

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 (aliskiren and hydrochlorothiazide) tablets, for oral use
Initial U.S. Approval: 2008

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning

- When pregnancy is detected, discontinue Tekturna HCT as soon as possible. (5.1)
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

RECENT MAJOR CHANGES

Warnings and Precautions (5.4) 10/2013

INDICATIONS AND USAGE

Tekturna HCT is a combination of aliskiren, a renin inhibitor, and hydrochlorothiazide (HCTZ), a thiazide diuretic, indicated for the treatment of hypertension, to lower blood pressure:

- In patients not adequately controlled with monotherapy
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals (1)

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarction.

DOSAGE AND ADMINISTRATION

- The antihypertensive effect is largely manifested within 1 week, with maximal effects seen at around 4 weeks. If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, titrate up to a maximum of 300/25 mg. (2.2)
- Order of increasing mean effect: 150/12.5 mg, 150/25 mg or 300/12.5 mg, and 300/25 mg (2.1)
- One tablet daily, with a routine pattern with regard to meals. (2.7)
- Add-on or Initial therapy: Initiate with 150/12.5mg. Titrate as needed up to a maximum of 300/25 mg. (2.3, 2.5)
- Replacement therapy: May be substituted for titrated components (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets (mg aliskiren/mg HCTZ): 150/12.5, 150/25, 300/12.5, 300/25 (3)

CONTRAINDICATIONS

Do not use with angiotensin receptor blockers (ARBs) or ACE inhibitors (ACEIs) in patients with diabetes (4)

Anuria (4)

Hypersensitivity to sulfonamide-derived drugs (4)

WARNINGS AND PRECAUTIONS

- Avoid concomitant use with ARBs or ACEIs in patients with renal impairment (GFR<60 mL/min) (5.2)
- Anaphylactic Reactions and Head and Neck Angioedema: Discontinue Tekturna HCT and monitor until signs and symptoms resolve. (5.3)
- Hypotension in volume and/or salt depleted patients or with combined use of other agents acting on RAAS: Correct imbalances prior to initiating therapy with Tekturna HCT. (5.4)
- Impaired renal function: Monitor serum creatinine periodically. (5.5)
- Hypersensitivity Reactions: May occur from HCTZ component (5.6)
- Hyperkalemia: Monitor potassium levels periodically. (5.9)
- Hydrochlorothiazide has been associated with acute angle-closure glaucoma (5.11)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 1.5\%$ 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.

DRUG INTERACTIONS

- Cyclosporine: Avoid concomitant use (7, 12.3)
- Itraconazole: Avoid concomitant use (7, 12.3)
- NSAIDs use may lead to increased risk of renal impairment and loss of antihypertensive effect (7)
- Antidiabetic Drugs: Dosage adjustment of antidiabetic may be required (7)
- Cholestyramine and Colestipol: Reduced absorption of thiazides (7)
- Lithium: Increased risk of lithium toxicity when used with diuretics. Monitor serum lithium concentrations during concurrent use. (7)

USE IN SPECIFIC POPULATIONS

Nursing Mothers: Nursing or drug should be discontinued. (8.3)

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

Revised: 10/2013

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue Tekturna HCT as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

1 INDICATIONS AND USAGE

Tekturna HCT is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including hydrochlorothiazide. There are no controlled trials demonstrating risk reduction with Tekturna HCT.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Add-On Therapy

A patient whose blood pressure is not adequately controlled with aliskiren 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.

Initial Therapy

Tekturna HCT may be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

The choice of Tekturna HCT as initial therapy should be based on an assessment of potential benefits and risks. Patients with Stage 2 hypertension are at a relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Data from the high-dose multifactorial study [see *Clinical Studies (14)*] provide estimates of the probability of reaching a target blood pressure with Tekturna HCT compared to aliskiren or hydrochlorothiazide monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Tekturna HCT 300/25 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable because of small numbers of subjects with high baseline blood pressures.

