CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-838

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

DESCRIPTION
ATACAND® (candesartan cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT1 subtype angiotensin II receptor antagonist.

Candesartan cilexetil, a nonpeptide, is chemically described as (S)-1-(4-(6-chloro-7-methyl-1H-benzimidazol-2-yl)phenyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl(methyl)-1H-tetrazol-5-yl-carboxylate.

Its empirical formula is C36H28N6O6 and its structural formula is:

\[
\begin{align*}
\text{CHClH}_2\text{HN} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{H} & \quad \text{CH}_3 \\
\text{H} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*}
\]

Site of ester hydrolysis.

Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemate composed of one optical center at the cyclohexylcarboxyloxyethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral.

ATACAND is available for oral use as tablets containing either 4 mg, 8 mg, 16 mg or 32 mg of candesartan cilexetil and the following inactive ingredients: hydroxypropyl cellulose, polyethylene glycol, lactose, corn starch, carboxymethylcellulose sodium, calcium, and magnesium stearate. Ferric oxide (reddish brown) is added to the 8 mg, 16 mg, and 32 mg tablets as a colorant.

CLINICAL PHARMACOLOGY
Mechanism of Action
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction. Stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT2 receptor found in many tissues, but AT1 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (\(\geq 10,000\)-fold) for the AT1 receptor than for the AT2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockage of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.

Pharmacokinetics
General
Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis from the gastrointestinal tract to candesartan, a selective AT1 subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once daily dosing.

Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (Cmax) is reached after 3-4 hours. Food with a high-fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Metabolism and Excretion
Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of 4 mg labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 20% in feces. Following an intravenous dose of 4 mg labeled candesartan approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

Distribution
The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, if at all. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Special Populations
Pediatric: The pharmacokinetics of candesartan cilexetil have not been investigated in patients <18 years of age.

Geriatric: The pharmacokinetics of candesartan have been studied in the elderly (\(\geq 65\) years), and in both sexes. The plasma concentration of candesartan was higher in the elderly (\(\geq 65\) years) compared to younger subjects. The pharmacokinetics of candesartan were similar in elderly and in the elderly, and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once daily administration. No initial dosage adjustment is necessary. (See DOSAGE AND ADMINISTRATION.) There is no difference in the pharmacokinetics of candesartan between male and female subjects.

Renal Insufficiency: In hypertensive patients with renal insufficiency, serum concentrations of candesartan were increased. After repeated dosing, the AUC and Cmax were approximately doubled in patients with severe renal impairment (creatinine clearance \(< 20\) mL/min/1.73 m²) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency: No differences in the pharmacokinetics of candesartan were observed in patients with mild to moderate chronic liver disease. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic insufficiency. No initial dosage adjustment is necessary in patients with mild hepatic disease. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: (See PRECAUTIONS, Drug Interactions.)

Pharmacodynamics
Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After one week of once daily dosing of 8 mg candesartan cilexetil the pressor effect was inhibited by approximately 90% at peak, with approximately 30% inhibition at 24 hours.
aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attempts should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of ATACAND in pregnant women. Oral doses ≥ 10 mg candesartan and 15 mg hydrochlorothiazide administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydropneumonia in the offspring. The 10 mg/kg/day dose in rats is approximately 2.8 times the maximum recommended daily human dose (MRHD) of 32 mg on a mg/m² basis (comparison assumes human body weight of 50 kg). Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day (approximately 1.7 times the MRHD on a mg/m² basis) caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight or on external, visceral or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg candesartan cilexetil/kg/day (approximately 138 times the MRHD on a mg/m² basis) were administered to pregnant mice.

Hypotension in Volume- and Salt-Depleted Patients
In patients with an activated renin angiotensin system, such as volume- and salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND, or the treatment should be started under close medical supervision (see DOSAGE AND ADMINISTRATION).

