# Tekturna HCT<sup>®</sup>

(aliskiren and hydrochlorothiazide)

# 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.

nitial U.S. Approval: 2008

## WARNING: AVOID USE IN PREGNANCY

See full prescribing information for complete boxed warning. When pregnancy is detected, discontinue Tekturna HCT as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. (5.1)

----- INDICATIONS AND USAGE -Tekturna HCT is a combination of aliskiren, a direct renin inhibitor, and hydrochlorothiazide (HCTZ). a thiazide diuretic, indicated for the treatment of hypertension, (1) Limitation of use: This fixed dose combination is not indicated for initial therapy. (1)

----- DOSAGE AND ADMINISTRATION -

- Order of increasing mean effect: 150/12.5 mg, 150/25 mg or 300/12.5 mg, and 300/25 mg (2.1)
- If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, titrate up to a max 300/25. (2.2) May be administered with other antihypertensive agents: additive effects with maximal doses o
- ACE inhibitors and beta blockers have not been demonstrated. (2.3) ----- DOSAGE FORMS AND STRENGTHS --

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

---- CONTRAINDICATIONS Anuria (4)

Hypersensitivity to sulfonamide-derived drugs (4)

# -WARNINGS AND PRECAUTIONS

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

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

dizziness and diarrhea. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or <u>www.fda.gov/medwatch</u>

----- DRUG INTERACTION

## Aliskiren:

Cyclosporine: Concomitant use is not recommended.

- ydrochlorothiazide: Alcohol, Barbiturates, Narcotics: Potentiation of orthostatic hypotension
- Antidiabetic Drugs: Dosage adjustment of antidiabetic may be required Cholestyramine and Colestipol: Reduced absorption of thiazides
- Corticosteroids, ACTH: Hypokalemia, electrolyte depletion Lithium: Reduced renal clearance and high risk of lithium toxicity when used with diuretics. Should not be given with diuretics.
- NSAIDs: Can reduce diuretic, natriuretic, and antihypertensive effects of diuretics. Observe

- USE IN SPECIFIC POPULATIONS Nursing Mothers: Adverse reactions may occur in nursing infants. (8.3)

## See 17 for PATIENT COUNSELING INFORMATION and FDA-approved pat t labeling. Revised: 1/2008

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## FULL PRESCRIBING INFORMATION

## WARNING: AVOID USE IN PREGNANCY

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

## INDICATIONS AND USAGE

Tekturna HCT is indicated for the treatment of hypertension

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

## 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.

<u>Replacement Therapy</u> Tekturna HCT may be substituted for the titrated components.

### Limitation of Use This fixed dose combination is not indicated for initial therapy.

DOSAGE AND ADMINISTRATION

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

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

## 2.2 Dose Titration

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

## 2.3 Use with Other Antihypertensive Drugs

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

### 2.4 Relationship to Meals

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

### 2.5 Dosing in Specific Populations

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

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

Because of the hydrochlorothiazide component. Tekturna HCT is contraindicated in patients with

Adverse Reactions (6.1). Hypersensitivity reactions may range from urticaria to anaphylaxis [see

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. If this drug is used during pregnancy, or if the patient

fetus. [See Use in Specific Populations (8.1)] In several dozen published cases, ACE inhibitor use

during the second and third trimesters of pregnancy was associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. In addition, first trimester use of ACE inhibitors has been associated with birth defects in

retrospective data. Thiazides cross the placenta, and use of thiazides during pregnancy is associated

with a risk of fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that

Angioedema of the face, extremities, lips, tongue, glottis and/or larvnx has been reported in patients

reated with a liskiren. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients, but whether angioedema rates are higher in Blacks with aliskiren is not known. Tekturna HCT should be promptly

liscontinued and appropriate therapy and monitoring provided until complete and sustained resolutior

Experience with ACE inhibitors indicates that even in those instances where only swelling of the

involvement. Very rarely, fatalities have been reported in patients with angioedema associated with

or larynx are more likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, appropriate therapy, e.g.,

subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and measures necessary to ensure a

An excessive fall in blood pressure (hypotension) was rarely seen (<1%) in patients with uncomplicated hypertension treated with Tekturna HCT in controlled trials. In patients with an

In patients with severe renal impairment (GFR <30 mL/min), loop diuretics are preferred to

des should be used with caution in severe renal disease. In patients with renal disease

rochlorothiazide zide diuretics should be used with caution in patients with impaired hepatic function or progressive

thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with

liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

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.