Figure 1: Probability of Achieving Systolic Blood Pressure (SBP) <140 mmHg

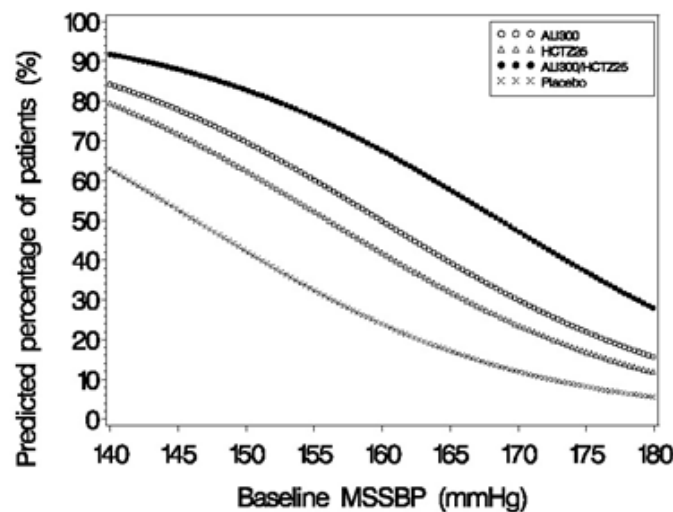


Figure 2: Probability of Achieving Systolic Blood Pressure (SBP) <130 mmHg

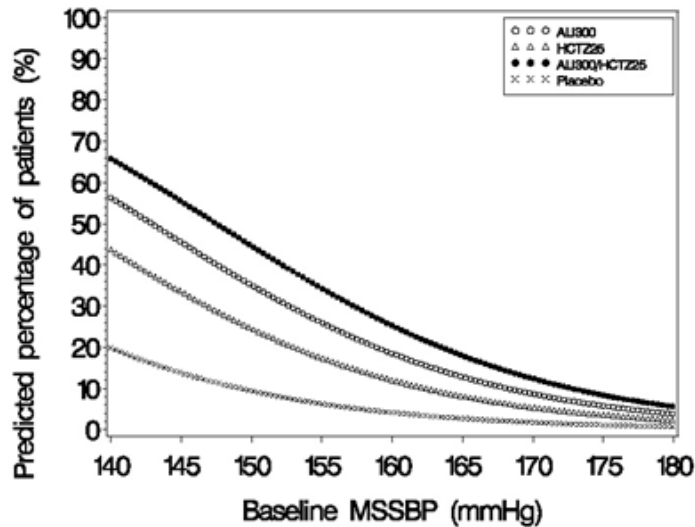


Figure 3: Probability of Achieving Diastolic Blood Pressure (DBP) <90 mmHg

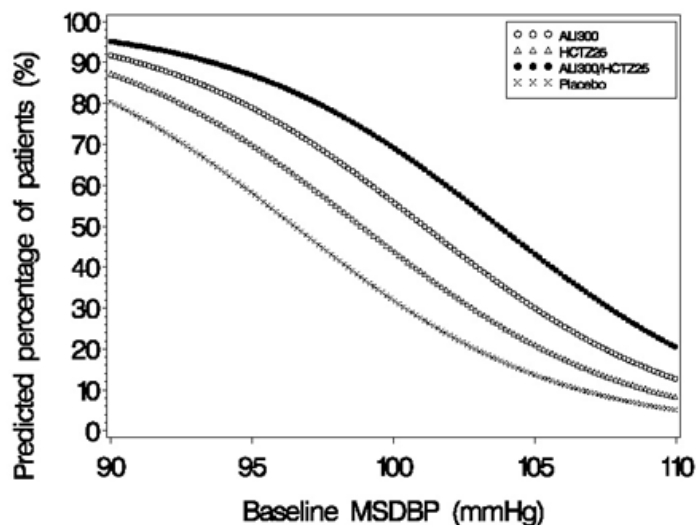
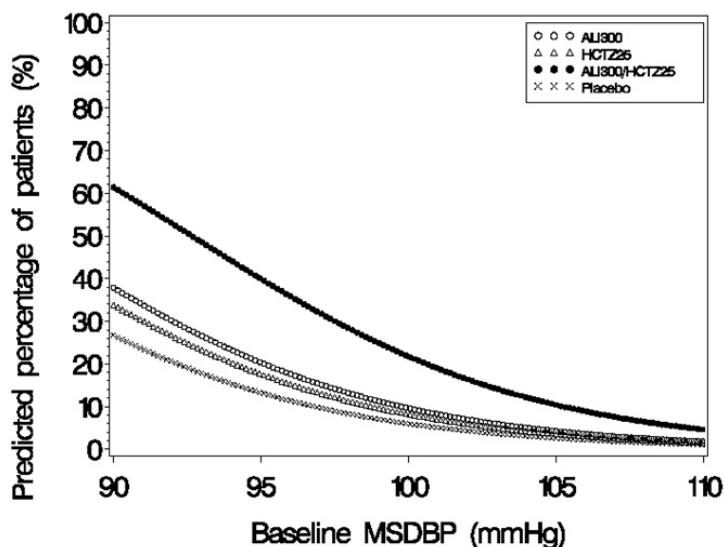


Figure 4: Probability of Achieving Diastolic Blood Pressure (DBP) <80 mmHg



At all levels of baseline blood pressure, the probability of achieving any given diastolic or systolic goal is greater with the combination than for either monotherapy. For example, the mean baseline msSBP/msDBP for patients participating in this multifactorial study was 154/99 mmHg. A patient with a baseline blood pressure of 154/99 mmHg has about a 62% chance of achieving a goal of <140 mmHg (systolic) and 61% chance of achieving <90 mmHg (diastolic) on aliskiren alone, and the chance of achieving these goals on hydrochlorothiazide alone is about 54% (systolic) and 49% (diastolic). The chance of achieving these goals on Tekturna HCT rises to about 77% (systolic) and 74% (diastolic). The chance of achieving these goals on placebo is about 34% (systolic) and 37% (diastolic) [see *Dosage and Administration (2) and Clinical Studies (14)*].

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.

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 aliskiren 300 mg/hydrochlorothiazide 25 mg.

