

The hospital now moves 90% of ST-segment elevation MI patients needing PCI to treatment in less than 90 minutes, an increase of 47% since the new procedures were put in place, Dr. Luis Haro explained.



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Quality Initiatives Shorten Mayo's Door-to-Balloon Time

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Contributing Writer

WASHINGTON — Implementing a quality improvement initiative for ST-segment elevation MI shortened the time to treatment with primary percutaneous intervention from 104 minutes to 75 minutes in less than 7 months, reported Luis Haro, M.D.

In addition, the percentage of patients with a time to PCI (called door-to-balloon time [DTBT]) of less than 90 minutes increased from 42% to 82% during the study period of May 17–December 31, 2004. Since then, that percentage has gone up to 90%, and DTBT has decreased to 72 minutes, Dr. Haro, of the department of emergency medicine at the Mayo Clinic, Rochester, Minn., told CARDIOLOGY NEWS.

Atacand® candesartan cilexetil

TABLETS

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.

BRIEF SUMMARY

Before prescribing, please see full Prescribing Information for ATACAND (candesartan cilexetil).

INDICATIONS AND USAGE

Hypertension

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

Heart Failure

ATACAND is indicated for the treatment of heart failure (NYHA class II-IV) in patients with left ventricular systolic dysfunction (ejection fraction $\leq 40\%$) to reduce cardiovascular death and to reduce heart failure hospitalizations. (See Clinical Trials.) ATACAND also has an added effect on these outcomes when used with an ACE inhibitor.

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. Post-marketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with ATACAND during pregnancy. 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 deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

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 fetuses, 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. Contraction 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 aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

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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, attention 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.

Oral doses ≥ 10 mg of candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis 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 external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg of 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/or salt-depleted patients (eg, those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patients 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.

Hypotension in Heart Failure Patients

Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given ATACAND commonly have some reduction in blood pressure. In patients with symptomatic hypotension this may require temporarily reducing the dose of ATACAND, or diuretic, or both, and volume repletion. In the CHARM program, hypotension was reported in 18.8% of patients on candesartan versus 9.8% of patients on placebo. The incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.1% compared with 2.0% in placebo-treated patients. Monitoring of blood pressure is recommended during dose escalation and periodically thereafter.

PRECAUTIONS

General

Impaired Hepatic Function—Based on pharmacokinetic data which demonstrate significant increases in candesartan AUC and C_{max} in patients with moderate hepatic impairment, a lower initiating dose should be considered for patients with moderate hepatic impairment. (See DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY, Special Populations.)

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 (eg, patients with severe heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin 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 or blood urea nitrogen (BUN) have been reported. There has been no long-term use of ATACAND in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

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In heart failure patients treated with ATACAND, increases in serum creatinine may occur. Dosage reduction or discontinuation of the diuretic or ATACAND, and volume repletion may be required. In the CHARM program, the incidence of abnormal renal function (e.g., creatinine increase) was 12.5% in patients treated with candesartan versus 6.3% in patients treated with placebo. The incidence of abnormal renal function (eg, creatinine increase) leading to drug discontinuation in candesartan-treated patients was 6.3% compared with 2.9% in placebo-treated patients. Evaluation of patients with heart failure should always include assessment of renal function and volume status. Monitoring of serum creatinine is recommended during dose escalation and periodically thereafter.

Hyperkalemia

In heart failure patients treated with ATACAND, hyperkalemia may occur, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone. In the CHARM program, the incidence of hyperkalemia was 6.3% in patients treated with candesartan versus 2.1% in patients treated with placebo. The incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.4% compared with 0.6% in placebo-treated patients. During treatment with ATACAND in patients with heart failure, monitoring of serum potassium is recommended during dose escalation and periodically thereafter.

Information for Patients

Pregnancy—Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been 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 glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers, or given with enalapril to patients with heart failure (NYHA class II and III). Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

Lithium—Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with ATACAND, so careful monitoring of serum lithium levels is recommended during concomitant use.

Carcinogenesis, 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 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage, whereas mice received the drug by dietary administration. These (maximally-tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

Candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell and rat hepatocyte unscheduled DNA synthesis assays and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assay.

Dr. Haro and colleagues implemented a quality initiative after a chart review of data from July 2002 to September 2003 showed that the hospital's DTBT was 200 minutes, he said at a meeting sponsored by the American Heart Association.

The initiative involved new processes to streamline communication between providers in the emergency department (ED), the catheterization lab, and the quality department.

"It was very hard to figure out where to find the data, since there are five or six areas to look for information, such as the ED chart and the cath lab report," said Dr. Haro, quality chair of emergency medi-

cine. A group from quality, communications, cardiology, nursing, and the ED met biweekly for 3 months before implementing the changes. The project's goals were to achieve a door-to-ECG time of 5 minutes, a door-to-activation time of 15 minutes, a door-to-departure-to-cath-lab time of 45 minutes, and a door-to-PCI time of 90 minutes. After closer scrutiny of the original data, the investigators adjusted the initial DTBT to 104 minutes.

The first change was to replace several ED clocks to server-based ones that display official U.S. time, since some of the original discrepancies in the data had to do with how times were recorded in the

charts. "Now that every minute counts, it must be accurate," said Dr. Haro.

Time stamps on a patient's small triage sheet track the initial door time, rather than the registration time, which was used as a point of reference in the past.

"When a patient has chest pain, we place them in a bed immediately and start the evaluation and initial management. Before, we had artificial times, since charts were sometimes generated after a patient had aspirin, oxygen, or an electrocardiogram, meaning 10-15 minutes were spent before their door time was recorded," said Dr. Haro. Door-to-ECG times dropped from 14.4 minutes to 9.1 minutes.