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

n the short-term controlled trials of various doses of Tekturna HCT the incidence of hypertensive

patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 2.2%; the incidence of

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

activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high

doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to

ation of Tekturna HCT, or the treatment should start under close medical superv

If an excessive fall in blood pressure occurs, the patient should be placed in the supine position and,

if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the

arvingeal edema or tongue edema with ACE inhibitors. Patients with involvement of the tongue, glottis

tongue is seen initially, without respiratory distress, patients may require prolonged observatic treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory

ecomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the

sible renal failure, and

## Hepatic Impairment

Adjustment of the starting dose is not necessary with hepatic impairment. stment of the starting dose is not required for elderly patients.

## Elderly Patients

CONTRAINDICATIONS

Adverse Reactions (6.1)].

have occurred in adults.

Aliskiren

5.2 Head and Neck Angioedema

of signs and symptoms has occurred

patent airway, should be promptly provided.

5.4 Patients with Severe Renal Impairment

5.5 Patients with Hepatic Impairment

5.7 Systemic Lupus Erythematosus

5.9 Serum Electrolyte Abnormalities

5.6 Hypersensitivity Reactions

thiazides, so Tekturna HCT is not recommended.

blood pressure has stabilized

<u>ekturna HCT</u>

Hydrochlorothiazide

impaired renal function

Hvdrochlorothiazide

5.8 Lithium Interaction

Hydrochlorothiazide

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

DOSAGE FORMS AND STRENGTHS

WARNINGS AND PRECAUTIONS Fetal/Neonatal Morbidity and Mortality

P-glycoprotein Effects: 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. Coadministration of aliskiren with Pop substrates or weak to moderate inhibitors such as atenolol, digoxin, and amlodipine did not result in clinically relevant interactions.

Atorvastatin: Coadministration of atorvastatin resulted in about a 50% increase in aliskiren Cmax and AUC after multiple dosing.

*ole:* Coadministration of 200 mg twice-daily ketoconazole, a potent Pgp inhibitor, wit aliskiren resulted in an approximate 80% increase in plasma levels of aliskiren. A 400-mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further. ne: Coadministration of 200 mg and 600 mg cyclosporine, a highly potent Pgp inhibitor.

with 75 mg alliskiren resulted in an approximately 2.5-fold increase in  $C_{max}$  and 5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with cyclosporine is not recommended. Drugs with no clinically significant effects: Coadministration of lovastatin, atenolol, warfarin

nide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.

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

ices that affect the

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

(RAS), conconitant use of Tektura HCT with potassium-sparing diuretics, potassium supplem salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium. If concomitant use is considered necessary, caution should be

No data are available on the use of Tekturna HCT in patients with unilateral or bilateral renal artery

Aliskiren When aliskiren was given with cyclosporine, the blood concentrations of aliskiren were significantly

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

na HCT has been evaluated for safety in more than 2 700 patients including over 700 treated

Head and neck angioedema [see Warnings and Precautions (5.2)] Hypotension in volume- and/or salt-depleted patients [see Warnings and Precautions (5.3)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates

observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of

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

Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with

Aliskiteri has been evaluated for safety in 6,450 patients, including 1,740 readed for longer than 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

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 with answine use in the clinic 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

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with

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

Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by

subgroups at 150 mg comparable to those seen at 300 mg for men or vounger 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

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskine was associated with a signification outgoin the placeborcontined studied strained any aliskine 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

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1%

vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients

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

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

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in

ive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric

Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia;

Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing anglitis (vasculitis and cutaneous

sculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic

Renal: renal failure, renal dysfunction, interstitial nephritis; Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including

In controlled clinical transformation of Tekturna HCT.

ine occurred in 11.8% and 0.9%, respectively, of patients taking Tekturna HCT, and 7% and

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

Serum Uric Acid: Uric acid related abnormalities were more commonly observed in patients treated

with Tekturna HCT, compared with placebo; 2.2% versus 0% had a uric acid increase >50% from baseline; gout and renal stones were less commonly observed.