2.3 Add-On Therapy

A patient whose blood pressure is not adequately controlled with aliskiren alone or hydrochlorothiazide alone may be switched to combination therapy with Tekturna HCT. The usual recommended starting dose is 150/12.5 mg once daily as needed to control blood pressure. The dose may be titrated up to a maximum of aliskiren 300 mg/hydrochlorothiazide 25 mg once daily.

2.4 Replacement Therapy

Tekturna HCT may be substituted for the individually titrated components.

2.5 Initial Therapy

The usual recommended starting dose is 150/12.5 mg once daily as needed to control blood pressure. The dose may be titrated up to a maximum of aliskiren 300 mg/hydrochlorothiazide 25 mg once daily.

Tekturna HCT is not recommended for use as initial therapy in patients with intravascular volume depletion [see *Warnings and Precautions (5.4)*].

2.6 Use with Other Antihypertensive Drugs

Tekturna HCT may be administered with some other antihypertensive agents. In diabetics, do not use in combination with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs) [see *Contraindications (4)*]. Concomitant use of aliskiren with an ARB or ACEI is not recommended in patients with GFR <60 ml/min [see *Warnings and Precautions (5.2)*]. There are no data available with use of Tekturna HCT with angiotensin-converting enzyme inhibitors or beta blockers [see *Clinical Studies (14)*].

2.7 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)*].

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/CSV

4 CONTRAINDICATIONS

Do not use aliskiren with ARBs or ACEIs in patients with diabetes [see *Warnings and Precautions (5.2)*, *Clinical Studies (14.4)*].

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 Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Tekturna HCT as soon as possible [*see Use in Specific Populations (8.1)*].

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 Tekturna HCT.

5.2 Renal Impairment/Hyperkalemia/Hypotension when Tekturna HCT is given in combination with ARBs or ACEIs

Tekturna HCT is contraindicated in patients with diabetes who are receiving ARBs or ACEIs because of the increased risk of renal impairment, hyperkalemia, and hypotension [*see Contraindications (4) and Clinical Studies (14.4)*].

Avoid use of Tekturna HCT with ARBs or ACEIs in patients with moderate renal impairment (GFR <60 ml/min).

5.3 Anaphylactic Reactions and Head and Neck Angioedema

Aliskiren

Hypersensitivity reactions such as anaphylactic reactions and angioedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients treated with Tekturna and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors or angiotensin receptor antagonists. Anaphylactic reactions have been reported from post-marketing experience with unknown frequency. If angioedema involves the throat, tongue, glottis or larynx, or if the patient has a history of upper respiratory surgery, airway obstruction may occur and be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation and appropriate monitoring measures since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 ml) and measures to ensure a patent airway may be necessary.

Discontinue Tekturna HCT immediately in patients who develop anaphylactic reactions or angioedema, and do not readminister.

5.4 Hypotension

Symptomatic hypotension may occur after initiation of treatment with Tekturna HCT in patients with marked volume depletion, patients with salt depletion, or with combined use of aliskiren and other agents acting on the renin-angiotensin-aldosterone system. The volume or salt depletion should be corrected prior to administration of Tekturna HCT, or the treatment should start under close medical supervision.

A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.5 Impaired Renal Function

Monitor renal function periodically in patients treated with Tekturna HCT. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin-aldosterone system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin-aldosterone system

(e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or patients receiving ARB, ACEI or non-steroidal anti-inflammatory (NSAID) therapy may be at particular risk of developing acute renal failure on Tekturna HCT [*see Contraindications (4), Warnings and Precautions (5.2), Clinical Studies (14.4)*]. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Tekturna HCT.

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 Interactions (7)*].

5.9 Serum Electrolyte Abnormalities

Tekturna HCT

In the short-term controlled trials of various doses of Tekturna HCT, in patients with hypertension not concomitantly treated with an ARB or ACEI, 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.

Aliskiren

Monitor serum potassium periodically in patients receiving aliskiren. Drugs that affect the renin-angiotensin-aldosterone system can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes, combination use with ARBs or ACEI [*see Contraindications (4), Warnings and Precautions (5.2), and Clinical Studies (14.4)*], NSAIDs, or potassium supplements or potassium sparing diuretics.

Hydrochlorothiazide

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion.

If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), Tekturna HCT should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides.

5.10 Cyclosporine or Itraconazole

Aliskiren

When aliskiren was given with cyclosporine or itraconazole, the blood concentrations of aliskiren were significantly increased. Avoid concomitant use of aliskiren with cyclosporine or itraconazole [*see Drug Interactions (7)*].

5.11 Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

5.12 Metabolic Disturbances

Hydrochlorothiazide

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving Tekturna HCT.

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 (5.3)*].
- Hypotension in volume- and/or salt-depleted patients [*see Warnings and Precautions (5.4)*].

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%).

Aliskiren

Aliskiren 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 aliskiren, versus 3.5% of patients given placebo. These data do not include information from the ALTITUDE study which evaluated the use of aliskiren in combination with ARBs or ACEIs [*see Contraindications (4), Warnings and Precautions (5.2), and Clinical Studies (14.4)*].

