Application Number: NDA 20838/S8

APPROVAL LETTER
AstraZeneca LP  
Attention: Ms. Cindy Lancaster  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

Dear Ms. Lancaster:

Please refer to your supplemental new drug application dated April 6, 2000, received April 10, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atacand (candesartan) Tablets, 4, 8, 16, 32 mg.

We note that this supplement was submitted as a ‘Special Supplement – Changes Being Effected’ under 21 CFR 314.70(c).

This supplemental new drug application provides for final printed labeling revised as follows:

1) Under **ADVERSE REACTIONS**, a new subsection has been added:

   **Post-Marketing Experience**

   Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of neutropenia, leukopenia and agranulocytosis.

2) Under **PRECAUTIONS, Drug Interactions** subsection, the second sentence has been modified to:

   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.

3) There were minor editorial changes throughout the package insert.

We have completed the review of this supplemental application, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your submission of April 6, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm  
Regulatory Health Project Manager  
(301) 594-5313

Sincerely,

/\S/ \6/14/00

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20838/S8

FINAL PRINTED LABELING
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.

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 is a nonpeptide, chemically described as (S)-1-[(2S)-2-(4-chlorophenyl)carboxamido]cyclohexyl[4-biphenyl]-2-ethyl-1H-tetrazol-5-yl]-1H-benzimidazole-7-carboxylate.

Its empirical formula is C36H36N6O7, and its molecular formula is CH₄Cl₅H₂₄N₆O₇.

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 racemic mixture containing one chiral center at the cyclohexylcarboxamido ethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the water ion 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 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). Kinase 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 vasconstrictor 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 AT2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (Kd = 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 (kinase II), it does not affect the response to bradykinin.

Whether this difference has clinical relevance is not yet known.

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Atacand® (candesartan cilexetil) Tablets
Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade 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 during absorption 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 has an active metabolite that 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 to 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 28% of the dose is excreted unchanged in urine. Following an oral dose of 14C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of 14C-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.

Gender—The pharmacokinetics of candesartan have been studied in the elderly (65 years) and in both sexes. The plasma concentration of candesartan was higher in the elderly (Cmax was approximately 50% higher, and AUC was approximately 50% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan 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 elevated. After repeated dosing, the AUC and Cmax were approximately doubled in patients with severe renal impairment (creatinine clearance <10 mL/min/1.73m²) compared to patients with normal kidney function. Pharmacokinetic studies 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.

Pharmacoynamics
Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours.
Plasma concentrations of angiotensin I and angiotensin II, and plasma renin activity (PRA), increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. ACE activity was not altered in healthy subjects after repeated candesartan cilexetil administration. The once-daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion, very little effect on serum potassium was observed.

In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with non-insulin-dependent (type 2) diabetes mellitus and hypertension, there was no change in the level of HbA1c.

Clinical Trials

The antihypertensive effects of ATACAND were examined in 14 placebo-controlled trials of 4- to 12-week duration, primarily at daily doses of 2 to 32 mg per day in patients with baseline diastolic blood pressures of 90 to 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 amloprine. These studies included a total of 2850 patients randomized to one of several doses of candesartan cilexetil and 1027 to placebo. Except for a study in diabetics, all studies showed significant effects, generally dose related, of 2 to 32 mg on trough (24 hour) systolic and diastolic pressures compared to placebo, with doses of 8 to 32 mg giving effects of about 8-12/4-8 mmHg. There were no exaggerated first-dose effects in these patients. Most of the antihypertensive effect was seen within 2 weeks of initial dosing, and the full effect in 4 weeks. With once-daily dosing, blood pressure effect was maintained over 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 1 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 lung hypoplasia, renal dysfunction, 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. 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 aware, however, that oligohydramnios does 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 hypertonia, 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 hypertonia and substituting for disordered renal function.

There is no clinical evidence with the use of ATACAND in pregnant women. Oral doses ≥ 10 mg of candesartan cilexetil/day administered to pregnant rats during late gestation and continued throughout lactation were associated with reduced survival and an increased incidence of hydrocephrosis in the offspring. The 10-mg/ml/day dose in rats is approximately 2.8 times the maximum recommended human dose (MRHD) of 32 mg on a mg/m² basis (comparable assumption 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 developme

Hypotension in Voluminous and 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 injection 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 system, for example patients with severe congestive 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.

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. In clinical trials, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 34 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 (AUC) 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 cilexetil was not genotoxic in the microbial mutagenesis and mammalian cell mutagenesis assays and in the in vitro and in vivo micronucleus and rat unscheduled DNA synthesis assays. In addition, candesartan was not genotoxic in the mammalian mutagenesis, mammalian cell mutagenesis, and in vitro and in vivo chromosome aberration assays.

