

ON THE BEAT

Obituary

Dr. James Whyte Black, a Nobel laureate whose discovery of the beta-blocker propranolol was a pharmacological breakthrough in the treatment of heart disease, died March 21 after a long illness. He was 85.



DR. JAMES
WHYTE BLACK

The Uddings-
ton, Scotland,
native received
the Nobel Prize
for Physiology
or Medicine in
1988 for his work
in the develop-
ment of propran-
olol in the early
1960s and the ul-
cer drug cimeti-
dine in the 1970s.

Dr. Black was raised in Fife, Scotland, where "I coasted, daydreaming, through most of my school years," he wrote in his autobiographical notes for the Nobel Foundation. He won a scholarship to study medicine at the University of St. Andrews in Fife, and after graduating in 1946, married Hilary Vaughan and joined the university's physiology department, where he studied the effects of iodoacetate on blood pressure. The couple moved to Singapore in 1947, where Dr. Black lectured at the King Edward VII College of Medicine. Three years later, after returning to Scotland, he established a physiology laboratory at the University of Glasgow, where he teamed with academic surgeons to study to the effects of 5-hydroxytryptamine on gastric acid secretion, and how to improve oxygen supply in patients with narrowed coronary arteries.

By 1956, he wrote, "I had clearly formulated the aim based on [Dr. Raymond] Ahlquist's dual adrenoceptor hypothesis, of finding a specific adrenaline receptor antagonist." Dr. Black left academia in 1958 to work for Imperial Chemical Industries, a drug company in Alderley Park, Cheshire, where he developed propranolol, the first successful beta-blocker.

Meanwhile, he had been working on a treatment for stomach ulcers, and he pursued this research after leaving ICI in 1964 to take a position as head of biological research at Smith, Kline, and French, where he remained until 1973. He moved on to University College, London, to head the physiology department, and in 1975, his ulcer drug, cimetidine, was marketed as Tagamet.

In 1978, Dr. Black changed course again, to direct therapeutic research at the Wellcome Research Laboratory. In

1984, he took the chairmanship of the pharmacology department at University College before becoming chancellor at the University of Dundee, Scotland, where he served from 1992 to 2006.

Propranolol and cimetidine, among the most frequently prescribed drugs worldwide, are considered two of the most significant pharmacological advances of the 20th century.

The 1988 Nobel prize was awarded jointly to Dr. Black and U.S. researchers Gertrude B. Elion and George H. Hitchings "for their discoveries of important principles for drug treatment," according

to the Nobel Foundation. Dr. Black received the Lasker Award in 1976 and the Artois-Baillet Latour Health Prize in 1979. In 1988, he founded the James Black Foundation, for scientists involved in new drug research. He was awarded the Order of Merit by the Queen of England in 2000, and received the Royal Medal in 2004. He was the first recipient of the University of Dundee's honorary degree of doctor of science in 2005, and in 2006, the university unveiled the Sir James Black Centre, for life sciences research.

He is survived by his second wife,

Atacand[®]

candesartan cilexetil

TABLETS

Warning: 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 AND PRECAUTIONS, 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 in adults and children 1 to <17 years of age. 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 adults with left ventricular systolic dysfunction (ejection fraction $\leq 40\%$) to reduce cardiovascular death and to reduce heart failure hospitalizations [see CLINICAL STUDIES in full Prescribing Information (14.2)]. ATACAND also has an added effect on these outcomes when used with an ACE inhibitor.

DOSAGE AND ADMINISTRATION

Adult 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 in full Prescribing Information (12.3)]. In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose [see CLINICAL PHARMACOLOGY in full Prescribing Information (12.3)]. 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 AND PRECAUTIONS]. 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.