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-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren 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.

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 reactions with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%) 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 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. Aliskiren was discontinued and there was no rechallenge in either case.

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

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 pneumonitis 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

Clinical Laboratory Test Abnormalities

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Tekturna HCT in patients with hypertension not concomitantly treated with an ARB or ACEI.

Blood Urea Nitrogen (BUN)/Creatinine: In patients with hypertension not concomitantly treated with an ARB or ACEI, 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.

6.2 Post-Marketing Experience

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

Aliskiren

Hypersensitivity: anaphylactic reactions and angioedema requiring airway management and hospitalization

Urticaria

Peripheral edema

Hepatic enzyme increase with clinical symptoms of hepatic dysfunction

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis

Pruritus

Erythema

Hydrochlorothiazide

Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, bone marrow failure, worsening of diabetes control, hypokalemia, blood lipids increased, hyponatremia, hypomagnesemia, hypercalcemia, hyperchloremic alkalosis, impotence, visual impairment

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic evaluation is necessary.

7 DRUG INTERACTIONS

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

Aliskiren

Cyclosporine: Avoid co-administration of cyclosporine with aliskiren.

Itraconazole: Avoid co-administration of itraconazole with aliskiren [*See Clinical Pharmacology (12.3)*].

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors with agents that affect the renin-angiotensin-aldosterone system, including aliskiren, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving aliskiren and NSAID therapy.

The antihypertensive effect of aliskiren may be attenuated by NSAIDs.

Dual Blockade of the renin-angiotensin-aldosterone system: The concomitant use of aliskiren with other agents acting on the renin-angiotensin-aldosterone system such as ACEIs or ARBs is associated with an increased risk of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Monitor blood pressure, renal function, and electrolytes in patients on aliskiren and other agents that affect the renin-angiotensin-aldosterone system [*see Warnings and Precautions (5.4, 5.5, 5.9)*].

The concomitant use of aliskiren with an ARB or an ACEI in diabetic patients is contraindicated and should be avoided in patients with moderate renal impairment [*see Contraindications (4) and Warnings and Precautions (5.2)*].

Furosemide: Oral co-administration of aliskiren and furosemide reduced exposure to furosemide. Monitor diuretic effects when furosemide is co-administered with aliskiren.

Hydrochlorothiazide

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

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

Lithium: Diuretic agents increase the risk of lithium toxicity. Refer to the package insert for lithium before use of such preparation with Tekturna HCT. Monitoring of serum lithium concentrations is recommended during concurrent use.

Nonsteroidal anti-inflammatory drugs: When Tekturna HCT and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Ion exchange resins: Staggering the dosage of hydrochlorothiazide and ion exchange resins (e.g., cholestyramine, colestipol) such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimize the interaction [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Tekturna HCT as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-

angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Tekturna HCT, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Tekturna HCT for hypotension, oliguria, and hyperkalemia. [*see Use in Specific Populations (8.4)*]

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.

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/m² basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m² 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/m² basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

When pregnant mice and rats were given hydrochlorothiazide at doses up to 3000 and 1000 mg/kg/day, respectively (about 600 and 400 times the MRHD) during their respective periods of major organogenesis, there was no evidence of fetal harm.

Hydrochlorothiazide

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not prevent or alter the course of EPH (Edema, Proteinuria, Hypertension) gestosis (pre eclampsia), these drugs should not be used to treat hypertension in pregnant women. The use of hydrochlorothiazide for other indications (e.g. heart disease) in pregnancy should be avoided.

8.3 Nursing Mothers

It is not known whether aliskiren is excreted in human milk, but aliskiren was secreted in the milk of lactating rats. Thiazides appear in human milk. 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Neonates with a history of in utero exposure to Tekturna HCT:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

8.5 Geriatric Use

In the short-term controlled clinical trials of Tekturna HCT, 325 (19.6%) patients treated with Tekturna HCT were ≥65 years and 53 (3.2%) were ≥75 years.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Safety and effectiveness of Tekturna HCT in patients with severe renal impairment ($\text{CrCl} \leq 30 \text{ mL/min}$) have not been established. No dose adjustment is required in patients with mild ($\text{CrCl} 60\text{-}90 \text{ mL/min}$) or moderate ($\text{CrCl} 30\text{-}60$) renal impairment.

8.7 Hepatic Impairment

Aliskiren

No dose adjustment is necessary for patients with mild-to-severe liver disease.

Hydrochlorothiazide

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

10 OVERDOSAGE

Aliskiren

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

Aliskiren is poorly dialyzed. Therefore, hemodialysis is not adequate to treat aliskiren overexposure [*see Clinical Pharmacology (12.3)*].

Hydrochlorothiazide

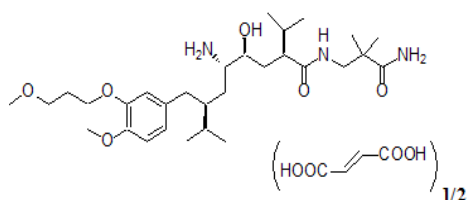
The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

11 DESCRIPTION

Tekturna HCT is a fixed combination of aliskiren, an orally active, nonpeptide, direct renin inhibitor, and hydrochlorothiazide, a thiazide diuretic that is provided as tablets for oral administration.