Several other changes were made. Registration personnel use wireless laptops at patients' bedsides to help capture real-time data, which is immediately displayed on a monitor in the ED. This allows providers to assess whether their performance goals are being accomplished for that given patient.

The ED physician now activates the cardiac catheterization team without a cardiac consultation. Previously, time was wasted through numerous phone calls made among the ED, the CCU and cath team to try and organize a PCI. Now, the entire team is activated by a single group page within 15 minutes of the patient's arrival. The pagers display text to state the problem, the patient's location, and when the patient will be on the table. "It runs similar to a trauma system," said Dr. Haro. Cath team members make one call in to a communications center to acknowledge the page, whereas CCU personnel just show up to join the team.

To improve door-to-departure times, 2-hour priority parking was given to cath lab members, who previously parked at a distance from the hospital; a dedicated phone line was established between the ED and the cath lab; and elevator keys were given to cath team members to bypass stopping at floors, which used to slow them down.

The American College of Cardiology recommends a 60-120 minute DTBT, while the Joint Commission on the Accreditation of Healthcare Organizations recently changed recommended times from 90 to 120 minutes. ■

Better GI Bleeding Prophylaxis Needed After Stenting

CHICAGO — Cardiologists might not be adequately protecting their coronary artery-stenting patients against the risk of upper GI bleeding due to antiplatelet therapy, according to a poster presented at the annual Digestive Disease Week.

The study, led by Steven Chang, M.D., was a chart review of 636 randomly selected patients who received stents at three institutions, including Chicago's Northwestern Memorial Hospital. Most patients received aspirin before (72%) and/or after (97%) stent placement, which increased their risk of peptic ulcer-related bleeding, according to Dr. Chang and his colleagues.

After stenting, however, only 24% were prescribed a proton pump inhibitor (PPI), reported Dr. Chang, who is a consultant to Santarus, a manufacturer of omeprazole.

Three of the stent recipients had a documented history of upper-GI bleeding, 23 had a history of peptic ulcer disease, and 30 were receiving NSAID therapy that was not stopped before stenting. "Few coronary stent patients who are started on aspirin and other antiplatelet agents receive appropriate GI prophylaxis," Dr. Chang wrote.

But it might not be cost effective to prescribe a PPI to all patients before stent placement, he added. "We recommend that cardiologists give PPIs to patients at risk [of upper GI bleeding] before stenting."

—Kathleen Loudon

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Fertility and reproductive performance were not affected in studies with male and female rats given 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 C (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 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

Hypertension

Of the total number of subjects in clinical studies of ATACAND, 21% (683/3260) were 65 and over, while 3% (87/3260) were 75 and over. 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. 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 mm Hg more than placebo.

Heart Failure

Of the 7599 patients with heart failure in the CHARM program, 4343 (57%) were age 65 years or older and 1736 (23%) were 75 years or older. In patients ≥ 75 years of age, the incidence of drug discontinuations due to adverse events was higher for those treated with ATACAND or placebo compared with patients < 75 years of age. In these patients, the most common adverse events leading to drug discontinuation at an incidence of at least 3%, and more frequent with ATACAND than placebo, were abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%). In addition to monitoring of serum creatinine, potassium, and blood pressure during dose escalation and periodically thereafter, greater sensitivity of some older individuals with heart failure must be considered.

ADVERSE REACTIONS

Hypertension

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 6 months and about 200 for at least 1 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 (7510 total) was 3.3% (ie, 108 of 3260) of patients treated with candesartan cilexetil as monotherapy and 3.5% (ie, 39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (ie, 57 of 2350) of patients treated with ATACAND and 3.4% (ie, 35 of 1027) of patients treated with placebo.

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

The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in 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 events 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

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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 3260 patients worldwide treated in clinical trials with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. **Body as a Whole:** asthenia, fever; **Central and Peripheral Nervous System:** paresthesia, 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 angina pectoris, myocardial infarction, and angioedema.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Heart Failure

The adverse event profile of ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM program, comparing ATACAND in total daily doses up to 32 mg once daily (n=3803) with placebo (n=3796), 21.0% of patients discontinued ATACAND for adverse events vs. 16.1% of placebo patients.

Post-Marketing Experience:

The following have been very rarely reported in post-marketing experience:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Metabolic and Nutritional Disorders: hyperkalemia, hyponatremia.

Renal: renal impairment, renal failure.

Skin and Appendages Disorders: Pruritis and urticaria.

Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Laboratory Test Findings

Hypertension

In controlled clinical trials, clinically important changes in standard laboratory parameters 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 grams/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone but were rarely of clinical importance. Anemia, leukopenia, and thrombocytopenia 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.

Heart Failure

In the CHARM program, small increases in serum creatinine (mean increase 0.2 mg/dL in candesartan-treated

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patients and 0.1 mg/dL in placebo-treated patients) and serum potassium (mean increase 0.15 mEq/L in candesartan-treated patients and 0.02 mEq/L in placebo-treated patients), and small decreases in hemoglobin (mean decrease 0.5 gm/dL in candesartan-treated patients and 0.3 gm/dL in placebo-treated patients) and hematocrit (mean decrease 1.6% in candesartan-treated patients and 0.9% in placebo-treated patients) were observed.

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.

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.

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.

DOSAGE AND ADMINISTRATION

Hypertension

Dosage must be individualized. Blood pressure response is dose related over the range of 2 to 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 4 to 6 weeks of treatment with ATACAND.

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). In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose (See CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (eg, 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.

Heart Failure

The recommended initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient.

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