Warnings and Precautions* (5.2)]
- Hypotension in volume- and/or salt-depleted patients [see *Warnings and Precautions* (5.3)]

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.

##### Tekturna HCT

Tekturna HCT has been evaluated for safety in more than 2,700 patients, including over 700 treated for 6 months and 190 for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event (including uncontrolled hypertension) occurred in 2.7% of patients treated with Tekturna HCT versus 3.6% of patients given placebo.

Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with Tekturna HCT and at a higher incidence than placebo included dizziness (2.3% vs. 1%), influenza (2.3% vs. 1.6%), diarrhea (1.6% vs. 0.5%), cough (1.3% vs. 0.5%), vertigo (1.2% vs. 0.5%), asthenia (1.2% vs. 0%), and arthralgia (1% vs. 0.5%).

##### Alsikiren

Alsikiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 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 alsikiren, versus 3.5% of patients given placebo.

Two cases of angioedema with respiratory symptoms were reported with alsikiren 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 alsikiren 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 alsikiren compared with 0.5% with placebo. In a long-term active-controlled study with alsikiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Alsikiren produces dose-related gastrointestinal (GI) adverse reactions. 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% to 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.

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

Other adverse reactions with increased rates for alsikiren 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 alsikiren in the clinical trials. One patient had 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. Alsikiren was discontinued and there was no rechallenge in either case.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with alsikiren, 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.

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with alsikiren.

##### Hydrochlorothiazide

Other adverse reactions that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

##### Body As A Whole: weakness;

*Digestive:* pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation;

*Hematologic:* aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonia and pulmonary edema, anaphylactic reactions;

*Metabolic:* hyperglycemia, glycosuria, hyperuricemia;

*Musculoskeletal:* muscle spasm;

*Nervous System/Psychiatric:* restlessness;

*Renal:* renal failure, renal dysfunction, interstitial nephritis;

*Skin:* erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis;

*Special Senses:* transient blurred vision, xanthopsia.

##### 6.2 Clinical Laboratory Test Abnormalities

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Tekturna HCT.

**Blood Urea Nitrogen (BUN)/Creatinine:** Elevations (greater than 50% increase) in BUN and creatinine occurred in 11.8% and 0.9%, respectively, of patients taking Tekturna HCT, and 7% and 1.1%, respectively, of patients given placebo in short-term controlled clinical trials. No patients were discontinued due to an increase in either BUN or creatinine.

**Hemoglobin and Hematocrit:** A greater than 20% decrease in hemoglobin and hematocrit were observed in <0.1% and 0.1%, respectively, of patients treated with Tekturna HCT, compared with 0% in placebo-treated patients. No patients were discontinued due to anemia.

**Liver Function Tests:** Occasional elevations (greater than 150% in ALT (SGPT)) were observed in 1.2% of patients treated with Tekturna HCT, compared with 0% in placebo-treated patients. No patients were discontinued due to abnormal liver function tests.

**Serum Uric Acid:** Uric acid related abnormalities were more commonly observed in patients treated with Tekturna HCT, compared with placebo; >2% versus 0% had a uric acid increase >50% from baseline; gout and renal stones were less commonly observed.

*Serum Electrolytes:* See *Warnings and Precautions* (5.8)

#### 7 DRUG INTERACTIONS

No drug interaction studies have been conducted with Tekturna HCT and other drugs, although studies with the individual alsikiren and hydrochlorothiazide components are described below.

##### Alsikiren

##### Effects of Other Drugs on Alsikiren

Based on *in vitro* studies, alsikiren is metabolized by CYP 3A4.

*Ibesartan:* Coadministration of irbesartan reduced alsikiren C<sub>max</sub> up to 50% after multiple dosing.

**P-glycoprotein Effects:** Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of alsikiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter. Coadministration of alsikiren with Pgp substrates or weak to moderate inhibitors such as atenolol, digoxin, and amlopidine did not result in clinically relevant interactions.

*Atorvastatin:* Coadministration of atorvastatin resulted in about a 50% increase in alsikiren C<sub>max</sub> and AUC after multiple dosing.