Aliskiren

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: $\text{C}_{30}\text{H}_{53}\text{N}_3\text{O}_6 \cdot 0.5 \text{C}_4\text{H}_4\text{O}_4$

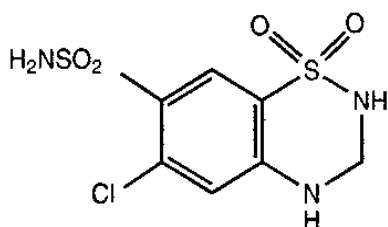
Aliskiren hemifumarate is a white to slightly yellowish crystalline powder with a molecular weight of 609.8 (free base- 551.8). It is soluble in phosphate buffer, n-octanol, and highly soluble in water.

Hydrochlorothiazide

Hydrochlorothiazide USP is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids.

Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Hydrochlorothiazide is a thiazide diuretic. Its empirical formula is C₇H₈ClN₃O₄S₂, its molecular weight is 297.73, and its structural formula is



Tekturna HCT tablets are formulated for oral administration to contain aliskiren and hydrochlorothiazide, USP 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg. The inactive ingredients for all strengths of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxide colorants, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide, and wheat starch.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aliskiren

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.

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.

Drug Interactions

Hydrochlorothiazide

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

Skeletal muscle relaxants: Possible increased responsiveness to muscle relaxants such as curare derivatives.

Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

12.3 Pharmacokinetics

Absorption and Distribution

Tekturna HCT

Following oral administration of Tekturna HCT combination tablets, the median peak plasma concentration time is 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.

Aliskiren

Aliskiren is poorly absorbed (bioavailability about 2.5%). 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.

Hydrochlorothiazide

The estimated absolute bioavailability of hydrochlorothiazide after oral administration is about 70%. Peak plasma hydrochlorothiazide concentrations (C_{max}) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of hydrochlorothiazide.

Hydrochlorothiazide binds to albumin (40 to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline bi-exponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours.

Metabolism and Elimination

Aliskiren

The effective half-life for aliskiren is 24 hours. Steady state blood levels are reached in about 7 – 8 days. 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. Aliskiren does not inhibit the CYP450 isoenzymes (CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A) or induce CYP 3A4.

Transporters: Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.

Hydrochlorothiazide

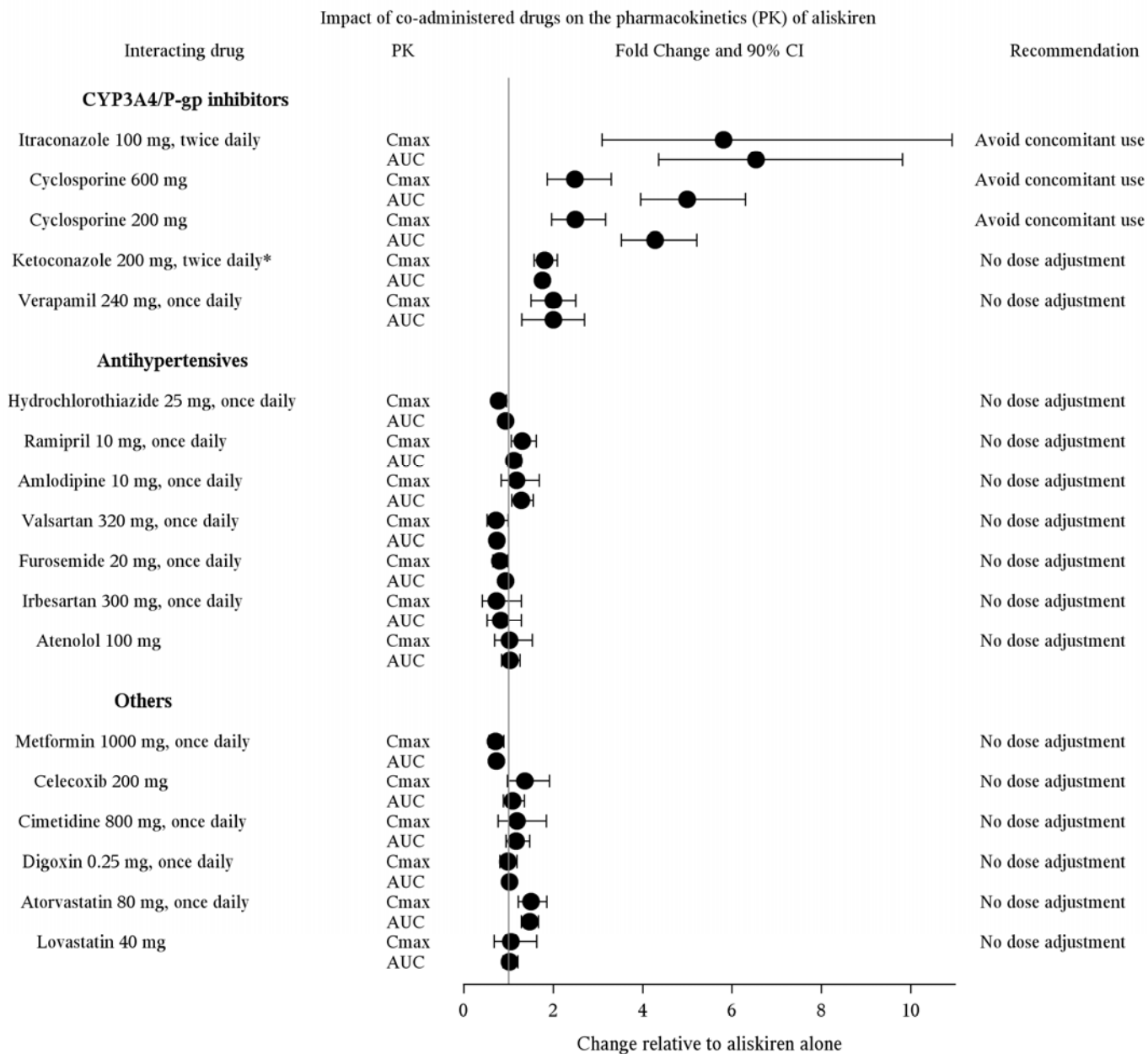
About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

