Application Number: NDA 20386/S8

APPROVAL LETTER
Merck Research Laboratories  
Attention: Jeffrey R. White, M.D.  
Sumneytown Pike, P.O. Box 4  
BLA-20  
West Point, PA 19486

Dear Dr. White:

Please refer to your supplemental new drug application dated December 18, 1997, received December 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets.


This supplemental new drug application provides for an additional tablet strength, 100 mg.

We have completed the review of this supplemental application, as amended, 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 final printed labeling included in your September 3, 1998 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

We note that you will change the storage statement on your container labels as existing stock is depleted to read “Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.”

Please describe this change in your next annual report, as provided for under 21 CFR 314.70(d)(3), an editorial or similar minor change in labeling.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

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:

Ms. Kathleen Bongiovanni  
Regulatory Health Project Manager  
(301) 594-5334

Sincerely yours,

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc: Archival NDA 20-386  
HFD-110/Div. Files  
HF-2/MedWatch (with labeling)  
HFD-002/ORM (with labeling)  
HFD-101/ADRA (with labeling)  
HFD-40/DDMAC (with labeling)  
HFD-613/OGD (with labeling)  
HFD-95/DDMS (with labeling)  
HFD-810/DNDC Division Director  
DISTRICT OFFICE  
HFD-110/K.Bongiovanni  
sb/9/23/98; 9/28/98  
Initialed by: C Ganley/9/24/98  
N Morgenstern/9/25/98  
R Mittal  
K Srinivasachar/9/24/98  
filename: 20386s008ap.doc  

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20386/S8

APPROVABLE LETTER
Merck & Company
Attention: Larry P. Bell, M.D.
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Bell:

Please refer to your December 18, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium), 25 and 50 mg Tablets.

The user fee goal date is June 19, 1998.

We acknowledge receipt of your amendment dated March 16, 1998.

The supplemental application provides for an additional strength of 100 mg for Cozaar Tablets.

We have completed the review of this supplemental application and it is approvable. Before this supplement may be approved, however, it will be necessary for you to revise the dissolution specification as follows:

\[
\text{This is the specification which is currently approved for the 25 and 50 mg strengths of Cozaar Tablets and the data you have provided show that all batches of the 100 mg strength meet this specification at } \quad \text{[]. Consequently, there is no basis for a different dissolution specification for the 100 mg strength of Cozaar Tablets.}
\]

Please consider using the following storage statement in the "How Supplied" section of the Package Insert and on the immediate container labels:

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

If space on the immediate container is limited, either of the following statements is acceptable provided the full statement (as above) appears on the outer carton and in the package insert:
"Store at 25°C (77°F); excursions 15-30°C (59-86°F). Keep container tightly closed. Protect from light"

or

"Store at 25°C (77°F); (see insert). Keep container tightly closed. Protect from light"

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5334

Sincerely yours,

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I
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 20386/S8

FINAL PRINTED LABELING
use in pregnancy
When used in pregnancy during the second and third trimesters, drugs that act directly on the renal tubular system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR® should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION
COZAAR® (losartan potassium), the first of a new class of antihypertensive agents, is an angiotensin II receptor (type AT1) antagonist.

Losartan potassium is a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[1-(1H-tetrazol-5-yl)ethyl]-1H-benzo[d]imidazole-5-sulfonic acid. Its empirical formula is C22H19ClN5O4S, and its structural formula is:

\[
\text{O} \quad \text{N} \\
\text{C} \quad \text{C} \\
\text{CH} \quad \text{CH} \\
\text{N} \quad \text{N} \\
\text{H} \quad \text{H} \\
\text{C} \quad \text{C} \\
\text{Cl} \quad \text{O} \\
\text{O} \quad \text{S}
\]

Losartan potassium is a white to off-white, free-flowing crystalline powder with a molecular weight of 463.6. It is freely soluble in water, soluble in alcohol, and slightly soluble in common organic solvents, such as acetone and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring leads to the formation of losartan acid.