**Ketoconazole:** Coadministration of 200 mg twice-daily ketoconazole, a potent Pgp inhibitor, with alsikiren resulted in an approximate 80% increase in plasma levels of alsikiren. A 400-mg once-daily dose was not studied but would be expected to increase alsikiren blood levels further.

**Cyclosporine:** Coadministration of 200 mg and 600 mg cyclosporine, a highly potent Pgp inhibitor, with 75 mg alsikiren resulted in an approximately 2.5-fold increase in C<sub>max</sub> and 5-fold increase in AUC of alsikiren. Concomitant use of alsikiren with cyclosporine is not recommended.

*Drugs with no clinically significant effects:* Coadministration of losvastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlopidine did not result in clinically significant increases in alsikiren exposure.

*Effects of Alsikiren on Other Drugs*
Alsikiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.

*Furosemide:* When alsikiren was coadministered with furosemide, the AUC and C<sub>max</sub> of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting alsikiren.

*Drugs with no clinically significant effects:* Coadministration of alsikiren did not significantly affect the pharmacokinetics of losvastatin, digoxin, valsartan, amlopidine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.

*Warfarin:* The effects of alsikiren on warfarin pharmacokinetics has not been evaluated.

##### Hydrochlorothiazide

When administered concurrently, the following drugs may interact with thiazide diuretics.

*Alcohol, barbiturates, or narcotics:* Potentiation of orthostatic hypotension may occur.

*Antidiabetic drugs (oral agents and insulin):* Dosage adjustment of the antidiabetic drug may be required.

*Other antihypertensive drugs:* Additive effect or potentiation.

*Cholestyramine and colestipol resins:* Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholest

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of agents that block the production or function of angiotensin II tends to reverse the potassium loss associated with these diuretics.

The mechanism of action of the antihypertensive effect of thiazides is unknown.

**12.2 Pharmacodynamics**

Tekturna HCT

In placebo-controlled clinical trials, PRA was decreased with aliskiren monotherapy (ranging from 54% to 65%) and increased with hydrochlorothiazide monotherapy (ranging from 4% to 72%).

Metabolism and Elimination

Aliskiren

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.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. The elimination half-life is between 5.8 and 18.9 hours.

Special Populations

Pediatric Patients

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

Aliskiren

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<sub>0-24h</sub>) basis, 1500 mg/kg/day in the rat is about 4 times and 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 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<sup>2</sup> basis.

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans nondisjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats represent 19 and 1.5 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

#### 14 CLINICAL STUDIES

Tekturna HCT

In all clinical trials including over 6,200 patients, more than 2,700 patients were exposed to combinations of aliskiren and hydrochlorothiazide. The safety and efficacy of Tekturna HCT were evaluated in patients with mild-to-moderate hypertension in an 8-week, randomized, double-blind, placebo-controlled, parallel-group, 15-arm factorial trial (n=2762). Patients were randomized to receive various combinations of aliskiren (75 mg to 300 mg) plus hydrochlorothiazide (6.25 mg to 25 mg) once daily (without titrating up from monotherapy) and followed for blood pressure response. The combination of aliskiren and hydrochlorothiazide resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure at trough of 10-14/5-7 mmHg at doses of 150-300 mg/12.5-25 mg, compared to 5-8/2-3 mmHg for aliskiren 150 mg to 300 mg and 6-7/2-3 mmHg for hydrochlorothiazide 12.5 mg to 25 mg, alone. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 1.

		Hydrochlorothiazide, mg			
	Placebo	0	6.25	12.5	25
Aliskiren, mg	Mean Change	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

The antihypertensive effect of Tekturna HCT was largely manifested within 1 week. The maximum antihypertensive effect was generally attained after about 4 weeks of therapy.

One active-controlled trial investigated the addition of 300 mg aliskiren in obese hypertensive patients who did not respond adequately to hydrochlorothiazide 25 mg, and showed decreases of systolic and diastolic blood pressure of approximately 7/4 mmHg.

In long-term follow-up studies (without placebo control) the effect of the combination of aliskiren and hydrochlorothiazide was maintained for over 1 year.

The antihypertensive effect was independent of age and gender. There were too few non-Caucasians to assess differences in blood pressure effects by race.

Aliskiren Monotherapy

The antihypertensive effects of 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 2.