Drug interactions:

Aliskiren

The effect of co-administered drugs on the pharmacokinetics of aliskiren and vice versa, were studied in several single and multiple dose studies. Pharmacokinetic measures indicating the magnitude of these interactions are presented in Figure 5 (impact of co-administered drugs on aliskiren) and Figure 6 (impact on co-administered drugs).

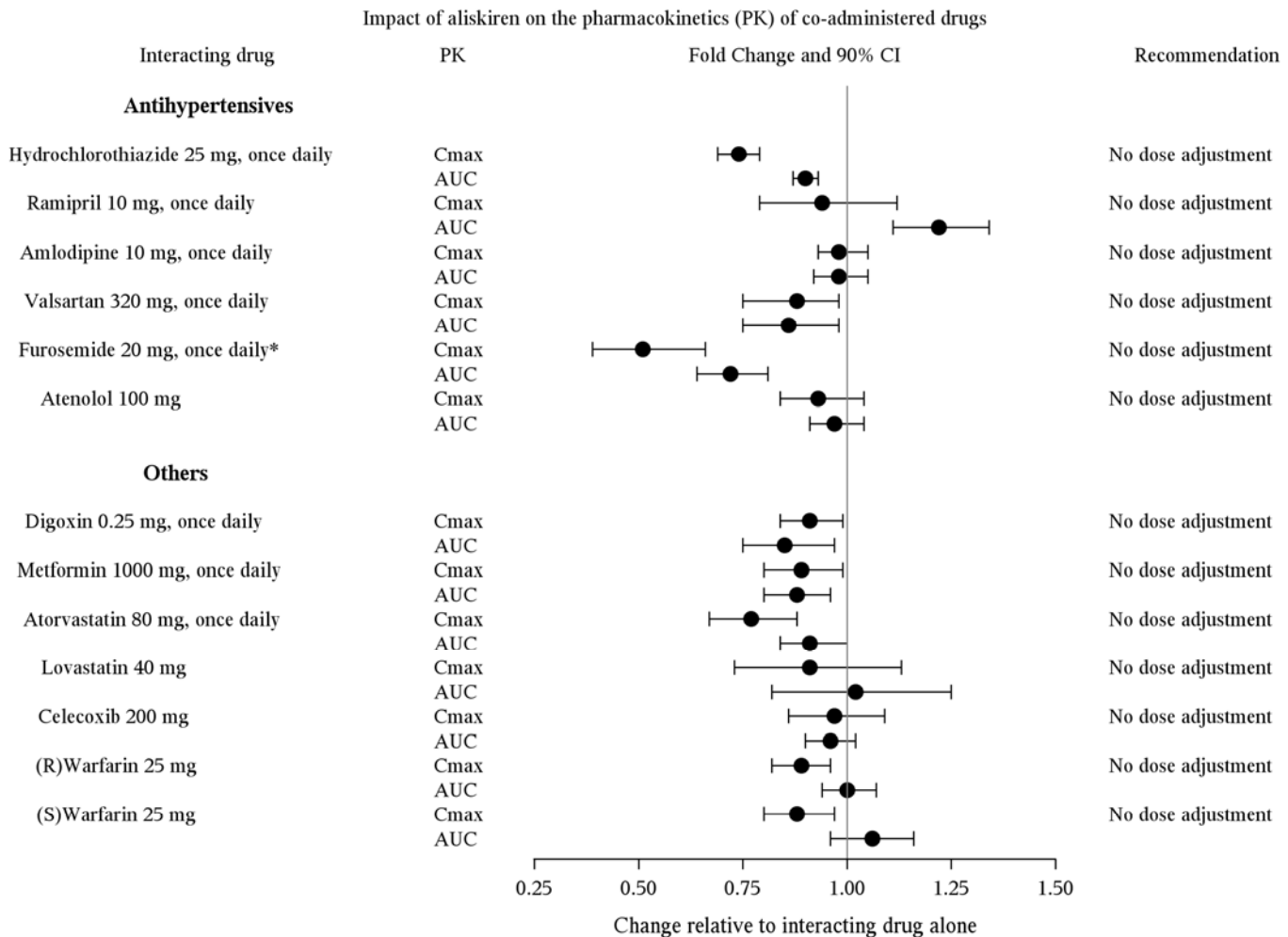
Figure 5: The impact of co-administered drugs on the pharmacokinetics of aliskiren



*A 400 mg once daily dose was not studied, but would be expected to increase aliskiren blood levels further.

