

## POLICY &amp; PRACTICE

**Bill to Thwart Medicare Cuts**

A bipartisan bill (H.R. 2356) introduced by Rep. Clay Shaw (R-Fla.) and Rep. Ben Cardin (D-Md.) seeks to halt impending cuts to Medicare physician payments and replace the flawed formula that determines those payments. Following up on a recommendation of the Medicare Payment Advisory Commission, the bill would increase payments by no less than 2.7% in 2006. It would also repeal the sustainable growth rate adjustment, replacing it with a method "that ensures adequate and appropriate payments as well as sta-

ble updates for Medicare providers," Rep. Cardin said in a statement. Physicians face a 4.3% cut in Medicare payments in 2006 and subsequent cuts totaling 30% from 2007 to 2012 if the formula isn't fixed. The bill was referred to the House Ways and Means and Energy and Commerce committees. A similar bill introduced in the Senate (S. 1081) would provide a positive update to Medicare payments for 2 years.

**Weight Loss Surgery Coverage**

The American Society for Bariatric Surgery (ASBS) is asking the Centers for Medicare

and Medicaid Services to provide coverage for bariatric surgery in an effort to improve access for Medicare beneficiaries. Obesity is significantly associated with 5 of the top 10 self-reported health conditions of Medicare beneficiaries, the group wrote in its request to CMS, which currently covers gastric bypass surgery if it is medically appropriate and if it is used to correct an illness that caused the obesity or was aggravated by it. ASBS is asking CMS to expand its coverage to include laparoscopic procedures. ASBS also pointed to the Medicare Coverage Advisory Committee's favorable vote on the safety and efficacy of bariatric surgery for severely obese patients.

**Smoking Rates Decline**

The percentage of U.S. adults who smoke cigarettes continues to decline, according to the Centers for Disease Control and Prevention. About 21.6% of U.S. adults are current smokers, which is a drop from the 22.5% who were smokers in 2002 and the 22.8% in 2001, according to data from the 2003 National Health Interview Survey. And for a second straight year, the number of people who have quit smoking—about 46 million—outnumber the 45 million who continue to smoke. The study, which was published in the *Morbidity and Mortality Weekly Report*, also noted that more interventions are needed to help address the remaining disparities in smoking by age, race and ethnicity, and educational levels.

**Healthy Eating**

Tweens can improve their eating habits if given the right education, according to a study in the June issue of *Pediatrics*. The study found that children aged 8-10 years who had attended a behavior-oriented nutrition education program and were taught to follow a specific diet adopted better eating habits over several years than children who received only general nutrition information. The results are based on a review of dietary recalls from 595 children aged 8-10 who had high blood cholesterol levels at the start of the study. "These new findings offer valuable lessons for finding effective ways to help children develop healthier eating habits—a critical need in light of the rising rates of obesity and related conditions among children," said Elizabeth G. Nabel, M.D., director of the National Heart, Lung, and Blood Institute, which sponsored the study.

**Medicaid Commission**

To strengthen Medicaid, the Department of Health and Human Services established an advisory commission to identify reforms necessary to stabilize the program. The commission must submit two reports to HHS Secretary Mike Leavitt. The first, due Sept. 1, will outline recommendations for Medicaid to save \$10 billion over the next 5 years, targeting potential long-term enhancements and performance goals. The second, due Dec. 31, 2006, will make recommendations to help ensure Medicaid's long-term sustainability. Secretary Leavitt plans to appoint up to 15 voting members to the commission with expertise in health care policy, finance, or administration.

**Studies on Gender Differences Stalled**

Research into gender differences is receiving limited funding at the National Institutes of Health, said the Society for Women's Health Research (SWHR). Grants awarded to study gender differences make up only a small percentage of of NIH grants, and in 2000-2003, none of the NIH institutes had devoted more than 8% of its funded grants to such research. Also during that time, an average of just 3% of grants focused on gender differences, according to an SWHR report. SWHR officials said they had hoped to see increasing levels of funding into gender differences, but they are encouraged that some NIH institutes have established mechanisms to foster this research.

—Mary Ellen Schneider

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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  $\geq 75$  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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Made in Sweden

Rev. 05/05

 AstraZeneca