COZAAR® is available for oral administration containing either 25 mg, 50 mg or 100 mg losartan potassium and the following inactive ingredients: mannitol, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR® 25 mg, 50 mg and 100 mg contain cornsilk extract in the following amounts: 3.12 mg (0.054 mg/dL), 6.25 mg (0.108 mg/dL) and 8.40 mg (0.215 mg/dL), respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action
Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)), is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT1 receptor and have much greater affinity (about 1000-fold) for the AT1 receptor than for the AT2 receptor. Binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II), the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor do they bind to or block other receptor agonists or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics

General
Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active hydroxylated metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of

Caution: Discontinue therapy at least 30 minutes before surgery if possible, to minimize blood pressure rebound, which may occur with abrupt discontinuation of the drug. Losartan is associated with increased potassium levels, which can cause hyperkalemia and may lead to cardiac arrhythmias. Losartan should be used with caution in patients with renal insufficiency, liver disease, or in those on concomitant medications that can cause hyperkalemia. It should also be used with caution in patients with a history of gout, hyperuricemia, or a history of peptic ulcer disease. Use with caution in patients with a history of lupus nephritis or systemic lupus erythematosus. Losartan is not recommended for use in patients with a history of allergy to any component of the formulation.

Drug Interactions
Losartan, administered for 12 days, did not affect the pharmacokinetics of orlistat, a dietary source of fat absorption, or the pharmacokinetics of orlistat and metformin, with or without ranitidine. Losartan administered with ranitidine was associated with a decrease in the clearance of losartan, with a corresponding increase in the area under the plasma concentration-time curve of losartan and its active metabolite, losartan acid. This effect was not clinically significant.

Losartan is associated with increased potassium levels, which can cause hyperkalemia and may lead to cardiac arrhythmias. Losartan should be used with caution in patients with renal insufficiency, liver disease, or in those on concomitant medications that can cause hyperkalemia. It should also be used with caution in patients with a history of gout, hyperuricemia, or a history of peptic ulcer disease. Use with caution in patients with a history of lupus nephritis or systemic lupus erythematosus. Losartan is not recommended for use in patients with a history of allergy to any component of the formulation.

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COZAAR® (Losartan Potassium Tablets)

ing for 24 hours. Removal of the negative feedback of angiotensin II causes a 2.5 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglan-
din concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease 0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR® were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparision of two doses (50, 100 and 150 mg) once daily or twice daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 in placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsis-
tent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant diastolic mean decreases in blood pressure, compared to pla-
ceto, in the range of 5.5-10.5/5.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing, 50-100 mg/day gave consistently larger trough responses than once-daily dosing at the same total dose. Peak 6 hour effects were uniformly, but modestly, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 50-90%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mmHg.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65 had generally similar responses. Black patients, however, had notably smaller responses to losartan monotherapy.

The effect of losartan is substantially pressure-dependent, but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo con-
trol) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt with-
drawal of losartan. There was essentially no change in aver-
age heart rate in losartan-treated patients in controlled trials.

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when chal-
enged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=307) or 25 mg hydrochlorothiazide (n=136). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

<table>
<thead>
<tr>
<th>Study 1</th>
<th>HCTZ</th>
<th>Losartan</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>25%</td>
<td>17%</td>
<td>69%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 2</th>
<th>Placebo</th>
<th>Losartan</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>35%</td>
<td>29%</td>
<td>61%</td>
</tr>
</tbody>
</table>

1 Demographics: 18% Caucasian, 64% Female
2 Demographics: 18% Caucasian, 51% Female

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

INDICATIONS AND USAGE

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

In considering the use of monotherapy with COZAAR®, it should be noted that in controlled trials COZAAR® had an effect on blood pressure that was notably less in black patients than in non-blacks, a finding similar to the small effect of angio-
tensin-converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

COZAAR® 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 adminis-
tered to pregnant women. Several dozen cases have been
COZAAR® (Losartan Potassium Tablets)

Drug Interactions
No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, clopidogrel, and phosphonbinodal (See CLINICAL PHARMACOLOGY, Drug Interactions). Potent inhibitors of cytochrome P450 3A4 and/or CYP have not been studied clinically, but in vitro studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketocanazole, troleandomycin, or clarithromycin) or P450 2C9 (sulfaphenazole in the presence of an inhibitor of sulfaphenazole). However, because of the conversion of losartan to the active metabolite, inhibition of cytochrome P450 2C9 has not been studied clinically. The pharmacokinetic consequences of coadministration of losartan and inhibitors of P450 2C9 have not been examined.