Warfarin: There was no clinically significant effect of a single dose of warfarin 25 mg on the pharmacokinetics of aliskiren.

Figure 6: The impact of aliskiren on the pharmacokinetics of co-administered drugs



*Patients receiving furosemide could find its effect diminished after starting aliskiren.

Furosemide: In patients with heart failure, co-administration of aliskiren (300 mg/day) reduced plasma AUC and Cmax of oral furosemide (60 mg/day) by 17% and 27%, respectively, and reduced 24 hour urinary furosemide excretion by 29%. This change in exposure did not result in statistically significant difference in total urine volume and urinary sodium excretion over 24 hours. However, a transient decrease in urinary sodium excretion and urine volume effects up to 12 hours were observed when furosemide was co-administered with aliskiren 300 mg/day.

Hydrochlorothiazide

Drugs that alter gastrointestinal motility: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, pro-kinetic drugs may decrease the bioavailability of thiazide diuretics.

Cholestyramine: In a dedicated drug interaction study, administration of cholestyramine 2 hours before hydrochlorothiazide resulted in a 70% reduction in exposure to hydrochlorothiazide. Further, administration of hydrochlorothiazide 2 hours before cholestyramine, resulted in 35% reduction in exposure to hydrochlorothiazide.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

Special Populations

Pediatric Patients

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

Geriatric Patients

Aliskiren

The pharmacokinetics of aliskiren were studied in the elderly (≥ 65 years). Exposure (measured by AUC) is increased in elderly patients.

Hydrochlorothiazide

A limited amount of data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

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

Aliskiren

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 [see *Use in Specific Populations (8.6)*].

The pharmacokinetics of aliskiren following administration of a single oral dose of 300 mg was evaluated in patients with End Stage Renal Disease (ESRD) undergoing hemodialysis. When compared to matched healthy subjects, changes in the rate and extent of aliskiren exposure (C_{max} and AUC) in ESRD patients undergoing hemodialysis were not clinically significant.

Timing of hemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, no dose adjustment is warranted in ESRD patients receiving hemodialysis.

Hydrochlorothiazide

In a study in individuals with impaired renal function, the mean elimination half-life of hydrochlorothiazide was doubled in individuals with mild/moderate renal impairment ($30 < CL_{cr} < 90$ mL/min) and tripled in severe renal impairment (≤ 30 mL/min), compared to individuals with normal renal function ($CL_{cr} > 90$ mL/min) [see *Use in Specific Populations (8.6)*].

Hepatic Impairment

Aliskiren

The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to-severe liver disease [see *Use in Specific Populations (8.7)*].

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_{0-24hr}) 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 was not teratogenic and 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

14.1 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 safety and efficacy of Tekturna HCT as initial therapy was evaluated in this trial. All patients randomized to the combination groups received the combination treatment of Tekturna HCT at assigned doses as initial therapy without titration from monotherapy. The figures [see *Indications and Usage (1)*] display the probability that a patient will achieve systolic or diastolic blood pressure goal with Tekturna HCT 300/25 mg, based upon their baseline systolic or diastolic blood pressure. At all levels of baseline blood pressure, the probability of achieving any given diastolic or systolic goal is greater with the combination than for either monotherapy.

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 incremental 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.

14.2 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.

14.3 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

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.

Amlodipine

Aliskiren 150 mg and 300 mg and amlodipine besylate 5 mg and 10 mg were studied alone and in combination in an 8-week, 1,685-patient, randomized, double-blind, placebo-controlled, multifactorial study. Treatment with aliskiren and amlodipine resulted overall in significantly greater reductions in diastolic and systolic blood pressure compared to the respective monotherapy components as shown in Table 4.

Table 4: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Amlodipine

Aliskiren, mg	Placebo mean change	Amlodipine, mg		
		0	5	10
0	5.4/6.8	--	5.6/9.0	8.5/14.3
150	--	2.6/3.9	8.6/13.9	10.8/17.1
300	--	4.9/8.6	9.6/15.0	11.1/16.4

ACE Inhibitors

Aliskiren has not been studied when added to maximal doses of ACE inhibitors to determine whether aliskiren produces additional blood pressure reduction.

There are no trials of the Tekturna HCT combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but the hydrochlorothiazide component has demonstrated such benefits.

