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%).

Treatment with Tekturna HCT resulted in PRA reductions ranging from approximately 46% to 63% in various doses despite the increase in PRA with hydrochlorothiazide treatment. The clinical implications of the differences in effect on PRA are not known.

Aliskiren
PRA reductions in clinical trials ranged from approximately 50% to 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.

Hydrochlorothiazide
After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours, and lasts about 6 to 12 hours.

12.3 Pharmacokinetics
Absorption and Distribution
Tekturna HCT
Following oral administration of Tekturna HCT combination tablets, the median peak plasma concentration time are within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide. When taken with food, mean AUC and C_{max} of aliskiren are decreased by 60% and 82%, respectively; mean AUC and C_{max} of hydrochlorothiazide increased by 13% and 10%, respectively. As a result, patients should establish a routine pattern for taking Tekturna HCT with regard to meals and should be advised that high-fat meals decrease absorption of aliskiren substantially.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

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.

Geriatric Patients
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 (2)*].

Race
Too few non-Caucasians have been studied with Tekturna HCT to assess pharmacokinetic differences among races. The pharmacokinetic differences among Blacks, Caucasians, and Japanese are minimal with aliskiren therapy.

Renal Impairment
The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal impairment. 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 (2)*].

Hepatic Impairment
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 (2)*].

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Tekturna HCT
No carcinogenicity, mutagenicity or fertility studies have been conducted with Tekturna HCT. However, these studies have been conducted for aliskiren as well as hydrochlorothiazide alone.

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 ($AUC_{0\text{-}24h}$) 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^2 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 mcgm/mL, and in the Aspergillums 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^2 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.

Table 1: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Hydrochlorothiazide

		Hydrochlorothiazide, mg			
		0	6.25	12.5	25
Aliskiren, mg	Placebo 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.

Table 2: Reductions in Seated Trough Cuff Blood Pressure in the Placebo-Controlled Studies of Aliskiren Monotherapy

		Aliskiren Daily Dose, mg			
		75	150	300	600
Study	Placebo 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 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.

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

		Valsartan, mg		
Aliskiren, mg	Placebo 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.

Table 4: Tekturna HCT Tablets Supply

Tablet	Color	Imprint	Imprint	NDC 0078- XXXX-XX		
Aliskiren/HCTZ		Side 1	Side 2	Bottle of 30	Bottle of 90	Blister Packages of 100
150 mg/12.5 mg	White	NVR	LCI	0521-15	0521-34	0521-35
150 mg/25 mg	Pale Yellow	NVR	CLL	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, Locholest 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, or call 1-888-NOW-NOVA (1-888-669-6682).

What are the ingredients in Tekturna HCT?
Active ingredients: Aliskiren and hydrochlorothiazide

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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