As with other drugs that block angiotensin II or its effects, caution is advised in patients with potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (210 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenomas. The maximally tolerated dosages (270 mg/kg/day in rats, 100 mg/kg/day in mice) provided systemic exposures for losartan and its active metabolite that were approximately 160- and 80-times (rats) and 30- and 15-times (mice) the exposure to a 50 kg human given 100 mg per day.

Losartan potassium was negative in the micronucleus test and in the in vitro alkaline elution chromosomal aberration test and the in vitro V-79 mammalian cell mutagenesis assays and in the in vitro alkaline elution chromosome aberration assay. In addition, the active metabolite showed no evidence of mutagenicity in the micronucleus test, in vitro alkaline elution, and in vitro chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic doses levels of females (300/200 mg/kg/day) was associated with significant decreases in body weight and delayed body weight gain and with increases in maternal and pup deaths. Oligohydramnios and congenital abnormalities were observed. The reduction in maternal and pup survival was attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hypertension — Volume-Depleted Patients
In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with COZAAR. Therefore, the usual starting dose of COZAAR should be increased after careful observation at a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS
General
Impaired Hepatic Function
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).
Hypersensitivity. See ADVERSE REACTIONS, Post-Marketing Experience.
Impaired Renal Function
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with COZAAR. In some patients, these changes in renal function were reversible upon discontinuation of therapy.
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and death. Similar outcomes have been reported with COZAAR.
In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with COZAAR, in some patients, these effects were reversible upon discontinuation of therapy.
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 exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.
COZAAR® (Losartan Potassium Tablets)

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were less frequent, in the placebo group: asthenia/taxis, edema; swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

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

A patient with known hypersensitivity to aspirin and penicillin, when treated with COZAAR, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 2 days after therapy was discontinued.

Superficial peeling of nails and high blood pressure was also reported in one subject.

In addition to the adverse events above, potentially important events that occurred in at least two patients treated with losartan or other adverse events that occurred in ≤1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan. Body as a whole: Rash, arthralgia, bone pain, cold symptoms, cough, dyspepsia, insomnia, influenza, back pain, myalgia, dizziness, dysgeusia, hypertension, hypotension, salivary gland enlargement, sialorrhea, syncope, chest pain, abdominal pain; eye: conjunctivitis, diplopia, dry eyes, exacerbation of allergy symptoms, eye pain, exophthalmos; ear and hearing: hearing loss, noise, vertigo; mouth and tongue: dysgeusia, glossitis, taste perversion, taste disturbances; nervous system: dizziness, syncope, vertigo; respiratory system: cough, dyspnea, pharyngitis, signs of respiratory tract infection; skin: rash, rash pruritus, urticaria; special senses: blurred vision, burning/itching in the eye, conjunctivitis, taste perversion;Continue

Post-Marketing Experience
The following additional adverse reactions have been reported in post-marketing experience: Hypersensitivity: Angioedema (involving swelling of the face, lips, pharynx, and/or tongue) has been reported rarely in patients treated with losartan; some of these patients had previously experienced angioedema with other drugs including ACE inhibitors; Digestive: Hepatitis (reported rarely); Hypokalemia has been reported.

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

Creatinine: Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1% of patients with essential hypertension treated with COZAAR alone.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred, in patients with essential hypertension treated with COZAAR alone, one patient (≤1.1%) was discontinued due to these laboratory adverse experiences.

OVERDOSE
Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic ( vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

DOSE AND ADMINISTRATION
The usual starting dose of COZAAR is 50 mg once daily, with 10 mg used in patients with possible delay of intravascular volume (e.g., patients treated with diuretics) (see WARNINGS: Hypotension — Volume Depleted Patients and patients with a history of hepatic impairment (see PRECAUTIONS, General). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using a once a day dosing is inadequate, a twice a day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.

If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMAcodynamics and Clinical Effects).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

COZAAR® may be administered with other antihypertensive agents.

COZAAR® may be administered with or without food.