14.4 Aliskiren in Patients with Diabetes treated with ARB or ACEI (ALTITUDE study)

Patients with diabetes with renal disease (defined either by the presence of albuminuria or reduced GFR) were randomized to aliskiren 300 mg daily (n=4283) or placebo (n=4296). All patients were receiving background therapy with an ARB or ACEI. The primary efficacy outcome was the time to the first event of the primary composite endpoint consisting of cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, onset of end stage renal disease, renal death, and doubling of serum creatinine concentration from baseline sustained for at least one month. After a median follow up of about 27 months, the trial was terminated early for lack of efficacy. Higher risk of renal impairment, hypotension and hyperkalemia was observed in aliskiren compared to placebo treated patients, as shown in the table below.

Table 5: Incidence of selected adverse events in ALTITUDE

	Aliskiren N=4283		Placebo N=4296	
	Serious Adverse Events* (%)	Adverse Events (%)	Serious Adverse Events* (%)	Adverse Events (%)
Renal impairment †	4.7	12.4	3.3	10.4
Hypotension ††	2.0	18.6	1.7	14.8
Hyperkalemia †††	1.1	36.9	0.3	27.1

†renal failure, renal failure acute, renal failure chronic, renal impairment

††dizziness, dizziness postural, hypotension, orthostatic hypotension, presyncope, syncope

††† Given the variable baseline potassium levels of patients with renal insufficiency on dual RAAS therapy, the reporting of adverse event of hyperkalemia was at the discretion of the investigator.

* A Serious Adverse Event (SAE) is defined as: an event which is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, requires inpatient hospitalization or prolongation of existing hospitalization, or is medically significant (i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes previously listed).

The risk of stroke (2.7% aliskiren vs 2.0% placebo) and death (6.9% aliskiren vs. 6.4% placebo) were also numerically higher in aliskiren treated patients.

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 6: Tekturna HCT Tablets Supply

Tablet	Color	Imprint		NDC 0078-XXXX-XX		
		Side 1	Side 2	Bottle of 30	Bottle of 90	Blister Packages of 100
Aliskiren/HCTZ						
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 original container.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient 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 Tekturna HCT during pregnancy. Discuss treatment options with women planning to become pregnant. 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.

Anaphylactic Reactions and Angioedema

Patients should be advised and told to report immediately any signs or symptoms suggesting a severe allergic reaction (difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain) or 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. Angioedema, including laryngeal edema, may occur at any time during treatment with Tekturna HCT.

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.

T2013-XX
October 2013

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.

What is the most important information I should know about Tekturna HCT?

Tekturna HCT can cause harm or death to an unborn baby. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant. If you get pregnant while taking Tekturna HCT, tell your doctor right away.

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)

Aliskiren (Tekturna) reduces the effect of renin, and the harmful process that narrows blood vessels. Aliskiren also helps blood vessels relax and widen so blood pressure is lower. Hydrochlorothiazide reduces the amount of salt and water in your body so your blood pressure is lower.

Tekturna HCT may be used to lower high blood pressure in adults

- when one medicine to lower high blood pressure is not enough
- as the first medicine to lower high blood pressure if your doctor decides that you are likely to need more than one medicine

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.

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. 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.

Tekturna HCT reduces high blood pressure. Medicines that lower your blood pressure lower your chance of having a stroke or heart attack. 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.

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.**

- **If you have diabetes and are taking a kind of medicine called an angiotensin-receptor-blocker or angiotensin-converting-enzyme-inhibitor.**
- **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 kidney problems
- are pregnant or planning to become pregnant. See “What is the most important information I should know about Tekturna HCT?”
- have any allergies or asthma
- 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 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:

- a kind of medicine called angiotensin receptor blocker or angiotensin converting enzyme inhibitor
- atorvastatin (medicine to lower cholesterol in your blood)
- 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)
- 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 every day, 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 “What is the most important information I should know about Tekturna HCT?”
- **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.
- **Severe Allergic Reactions and Angioedema.** Aliskiren, one of the medicines in Tekturna HCT, can cause difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain (signs of a severe allergic reaction). Aliskiren can also cause swelling of the face, lips, tongue, throat, arms and legs, or the whole body (signs of angioedema). 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.
- **Renal impairment or failure.** Aliskiren, one of the medicines in Tekturna HCT, may cause renal disorder with symptoms such as severely decreased urine output or decreased urine output (signs of renal impairment or failure).
- **Active or worsened Systemic Lupus Erythematosus (SLE).** If you have SLE, tell your doctor right away if you get any new or worse symptoms.
- **Eye problems.** One of the medicines in Tekturna HCT can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting Tekturna HCT. Tell your doctor right away if you have:
 - Decrease in vision
 - Eye pain

Common side effects of Tekturna HCT include:

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

- high levels of potassium in the blood (hyperkalemia)

Less common side effects include skin rash, severe skin reactions (signs may include severe blistering of the lips, eyes or mouth, rash with fever and skin peeling) and liver disorder (signs may include nausea, loss of appetite, dark colored urine or yellowing of skin and eyes).

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 1-888-669-6682.

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, 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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