Fertility and reproductive performance were not affected in studies with males and female rats given oral doses of up to 300 mg/kg/day (63-times the maximum human daily dose of 32 mg on a body surface area basis).

Pregnancy

Pregnancy Category 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 detected in the milk of lactating rats (0.2% of the maternal dose). Because of the potential for adverse effects on nursing infants, 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 or over, and while 5% were 75 or 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 placebo-controlled trials of about 200 elderly hypertensive patients (ages 65 to 79 years), approximately 25% of patients treated with ATACAND and 21% of patients treated with placebo, the reduction in supine and standing blood pressure was about 12/6 mm Hg 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 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 3.5% (ie, 106 of 3020) 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 was in 2.5% (ie, 57 of 2305) 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 (2% vs 2%), dizziness (4% vs 3%), upper respiratory tract infection (6% vs 4%), pharyngitis (2% vs 1%), and thirst (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 edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, anhidrosis, stomatitis.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of less than 0.3% worldwide treated 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, gastrointestinal; Heart Rate and Rhythm Disorders: tachycardia, palpitation; Metabolic and Nutritional Disorders: creatine phosphokinase increased, hyperglycemia, hypercholesterolemia, hyperuricemia; Musculoskeletal System Disorders: myalgia; Platelet disorders: bleeding; Clotting Disorders: epistaxis; Psychiatric Disorders: anxiety, depression, somnolence; Respiratory System Disorders: dyspnea; Skin and Appendage Disorders: rash, sweats 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, in older and younger patients, and in black and nonblack patients.
Atacand® (candesartan cilexetil) Tablets

Post-Marketing Experience
Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of neutropenia, leukopenia, and agranulocytosis.

Laboratory Test Findings
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.

Hemoglobin and Hematocrit— Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 g/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 with congestive heart failure that 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 chemistry. All had elevated transaminases. Two had mildly elevated total bilirubin, but none 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 conjunction with multiple other pharmaceutical agents (Eplerenone, nizatidine, sodium, diphenhydramine hydrochloride, and labetalol). 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 overdose, 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 (vanil) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

DOSEAGE AND ADMINISTRATION
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). 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.

HOW SUPPLIED
No. 3781 — Tablets ATACAND, 4 mg, are white to off-white, circular/biconvex-shaped, non-coated tablets, coded ACF on one side and 004 on the other. They are supplied as follows: NDC 0186-0004-31 unit of use bottles of 30.

No. 3782 — Tablets ATACAND, 8 mg, are light pink, circular/biconvex-shaped, non-coated tablets, coded ACG on one side and 008 on the other. They are supplied as follows: NDC 0186-0006-31 unit of use bottles of 30.

No. 3783 — Tablets ATACAND, 16 mg, are pink, circular/biconvex-shaped, non-coated tablets, coded ACH on one side and 016 on the other. They are supplied as follows: NDC 0186-0016-31 unit of use bottles of 30

No. 3784 — Tablets ATACAND, 32 mg, are pink, circular/biconvex-shaped, non-coated tablets, coded ACL on one side and 032 on the other. They are supplied as follows: NDC 0186-0032-31 unit of use bottles of 30

NDC 0186-0032-24 unit of use bottles of 90

NDC 0186-0032-26 unit of use bottles of 100.

Storage
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

Manufactured under the license from Takeda Chemical Industries, Ltd. by Astra AB, S-151 85 Södertälje, Sweden.

Packaged by: March & Co., Inc., West Point, PA 19486

Distributed by: Astra Pharmaceuticals, L.P., Wayne, PA 19087

Revised February 2000
CSO Review of Final Printed Labeling

Application: NDA 20-838/S-008

 Applicant: AstraZeneca

Document Date: April 6, 2000

Receipt Date: April 10, 2000

Product Name: Atacand (candesartan) Tablets, 4, 8, 16, 32 mg

Background: This supplemental application was submitted as “Changes Being Effected”, with final printed labeling revised to include under ADVERSE REACTIONS, a new Post-Marketing Experience subsection. The sponsor has submitted MEDWATCH data describing very rare occurrences of white blood cell dyscrasias in patients taking candesartan cilexetil.

Evaluation: When compared with the most recently approved labeling (original NDA 20-838, approved June 4, 1998), the following changes were noted:

1) Under ADVERSE REACTIONS, a new subsection has been added:

Post-Marketing Experience
Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of neutropenia, leukopenia and agranulocytosis.

2) Under PRECAUTIONS, Drug Interactions subsection, the second sentence has been modified with editorial changes for clarity to:

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.

3) There were minor editorial changes throughout the package insert.

Comments/Recommendations: An approval letter should issue for these supplements as set forth under 21 CFR 314.70 (c)(i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

Edward Fromm
Consumer Safety Officer

Ef/5-25-2000

cc: NDA 20-838
HFD-2
HFD-110
HFD-110/EFfromm
HFD-110/Bローン