		Aliskiren Daily Dose, mg			
	Placebo	75	150	300	600
Study	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	--	6.5/2.9*	10.5/5.4*	10.4/5.2*
3	1/0/6	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 mg to 600 mg of aliskiren and 1,231 patients given placebo. As shown in Table 2, there is some increase in response with administered dose in all studies, with reasonable effects seen at 150 mg to 300 mg, and no clear further increase at 600 mg. A substantial proportion (85% to 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, e.g., 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.

The effectiveness of aliskiren was demonstrated across all demographic subgroups, although Black patients tended to have smaller reductions in blood pressure than Caucasians and Asians, as has been seen with ACE inhibitors and ARBs.

Aliskiren in Combination with Other Antihypertensives

Valsartan

Aliskiren 150 mg and 300 mg and valsartan 160 mg 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 mg 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.

		Valsartan, mg		
	Placebo	0	160	320
Aliskiren, mg	Mean Change	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 coadministered with amlodipine 5 mg in one study, but the combination was not statistically significantly better than amlodipine 10 mg.

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

Tekturna HCT is supplied as biconvex, ovaloid film-coated tablets.

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

Tablet	Color	Table 4: Tekturna HCT Tablets Supply		NDC 0078- XXXX-XX		Blister Packages of 100
		Imprint	Imprint	Bottle of 30	Bottle of 90	
Aliskiren/HCTZ		Side 1	Side 2			
150 mg/12.5 mg	White	NVR	LCI	0521-15	0521-34	0521-35
150 mg/25 mg	Pale Yellow	NVR	LLI	0522-15	0522-34	0522-35
300 mg/12.5 mg	Violet White	NVR	CVI	0523-15	0523-34	0523-35
300 mg/25 mg	Light Yellow	NVR	CVV	0524-15	0524-34	0524-35

Storage

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

Protect from moisture.

Dispense in tight container (USP).

#### 17 PATIENT COUNSELING INFORMATION

##### 17.1 Important Information

Healthcare professionals should instruct their patients to read the Patient Package Insert before starting Tekturna HCT and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

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. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

A patient receiving Tekturna HCT should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Tekturna HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements

A patient receiving Tekturna HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Relationship to Meals

Patients should establish a routine pattern for taking Tekturna HCT with regard to meals. High-fat meals decrease absorption substantially.

#### 17.2 FDA-Approved Patient Labeling

##### Patient Information

**Tekturna HCT® (tek-turn-a HCT) (aliskiren and hydrochlorothiazide, USP) Combination Tablets**

Read the Patient Information that comes with Tekturna HCT before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition and treatment.

**IMPORTANT WARNING: Tekturna HCT may harm an unborn baby, causing injury and even death. If you get pregnant, stop taking Tekturna HCT and call your doctor right away. If you plan to become pregnant, talk to your doctor about other medicines to treat your high blood pressure before taking Tekturna HCT.**

##### What is Tekturna HCT?

Tekturna HCT contains two prescription medicines in one tablet that work together to lower blood pressure. It contains:

- aliskiren (Tekturna), a direct renin inhibitor (DRI)
- hydrochlorothiazide, a diuretic (water pill)

Tekturna HCT should not be the first medicine used to treat your high blood pressure.

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

Your doctor may prescribe other medicines for you to take along with Tekturna HCT to treat your high blood pressure.

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. One cause of high blood pressure is renin, 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.

Blood pressure is reduced more with Tekturna HCT than when either Tekturna or hydrochlorothiazide is taken by itself.

##### Who should not take Tekturna HCT?

- If you get pregnant, stop taking Tekturna HCT 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 HCT if you make very little or no urine due to kidney problems.**
- Do not take Tekturna HCT if you are allergic to any of its ingredients. See the end of this leaflet for a complete list of the ingredients in Tekturna HCT.**

#### What should I tell my doctor before taking Tekturna HCT?

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

- have any allergies or asthma
- have kidney problems
- have liver problems
- have systemic lupus erythematosus (SLE). Tekturna HCT can make your SLE active or worse.
- have ever had a reaction called angioedema, to an ACE inhibitor medicine. Angioedema causes swelling of the face, lips, tongue, throat, arms and legs, and may cause difficulty breathing.
- are pregnant or planning to become pregnant. See IMPORTANT WARNING.
- are breast-feeding. It is not known if Tekturna HCT passes into your breast milk.