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

PRECAUTIONS

General
Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with ATACAND. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotension receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with ATACAND. (See CLINICAL PHARMACOLOGY, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine and/ or blood urea nitrogen (BUN) have been reported. Therefore, no long-term use of ATACAND in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Formation for Patients

Pregnancy: Female patients of childbearing age should be informed of the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system, that they should be told that these consequences do not necessarily occur to have resulted from intrauterine drug exposure that was limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions
No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyci
de, nifedipine, digoxin, warfarin, hydrochlorothiazide and Plaxine/ Cardioprotect in healthy volunteers. Because candesartan is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

Genetics, Mutagenesis, Impairment of Fertility
There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 3500 and 1000 mg/kg/day respectfully. Rats received the drug by gavage whereas mice received the drug by dietary administration. These maximally tolerated doses of candesartan cilexetil resulted in systemic exposures to candesartan (AUCs) that were, respectively, approximately 7 times and in rats, more than 70 times the exposure in man at the maximum recommended human dose (32 mg).

candesartan cilexetil was not genotoxic in the microbial agasosis and mammalian cell mutagenesis assays with and without metabolic activation in vivo and in vitro and in vivo chromosomal aberration and rat unscheduled DNA synthesis assays. In addition, candesartan was not genotoxic in a microbial mutagenesis, mammalian cell mutagenesis in vitro and in vivo chromosomal aberration assays.

Efficacy and reproductive performance were not affected in studies with male and female rats treated oral doses of up to 300 mg/kg/day (83-times the maximum daily human dose of 32 mg on a body surface area basis).

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

Nursing Mothers
It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Of the total number of subjects in clinical studies of ATACAND, 21% were 65 and over, while 3% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. In a placebo-controlled trial of about 200 elderly hypertensive patients (ages 65 to 87 years), administration of candesartan cilexetil was well tolerated and lowered blood pressure by about 12/6 mmHg among more than placebo.

ADVERSE REACTIONS
ATACAND has been evaluated for safety in more than 3600 patients/subjects including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least six months and about 200 patients for at least one year. In general, treatment with ATACAND was well tolerated. The overall incidence of adverse events reported with ATACAND was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7/10 total) was 5.1% of i.e., /3 patients in 76.8/2 patients treated with candesartan cilexetil at 4 to 12 mg/day and 3.5% of i.e., 196 of 5110 patients treated with placebo. In placebo controlled trials, discontinuation of therapy due to clinical adverse events occurred in 4.4% of i.e., 57 of 350 patients treated with ATACAND and 3.4% of i.e., 35 of 1027 patients treated with placebo.

The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%).

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in patients treated with candesartan cilexetil (n=2350) than placebo (n=1027) patients included back pain (3% vs. 2%), dizziness (4% vs. 3%), upper respiratory tract infection (6% vs. 4%), pharyngitis (2% vs. 1%), and rhinitis (2% vs. 1%).

The following adverse experiences occurred in placebo-controlled clinical trials at a more than 1% rate, but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment with an incidence of 0.5% or greater from the more than 3200 patients worldwide treated with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. Body as a Whole: asthenia; Central and Peripheral Nervous System: parasthesia, vertigo; Gastrointestinal System Disorder: dyspepsia, gastroenteritis; Heart Rate and Rhythm Disorders: tachycardia, palpitation; Metabolic and Nutritional Disorders: creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; Musculoskeletal System Disorders: myalgia; Platelet/ Bleeding Clotting Disorders: epistaxis; Psychiatric Disorders: anxiety, depression, somnolence; Respiratory System Disorders: dyspnea; Skin and Appendages Disorders: rash, sweating increased; Urinary System Disorders: hematuria.

Other reported events seen less frequently included anemia, purpura, necrolytic acanthosis, and non-black patients.

Laboratory Test Findings
In controlled clinical trials, clinically important changes in standard laboratory tests were rarely associated with the administration of ATACAND.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

Hyperuricemia: Hyperuricemia was rarely found (19 or 0.6% of 3260 patients treated with candesartan cilexetil and 5 or 0.5% of 1106 patients treated with placebo).

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 gram/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone, but were part of the usual anemia. Blood chemistry and other
Clinical Trials

The antihypertensive effects of ATACAND were examined in 4 placebo-controlled trials of 6 to 12 weeks duration, primarily at daily doses of 1 to 3 mg per day in patients with baseline diastolic blood pressures of 95-114 mmHg. Most of the trials were of candesartan cilexetil as a single agent but it was also studied as add-on to hydrochlorothiazide and amloptine. These studies included a total of 1450 patients randomized to one of several doses of candesartan cilexetil and 527 to placebo. Except for a study in diabetics, all studies showed significant effects, generally dose related, of 0.3-4 mg per day (24 hour) systolic and diastolic pressures compared to placebo, with doses of 0.3-3 mg giving effects of about 8-12/1-3 mmHg. There were no exaggerated first dose effects in these patients. Most of the antihypertensive effect was seen within two weeks of initial dosing, and the full effect in four weeks. With once daily dosing, blood pressure effect was maintained 24 hours, with trough to peak ratios of blood pressure effect generally over 80%. Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The antihypertensive effect was similar in men and women and in patients older and younger than 65. Candesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). This has been generally true for angiotensin II antagonists and ACE inhibitors.