No drug interaction studies have been conducted with Tekturna HCT and other drugs, although

Irbesartan: Coadministration of irbesartan reduced aliskiren Cmay up to 50% after multiple dosing.

studies with the individual aliskiren and hydrochlorothiazide components are described below

1.2% of patients treated with Tekturna HCT, compared with 0% in placebo-treated patients. No

Blood Urea Nitrogen (BUN)/Creatinine: Elevations (greater than 50% increase) in BUN and

1.1%, respectively, of patients given placebo in short-term controlled clinical trials. No patients during respectively, of patients given placebo in short-term controlled clinical trials. No patients during the statement of th

Hemoglobin and Hematocrit: A greater than 20% decrease in hemoglobin and hematocrit wer

Other adverse reactions that have been reported with hydrochlorothiazide, without regard to

Allshifts produces user-related gasholines intar (ci) adverse reactions. Dialmea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age  $\geq$ 65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these

(2.3% vs. 1.6%), diarrhea (1.6% vs. 0.5%), cough (1.3% vs. 0.5%), vertigo (1.2% vs. 0.5%), asthenia

n has been evaluated for safety in 6.460 patients, including 1,740 treated for longer than 6

increased. Concomitant use of aliskiren with cyclosporine is not recommended [see Drug

Risk of fetal/neonatal morbidity and mortality [see Warnings and Precautions (5.1)]

crease of serum potas

5.10 Renal Artery Stenosis

ADVERSE REACTIONS

5.11 Cyclosporine

Interactions (7)].

Tekturna HCT

Aliskiren

stenosis or stenosis of the artery to a solitary kidney

another drug and may not reflect the rates observed in practice.

treated with Tekturna HCT versus 3.6% of patients given placebo.

patients treated with aliskiren, versus 3.5% of patients given placebo.

(1.2% vs. 0%), and arthralgia (1% vs. 0.5%).

aliskiren use, including 4 leading to discontinuation

whole body was 0.4% in both treatment arms.

completed studies was 0.06%.

in the ACE inhibitor arms.

challenge in either cas

patients treated with aliskir

causality, are listed below

Body As A Whole: weakness

Musculoskeletal: muscle spasma

toxic epidermal necrolvsis:

Metabolic: hyperglycemia, glycosuria, hyperuricemia

Special Senses: transient blurred vision, xanthopsia

patients were discontinued due to abnormal liver function tests.

<u>Effects of Other Drugs on Aliskiren</u> Based on in vitro studies, aliskiren is metabolized by CYP 3A4.

Serum Electrolytes: See Warnings and Precautions (5.8)

**DRUG INTERACTIONS** 

Aliskiren

6.2 Clinical Laboratory Test Abnormalities

Nervous System/Psychiatric: restlessness

Hydrochlorothiazide

infection, back pain and cough.

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

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

Drugs with no clinically significant effects: Coadministration of aliskiren did not significantly affect the kinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celed atorvastatin, ramipril or hydrochlorothiazide. Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Hydrochlorothiazide

When administered concurrently, the following drugs may interact with thiazide diuretics. Alcohol barbiturates or parcotics: Potentiation of orthostatic Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be

Other antihypertensive drugs: Additive effect or potentiation Abolestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia. Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine); Possible increased responsiveness to the muscle relaxants.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of Limium: Should not generally be given with duretics. Duretic agents reduce the rehat clearance of lithium and increase the risk of lithium toxicity. Refer to the package insert for lithium before use of such preparation with Tekturna HCT.