HOW SUPPLIED
No. 3612 — Tablets COZAAR, 25 mg, are light green, tear-drop-shaped, film-coated tablets with code MMX on one side and 961 on the other. They are supplied as follows:

NDC 0006-0195-54 unit of use bottles of 90 (0505-01-14-4082, 25 mg, 100)
NDC 0006-0195-68 unit of use bottles of 100 (0505-01-14-4082, 25 mg, 100)
NDC 0006-0951-28 unit dose packages of 100 (0505-01-14-4082, 25 mg, individually sealed 100s)
NDC 0006-0951-92 unit of use bottles of 30 (0505-01-14-4082, 25 mg, 30s)
NDC 0006-0951-54 unit of use bottles of 90 (0505-01-14-4082, 25 mg, 100)
NDC 0006-0951-58 unit of use bottles of 100 (0505-01-14-4082, 25 mg, 100)
NDC 0006-0951-31 unit of use bottles of 30 (0505-01-14-4082, 25 mg, 30s)
NDC 0006-0952-54 unit of use bottles of 90 (0505-01-14-4082, 50 mg, 100)
NDC 0006-0952-58 unit of use bottles of 100 (0505-01-14-4082, 50 mg, 100)
NDC 0006-0952-82 unit dose packages of 100 (0505-01-14-4082, 50 mg, individually sealed 100s)
NDC 0006-0953-31 unit of use bottles of 30 (0505-01-14-4082, 50 mg, 30s)
NDC 0006-0960-54 unit of use bottles of 90 (0505-01-14-4082, 50 mg, 100)
NDC 0006-0960-58 unit of use bottles of 100 (0505-01-14-4082, 50 mg, 100)
NDC 0006-0960-28 unit dose packages of 100 (0505-01-14-4082, 50 mg, individually sealed 100s)

No. 6364 — Tablets COZAAR, 50 mg, are green, tear-drop-shaped, film-coated tablets with code MMX on one side and 962 on the other. They are supplied as follows:

NDC 0006-0952-54 unit of use bottles of 90 (0505-01-14-4082, 50 mg, 100)
NDC 0006-0952-58 unit of use bottles of 100 (0505-01-14-4082, 50 mg, 100)
NDC 0006-0953-31 unit of use bottles of 30 (0505-01-14-4082, 50 mg, 30s)
NDC 0006-0960-54 unit of use bottles of 90 (0505-01-14-4082, 50 mg, 100)
NDC 0006-0960-58 unit of use bottles of 100 (0505-01-14-4082, 50 mg, 100)
NDC 0006-0960-28 unit dose packages of 100 (0505-01-14-4082, 50 mg, individually sealed 100s)

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. Protect from light.

Used by
MERCK & CO, INC. West Point, PA 19486, USA

by
DU PONT

PHARMA

Wilmington, DE 19803 USA

Issued August 1998
Printed in USA
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20386/S8

CHEMISTRY REVIEW(S)
DIVISION OF CARDIO-RENAZAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-386 REVIEW DATE: 11-MAY-98 REVISED DATE: 03-JUNE-98

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
SCS-008 18-DEC-97 19-DEC-97 24-DEC-97
SCS-008(BC) 16-MAR-97 17-MAR-97 19-MAR-97

NAME & ADDRESS OF APPLICANT
Merck Research Laboratories
Merck & Co. Inc.
West Point, PA 19486

Telephone: 610-397-2310

DRUG PRODUCT NAME
Proprietary: COZAAR
Nonproprietary/USAN: Losartan Potassium
Code Name/#: MK-954; DuP-753; 1-158,086; L-158,086-005H; E-3340
Chem. Type/Ther. Class: 1S

Supplement Provides For:
the addition of 100 mg tablet strength.

PHARMACOL. CATEGORY/INDICATION:
An angiotensin II receptor agonist; said to reduce systolic and diastolic
blood pressure in patients with mild to moderate essential hypertension.

DOSAGE FORM: tablets STRENGTH: 20, 50 and 100 mg

ROUTE OF ADMINISTRATION: ORAL DISPENSED: Rx

CHEMICAL NAME: 2-butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)-[1,1'-
biphenyl]-4-yl]-methyl]-1H-imidazole-5-methanol,
monopotassium salt.

CAS #: 124750-99-8

MOLECULAR FORMULA: C22H22ClKN6O MOLECULAR WEIGHT: 461.01

STRUCTURAL FORMULA:
SUPPORTING DOCUMENTS:
None.

RELATED DOCUMENTS:
None.

CONSULTS:
None.

REMARKS/COMMENTS:

The supplement is approvable but the applicant should keep the same dissolution specifications as approved for 25 and 50 mg tablets.