In long-term studies of up to one year, the antihypertensive effectiveness of candesartan cilexetil was maintained and there was no rebound after abrupt withdrawal.

There were no changes in the heart rate of patients treated with candesartan cilexetil in controlled trials.

INDICATIONS AND USAGE

ATACAND is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

ATACAND is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

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

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformations, hypoplastic lung development, prematurity, intracerebral growth retardation, and patent ductus arteriosus. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ATACAND as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their amniotic fluid and fetal development, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, ATACAND should be discontinued unless it is considered life-saving for the mother. Contractions stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be
Bocytopenia were associated with withdrawal of one patient each from clinical trials.

Potassium: A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with ATACAND alone, but was rarely of clinical importance. One patient from a congestive heart failure trial was withdrawn for hyperkalemia (serum potassium = 7.5 mEq/L). This patient was also receiving spironolactone.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to candesartan cilexetil in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin but one of these patients was diagnosed with Hepatitis A.

OVERDOSAGE

No lethality was observed in acute toxicity studies in mice, rats and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil. In mice given single oral doses of the primary metabolite, candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

Limited data are available in regard to overdosage in humans. In one recorded case of an intentional overdose, a 43 year old female patient (Body Mass Index of 31 kg/m²) ingested an estimated 180 mg of candesartan cilexetil, in combination with multiple other pharmaceutical agents (ibuprofen, naproxen sodium, diphenhydramine hydrochloride and ketoprofen). Gastric lavage was performed, the patient was monitored in hospital for several days and was discharged without sequelae.

Candesartan cannot be removed by hemodialysis.

Treatment: To obtain up-to-date information about the treatment of overdose, consult your Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

The most likely manifestation of overdosage with ATACAND would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

DOSE AND ADMINISTRATION

Dosage must be individualized. Blood pressure response is dose-related over the range of 2-32 mg. The usual recommended starting dose of ATACAND is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. ATACAND can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Larger doses do not appear to have a greater effect and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks and maximal blood pressure reduction is generally obtained within four to six weeks of ATACAND treatment.

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), ATACAND should be initiated under close medical supervision and consideration should be given to administration of a lower dose (see WARNINGS, Hypotension in Volume- and Salt-Depleted Patients).

ATACAND may be administered with or without food. If blood pressure is not controlled by ATACAND alone, a diuretic may be added. ATACAND may be administered with other antihypertensive agents.

HOW SUPPLIED

No. 3782 — Tablets ATACAND, 4 mg, are white to off-white, circular/biconvex shaped, non film-coated tablets, coded ACF on one side and 004 on the other. They are supplied as follows:

NDC 51113-004-31 unit of use bottles of 30
NDC 51113-004-54 unit of use bottles of 90
NDC 51113-004-28 unit dose packages of 100
NDC 51113-004-82 bottles of 1000.

No. 3780 — Tablets ATACAND, 8 mg, are light pink, circular/biconvex shaped, non film-coated tablets, coded ACG on one side and 008 on the other. They are supplied as follows:

NDC 51113-008-31 unit of use bottles of 30
NDC 51113-008-54 unit of use bottles of 90
NDC 51113-008-28 unit dose packages of 100
NDC 51113-008-82 bottles of 1000.

No. 3781 — Tablets ATACAND, 16 mg, are pink, circular/biconvex shaped, non film-coated tablets, coded ACH on one side and 016 on the other. They are supplied as follows:

NDC 51113-016-31 unit of use bottles of 30
NDC 51113-016-54 unit of use bottles of 90
NDC 51113-016-28 unit dose packages of 100
NDC 51113-016-82 bottles of 1000.

No. 3791 — Tablets ATACAND, 32 mg, are pink, circular/biconvex shaped, non film-coated tablets, coded ACL on one side and 032 on the other. They are supplied as follows:

NDC 51113-032-31 unit of use bottles of 30
NDC 51113-032-54 unit of use bottles of 90
NDC 51113-032-28 unit dose packages of 100
NDC 51113-032-82 bottles of 1000.