Pediatric Hypertension 1 to <17 Years of age ATACAND may be administered once daily or divided into two equal doses. Adjust the dosage according to blood pressure response. For patients with possible depletion of intravascular volume (eg, patients treated with diuretics, particularly those with impaired renal function), initiate ATACAND under close medical supervision and consider administration of a lower dose [see WARNINGS AND PRECAUTIONS]. Children 1 to <6 years of age: The dose range is 0.05 to 0.4 mg/kg per day. The recommended starting dose is 0.20 mg/kg (oral suspension). Children 6 to <17 years of age: For those less than 50 kg, the dose range is 2 to 16 mg per day. The recommended starting dose is 4 to 8 mg. For those greater than 50 kg, the dose range is 4 to 32 mg per day. The recommended starting dose is 8 to 16 mg. Doses above 0.4 mg/kg (1 to <6 year olds) or 32 mg (6 to <17 year olds) have not been studied in pediatric patients [see CLINICAL STUDIES in full Prescribing Information (14.1)]. An antihypertensive effect is usually present within 2 weeks, with full effect generally obtained within 4 weeks of treatment with ATACAND. Children <1 year of age must not receive ATACAND for hypertension. All pediatric patients with a glomerular filtration rate less than 30 mL/min/1.73m² should not receive ATACAND since ATACAND has not been studied in this population [see WARNINGS AND PRECAUTIONS]. For children who cannot swallow tablets, an oral suspension may be substituted [see Preparation of Oral Suspension]. **Preparation of Oral Suspension:** ATACAND oral suspension can be prepared in concentrations within the range of 0.1 to 2.0 mg/mL. Typically, a concentration of 1 mg/mL will be suitable for the prescribed dose. Any strength of ATACAND tablets can be used in the preparation of the suspension. Follow the steps below for preparation of the suspension. The number of tablets and volume of vehicle specified below will yield 160 mL of a 1 mg/mL suspension. • Prepare the vehicle by adding equal volumes of *Ora-Plus[®] (80 mL) and *Ora-Sweet SF[®] (80 mL) or, alternatively, use †Ora-Blend SF[®] (160 mL). • Add a small amount of vehicle to the required number of ATACAND tablets (five 32 mg tablets) and grind into a smooth paste using a mortar and pestle. • Add the paste to a preparation vessel of suitable size. • Rinse the mortar and pestle clean using the vehicle and add this to the vessel. Repeat, if necessary. • Prepare the final volume by adding the remaining vehicle. • Mix thoroughly. • Dispense into suitably sized amber PET bottles. • Label with an expiry date of 100 days and include the following instructions: Store at room temperature (below 30°C/86°F). Use within 30 days after first opening. Do not use after the expiry date stated on the bottle. Do not freeze. Shake well before each use.

* Ora-Plus[®], Ora-Sweet SF[®], and Ora-Blend SF[®] are registered trademarks of Paddock Laboratories, Inc.

† Supplied as a 50/50% pre-mix of Ora-Plus[®] and Ora-Sweet SF[®].

Adult 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.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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-uterine 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. 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.

Morbidity in Infants Children <1 year of age must not receive ATACAND for hypertension. The consequences of administering drugs that act directly on the renin-angiotensin system (RAS) can have effects on the development of immature kidneys.

Hypotension In adult or children 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. 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 ATACAND versus 9.8% of patients on placebo. The incidence of hypotension leading to drug discontinuation in ATACAND-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. **Major Surgery/Anesthesia** Hypotension may occur during major surgery and anesthesia in patients treated with angiotensin II receptor antagonists, including ATACAND, due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

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 CLINICAL PHARMACOLOGY in full Prescribing Information (12.3)].

Renal Function Deterioration As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in some 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 in full Prescribing Information (12.3)]. 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. In

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Rona McLeod MacKie, and a daughter, Stephanie, from his first marriage. His first wife died in 1986.

Dr. Mario J. Garcia, an expert in the development and implementation of CT coronary angiography, has been appointed codirector of the Montefiore-Einstein Heart Center, chief of cardiology in the department of medicine at Montefiore Medical Center, and professor of medicine at Albert Einstein College of Medicine of Yeshiva University in New York.