CONCLUSIONS & RECOMMENDATIONS:

Biopharm has recommended that the dissolution specifications proposed by the applicant are not acceptable. Since all the batches are passing at dissolution testing or dissolution testing, there is no basis for setting a different specification for the 100 mg tablets. Based on the dissolution data submitted by the applicant, the following dissolution and medium specifications are recommended:

Medium:
Method:
Specifications:

The applicant should be requested to consider using the following storage statement in the "How Supplied" section of the Package Insert and on the immediate container labels:

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

If space on the immediate container is limited, either of the following statements is acceptable provided the full statement (as above) appears on the outer carton and in the package insert:

"Store at 25°C(77°F); excursions 15-30°C(59-86°F). Keep container tightly closed. Protect from light"

or

"Store at 25°C(77°F); (see insert). Keep container tightly closed. Protect from light"
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-386
SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
SCS-008 (AF) 03-SEP-98 04-SEP-98 04-SEP-98
(Amendment)

NAME & ADDRESS OF APPLICANT
Merck Research Laboratories
Merck & Co. Inc.
West Point, PA 19486
Telephone: 610-397-2310

DRUG PRODUCT NAME
Proprietary: COZAAR
Nonproprietary/USAN: Losartan Potassium
Code Name/#: MK-954; DuP-753; 1-158,086; L-158,086-005H; E-3340
Chem.Type/Ther.Class: 1S

Amendment to Supplement Provides For:
the revision of the dissolution specifications and storage statements in the

PHARMACOL. CATEGORY/INDICATION:
An angiotensin II receptor agonist, said to reduce systolic and diastolic
blood pressure in patients with mild to moderate essential hypertension.

DOSAGE FORM: tablets STRENGTH: 20, 50 and 100 mg
ROUTE OF ADMINISTRATION: ORAL DISPENSED: Rx
CHEMICAL NAME: 2-buty1-4-chloro-1[{2’-(1H-tetrazol-5-yl)-[1,1’-
biphenyl]-4-yl}-methyl]-1H-imidazole-5-methanol, monopotasium salt.
CAS #: 124750-99-8
MOLECULAR FORMULA: C$_2$H$_2$ClKN$_4$O MOLECULAR WEIGHT: 461.01

STRUCTURAL FORMULA:
SUPPORTING DOCUMENTS:

None.

RELATED DOCUMENTS:

None.

CONSULTS:

None.

REMARKS/COMMENTS:

Storage statement in the Paste-up of the circular is acceptable.

CONCLUSIONS & RECOMMENDATIONS:

Satisfactory. The supplement may be approved.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: KSrinivasachar

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20386\20386AF.008
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-386 (Supplement SCS-008)  SUBMISSION DATES: December 18, 1997
COZAAR® (Losartan Potassium) Tablets (100 mg)  (Consult to OCPB - 4/14/98)

MERCK RESEARCH LABORATORIES.  REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NDA SUPPLEMENT

BACKGROUND: Losartan (COZAAR® tablet) is an angiotensin II receptor (AT₁) antagonist approved for the treatment of hypertension. Three strengths of the formulation were approved (25, 50 and 100 mg) but the sponsor decided not to market the 100 mg formulation at the time of approval. The formula for the 100 mg tablet is a weight multiple of the approved 25 and 50 mg tablets. The core tablets for the three tablet strengths are prepared from a powder blend of the same formula composition and the core tablet weight is adjusted to obtain the appropriate dose. The sponsor proposed a dissolution specification of in the NDA but Agency approved . The sponsor now intends to market the 100 mg tablet formulation and has requested for a different dissolution specification based on stability data from the original NDA supplemented with up to and including 36 months data on the 100 mg tablet. The sponsor claimed that using the approved specification for the 100 mg tablet formulation, the initial dissolution data (Table 1) indicate that testing would be required in two of the ten lots where 6 tablets were tested and testing would be required for two of the four lots in which twelve tablets were tested. Based on these data the sponsor requests for a specification of for the 100 mg tablet.

COMMENTS TO BE SENT TO THE FIRM:
Since all the batches are passing at the dissolution testing or dissolution testing, there is no basis set a different specification for the 100 mg tablet.