**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
- cyclosporine (a medicine used to suppress the immune system)**
- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium**
- cholestyramine (for example; Questran, Questran Light, Cholestyramine Light, Cholestol Light, Locholest, Prevalite) (medicines to lower the cholesterol in your blood)
- colestipol (for example; Colestipol hydrochloride, Colestid, Flavored Colestid) (medicines to lower the cholesterol in your blood)
- potassium supplements
- medicines to treat diabetes, including insulin
- lithium, a medicine used in some types of depression. Do not take Tekturna HCT if you are taking lithium.
- Nonsteroidal anti-inflammatory (NSAIDs) medicines. Ask your doctor if you are not sure if you are taking one of these medicines.
- blood thinners
- barbiturate or narcotic medicines. Ask your doctor if you are not sure if you are taking one of these medicines.

Your doctor or pharmacist will know what medicines are safe to take together. Know your medicines. Keep a list of your medicines and show it to your doctor or pharmacist when you get a new medicine.

##### How should I take Tekturna HCT?

- Take Tekturna HCT exactly as prescribed by your doctor. It is important to take Tekturna HCT every day to control your blood pressure.
- Take Tekturna HCT once each day, about the same time each day.
- Take Tekturna HCT the same way everyday, either with or without a meal.
- Your doctor may change your dose of Tekturna HCT if needed.
- If you miss a dose of Tekturna HCT, 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 HCT, call your doctor or a Poison Control Center, or go to the nearest hospital emergency room.

##### What are the possible side effects of Tekturna HCT?

Tekturna HCT may cause serious side effects:

- Injury or death to an unborn baby.** See IMPORTANT WARNING.
- 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. Drinking alcohol and taking certain medicines (barbiturates or narcotics) can cause low blood pressure to get worse. Lie down if you feel faint or dizzy, and call your doctor right away.
- Angioedema.** Aliskiren in Tekturna HCT can cause swelling of the face, lips, tongue, throat, arms and legs, or the whole body. Get medical help right away and tell your doctor if you get any one or more of these symptoms. Angioedema can happen at any time while you are taking Tekturna HCT.
- Active or worsened Systemic Lupus Erythematosus (SLE).** If you have SLE, tell your doctor right away if you get any new or worse symptoms.

##### Common side effects of Tekturna HCT include:

- dizziness
- flu-like symptoms
- diarrhea
- cough
- tiredness

Other less common side effects include skin rash.

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of Tekturna HCT. For a complete list of side effects, ask your doctor or pharmacist.

##### How do I store Tekturna HCT?

- Store Tekturna HCT tablets at room temperature between 59°F-86°F (15°C-30°C).
- Keep Tekturna HCT in the original prescription bottle in a dry place. Do not remove the desiccant (drying agent) from the bottle.

**Keep Tekturna HCT and all medicines out of the reach of children.**

##### General information about Tekturna HCT

Medicines are sometimes prescribed for conditions not listed in the patient information leaflet. Do not take Tekturna HCT for a condition for which it was not prescribed. Do not give Tekturna HCT 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 HCT. If you have questions about Tekturna HCT talk with your doctor. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

**For more information about Tekturna HCT, visit [www.TekturnaHCT.com](http://www.TekturnaHCT.com), or call 1-888-NOW-NOVA (1-888-669-6682).**

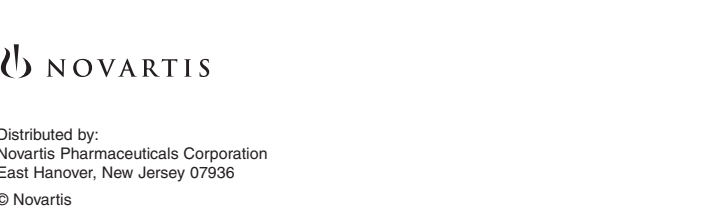
##### What are the ingredients in Tekturna HCT?

Active ingredients: Aliskiren and hydrochlorthiazide

Inactive ingredients: Colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxide colorants, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide, and wheat starch

#### Call your doctor for medical advice about side effects.

#### You may report side effects to FDA at 1-800-FDA-1088.



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