The medical centers and the universi-



DR. MARIO J. GARCIA

ty are located in the Bronx borough, which has a high prevalence of diabetes, obesity, atherosclerosis, and hypertension. "We see an explosion of risk factors for heart disease coupled with a demand to practice evidence-based medicine and to lower costs," Dr. Garcia said in a statement, adding that

his goal as codirector of the heart center is to set new standards for technology, diagnosis, and treatment.

His interests in cardiac imaging include coronary artery disease diagnosis, diastolic heart failure, cardiomyopathies, and valvular heart disease.

Dr. Garcia previously was director of cardiovascular imaging and professor of medicine and radiology at Mount Sinai School of Medicine in New York. From 2000 to 2006, he directed the departments of echocardiography and cardiovascular imaging at the Cleveland Clinic.

Over the past 2 decades, with funding

from the National Institutes of Health, NASA, and industry, Dr. Garcia has explored noninvasive methods of evaluating the cardiovascular system. His methods have been used in hospitals, on manned space flights, and in the battlefield via telemedicine, according to a statement from Montefiore.

Dr. Garcia received his medical degree in 1986 from Universidad Nacional Pedro Henríquez Ureña in Santo Domingo, Dominican Republic. He did his cardiology fellowship at Massachusetts General Hospital in Boston.

—Jane Locastro

ATACAND® (candesartan cilexetil) Tablets

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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 ATACAND versus 6.3% in patients treated with placebo. The incidence of abnormal renal function (eg, creatinine increase) leading to drug discontinuation in ATACAND-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. Pediatrics - ATACAND has not been studied in children with estimated glomerular filtration rate <30 mL/min/1.73 m².

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 ATACAND versus 2.1% in patients treated with placebo. The incidence of hyperkalemia leading to drug discontinuation in ATACAND-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.

ADVERSE REACTIONS

Clinical Studies Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **Adult 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 ATACAND 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 ATACAND: 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 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. **Pediatric Hypertension** Among children in clinical studies, 1 in 93 children age 1 to <6 and 3 in 240 age 6 to <17 experienced worsening renal disease. The association between candesartan and exacerbation of the underlying condition could not be excluded. **Heart Failure** The adverse event profile of ATACAND in adult 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.

Postmarketing Experience The following adverse reactions were identified during post-approval use of ATACAND. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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:** Pruritus 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 ATACAND 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 [see **WARNINGS AND PRECAUTIONS** (5.6)]. **Liver Function Tests** Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to ATACAND 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 patients and 0.1 mg/dL in placebo-treated patients) and serum potassium (mean increase 0.15 mEq/L in ATACAND-treated patients and 0.02 mEq/L in placebo-treated patients), and small decreases in hemoglobin (mean decrease 0.5 gm/dL in ATACAND-treated patients and 0.3 gm/dL in placebo-treated patients) and hematocrit (mean decrease 1.6% in ATACAND-treated patients and 0.9% in placebo-treated patients) were observed.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Categories C (first trimester) and D (second and third trimesters) [see **WARNINGS AND PRECAUTIONS**].

Labor and Delivery The effect of ATACAND on labor and delivery in humans is unknown [see **WARNINGS AND PRECAUTIONS**].

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 ATACAND, taking into account the importance of the drug to the mother.

Pediatric Use The antihypertensive effects of ATACAND were evaluated in hypertensive children 1 to <17 years of age in randomized, double-blind clinical studies [see **CLINICAL STUDIES** in full Prescribing Information (14.1)]. The pharmacokinetics of ATACAND have been evaluated in pediatric patients 1 to <17 years of age [see **Pharmacokinetics** in full Prescribing Information (12.3)]. Children <1 year of age must not receive ATACAND for hypertension [see **WARNINGS AND PRECAUTIONS**].

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 adult 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.

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.

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