Nonsteroidal anti-inflammatory drugs: In some patients, the administration of a nonsteroidal antiinflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, 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.

USE IN SPECIFIC POPULATIONS

required.

espectively.

**8.1 Pregnancy** Pregnancy Category D [*See Warnings and Precautions (5.1*)]

Tekturna HCT contains both aliskiren (a direct renin inhibitor) and hydrochlorothiazide (a thiazide diuretic). When administered during the second or third trimester of pregnancy, drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death

Thiazides can cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults. Tekturna HCT can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skul hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also eported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung developme Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin system has been associated with a potential risk of birth defects in retrospective data

When pregnancy occurs in a patient using Tekturna HCT, the physician should discontinue Tekturna HCT treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to Tekturna HCT (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done

In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient rail ultrasos when another analyze tensive agent cannot be used to theat the pregnant patient, rail ultrasound examinations should be performed to assess the intraamniotic environment. butine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnio occurs in these situations individualized decisions about continuing or discontinuing Tekturna HCT treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with istories of in utero exposure to Tekturna HCT should be closely observed for hypotension, oliguria. and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

No reproductive toxicity studies have been conducted with the combination of aliskiren and hydrochlorothiazide. However, these studies have been conducted for aliskiren as well as ydrochlorothiazide alone.

Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicit at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose [MRHD] of 300 mg/day on a mg/m<sup>2</sup> basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m<sup>2</sup> basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m<sup>2</sup> 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.

## 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.

# 8.5 Geriatric Use

n the short-term controlled clinical trials of Tekturna HCT, 325 (19.6%) patients treated with Tekturna HCT were  $\geq$ 65 years and 53 (3.2%) were  $\geq$ 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.

# 10 OVERDOSAGE

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

# Hvdrochlorothiazide

Aliskirer

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hypopnatremia) and dehydration resulting fror 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  $\rm LD_{50}$  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, potent direct renir hiazide, a thiazide diure

Hydrochlorothiazide is a thiazide diuretic. Its empirical formula is  $C_7H_8CIN_3O_4S_2$ , its molecular weight is 297.73, and its structural formula is

Tekturna HCT tablets are form tablets are formulated for oral administration to contain aliskiren and azide, 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, hydroxyprop

**Tekturna HCT®** aliskiren and hydrochloro

> aliskiren and nyuroom Tekturna HCT<sup>®</sup>

**Tekturna HCT®** (aliskiren and hydrochlorothiazide HCT® na Ina

hemifumarate is chemically described as (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-Aliskiren nermiumatate is chemicany described as [26,-2,55, 5, 1] amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate and its structural formula is

Molecular formula: C<sub>30</sub>H<sub>53</sub>N<sub>3</sub>O<sub>6</sub> • 0.5 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

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. Hvdrochlorothiazide

Aydrochlorothiazide USP is a white, or practically white, practically odorless, crystalline powder. It is sightly 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*-1,2,4benzothiadiazine-7-sulfonamide 1 1-dioxide

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 1 Mechanism of Action

<u>Aliskiren</u>

Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion Renin is secreted by the kontey in response to decreases in blood volume and renal perusion. 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 aliskirer 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. And I and And II are Il reduced, whether aliskiren is used as monotherapy or in comb

### 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 consequer 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 ated with these diuretics The mechanism of action of the antihypertensive effect of thiazides is unknown

12.2 Pharmacodynamics

## Tekturna HCT

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

# Metabolism and Elimination

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

### Hvdrochlorothiazid

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

Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic (rasH2) mouse Carcinogenic potential was assessed in a 2-year rat sludy and a ornionin manyemic (cash 2) mou-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 identification is not not a colonic adenome identification protection and the other of the other of identified in one rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure (AUC<sub>0.24hr</sub>) basis, 1500 mg/kg/day in the rat is about 4 times and in the mouse about 1.5 times the maximum recommended human dose (300 mg aliskiren/day). Mucosal hyperplasia in the cecum or colon of rats was also observed at doses of 250 mg/kg/day (the lowest tested dose) as well as at higher doses in 4- and 13-week studies.

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

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

o-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

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

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies Hydrochioroninazide had no adverse enects on the lenting of mice and rats of entire sex in studies wherein these species were exposed, via their diet, to doeso fur pto 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. These doeso of hydrochlorothiazide in mice and rats protocol many and the unsequence of the maximum recommended human does on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

## 14 CLINICAL STUDIES Tekturna HCT

In all clinical trials including over 6,200 patients, more than 2,700 patients were exposed to combinations of aliskiren and hydrochlorothiazide. The safety and efficiacy 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 re 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 nation with Hvdrochlorothiazid

		Hydrochlorothiazide, mg				
	Placebo	0	6.25	12.5	25	
Aliskiren,	Mean	Placebo-	Placebo-	Placebo-	Placebo-	
mg	Change	subtracted	subtracted	subtracted	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 hyperte 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

The antihypertensive effect was independent of age and gender. There were too few non-Caucasians

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

# Table 2: Reductions in Seated Trough Cuff Blood Pressure in the Placebo-Controlled Studies

		Aliskiren Dally Dose, mg				
	Placebo	75	150	300	600	
	Mean	Placebo-	Placebo-	Placebo-	Placebo-	
Study	Change	subtracted	subtracted	subtracted	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. <sup>†</sup>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 monitorin 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

Aliskiren 150 mg and 300 mg and valsartan 160 mg and 320 mg were studied alone and in Auskiel 150 mg and 300 mg and valsarian 100 mg and 320 mg were studied and a final and a 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

			vaisariari, riig			
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.

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

<u>Aliskiren</u> 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 ation time are within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide. When taker with food, mean AUC and Cmay 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

Geriatric Patients

The pharmacokinetics of aliskiren were studied in the elderly (>65 years). Exposure (measured b AUC) is increased in elderly patients. Adjustment of the starting dose is not required in these patients [see Dosage and Administration (2)].

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 impairmer Rate and extent of exposure (AUC and C<sub>max</sub>) 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 Dosage and Administration (2)].

## NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

turna HC1

icity, mutagenicity or fertility studies have been conducted with Tekturna HCT. ever, these studies have been conducted for aliskiren as well as hydrochlorothi

rochlorothiazide was maintained for over 1 year

to assess differences in blood pressure effects by race.

		Aliskiren Daily Dose, mg						
	Placebo	75	150	300	600			
	Mean	Placebo-	Placebo-	Placebo-	Placebo-			
Study	Change	subtracted	subtracted	subtracted	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*			

- · 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.

Storage

Pregnancy

# Potassium Supplements Relationship to Meals

## ACE inhibitors and Amlodipine

Aliskiren has not been studied when added to maximal doses of ACE inhibitors to determine whether Aliskiren 150 mg provided additional blood pressure reduction with a maximal doses of ACE limitotion of bettermine whether 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

## Table 4: Tekturna HCT Tablets Supply

Tablet	Color	Imprint	Imprint	NDC 0078- XXXX-XX		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

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

Protect from moistur

## Dispense in tight container (USP) PATIENT COUNSELING INFORMATION

## 17.1 Important Information

are professionals should instruct their patients to read the Patient Package Insert before Institution of the starting Technical Protocol and the patients to read the reader and and protocol starting Technical 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.

le patients of childbearing age should be told about the consequences of exposure to drugs remain patients of childbearing age should be found about the consequences of exposure to that act on the renin-angiotensin system. Discuss other treatment options with female patient 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 An patients should be callioned that intradequate huid intrate, excessive perspiration, dat vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

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

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<sup>®</sup> (tek-turn-a HCT) (aliskiren and hydrochlorothiazide, USP) ombination 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 iniury 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?

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 vo

- 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 guestions 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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