DISSOLUTION: Based on the dissolution data submitted by the sponsor, the approved dissolution medium and specifications should be:
Medium:
Method:
Specifications:

RECOMMENDATION:
The Division of Pharmaceutical Evaluation I has reviewed the sponsor’s supplement to the NDA and recommends that the dissolution specification for the 100 mg tablet should
FT Initialed by A. Parekh, Ph.D.  

cc: NDA 20-386, (HFD-110, HFD-860 (Fadiran), Short (Chemist Team Leader, HFD-110), CDR (Attn: Barbara Murphy).
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-386 (Supplement SCS-008)  SUBMISSION DATES: December 18, 1997
COZAAR® (Losartan Potassium) Tablets (100 mg)  (Consult to OCPB - 4/14/98)

MERCK RESEARCH LABORATORIES.  REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: CORRECTION OF RECOMMENDATION

BACKGROUND: Losartan (COZAAR® tablet) is an angiotensin II receptor (AT₁) antagonist approved for the treatment of hypertension. Three strengths of the formulation were approved (25, 50 and 100 mg) but the sponsor decided not to market the 100 mg formulation at the time approval. The formula for the 100 mg tablet is a weight multiple of the approved 25 and 50 mg tablets. The core tablets for the three tablet strengths are prepared from a____of the same formula composition and the core tablet weight is adjusted to obtain the appropriate dose. The sponsor proposed a dissolution specification of____in the NDA but Agency approved____. The sponsor now intends to market the 100 mg tablet formulation and has requested for a different dissolution specification based on stability data from the original NDA supplemented with up to and including 36 months data on the 100 mg tablet. The sponsor claimed that using the approved specification for the 100 mg tablet formulation, the initial dissolution data (Table 1) indicate that____dissolution testing would be required in two of the ten lots where 6 tablets were tested and____testing would be required for two of the four lots in which twelve tablets were tested. Based on these data the sponsor requests for a specification of____for the 100 mg tablet.

COMMENTS TO BE SENT TO THE FIRM:
Since all the batches are passing at the____dissolution testing or____dissolution testing, there is no basis set a different specification for the 100 mg tablet.

DISSOLUTION: Based on the dissolution data submitted by the sponsor, the approved dissolution medium and specifications should be:
Medium:
Method:
Specifications:

RECOMMENDATION:
The Division of Pharmaceutical Evaluation I has reviewed the sponsor's supplement to the NDA and recommends that the dissolution specification for the 100 mg tablet should____AS STATED IN THE REVIEW DATED 5/4/98).
Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation

FT Initialed by A. Parekh, Ph.D.  6/2/98

cc: NDA 20-386, HFD-110, HFD-860 (Fadiran), Short (Chemist Team Leader, HFD-110), CDR (Attn: Barbara Murphy).
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20386/S8

ADMINISTRATIVE DOCUMENTS
RHPM Review of Labeling

NDA: 20-386/SCS-008 Cozaar (losartan potassium) Tablets

Date of submission: September 3, 1998
Date of receipt: September 4, 1998
Applicant: Merck Research Laboratories

Background: SCS-008 provides for a 100 mg tablet strength of Cozaar (losartan potassium) Tablets. Merck has submitted final printed labeling in response to the June 11, 1998 approvable letter signed by Dr. Srinivasachar.

The approvable letter included a request for a revised dissolution specification, and asked the firm to consider using the following storage statement in the HOW SUPPLIED section of the package insert and on the immediate container labels:

“Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.”

If space on the immediate container is limited, either of the following statements is acceptable provided the full statement (as above) appears on the outer carton and in the package insert:

“Store at 25° C (77° F); excursions 15-30° C (59-86° F). Keep container tightly closed. Protect from light.” Or

“Store at 25° C (77° F); (see insert). Keep container tightly closed. Protect from light.”

Review: The submitted final printed labeling has been revised as follows:

DESCRIPTION:
The first sentence of the fifth paragraph has been revised to include 100 mg; it now reads, “COZAAR is available for oral administration containing either 25 mg, 50 mg, or 100 mg of losartan potassium ...”

The single sentence in the sixth paragraph has been revised to add information on the 100 mg tablet; it now reads, “COZAAR 25 mg, 50 mg and 100 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq), respectively.

The DESCRIPTION section of COZAAR does not include the type of dosage form, as described in the regulations (21 CFR 201.57 (a)(ii). Upon review, neither does the package insert for HYZAAR. I called Dr. Jeffrey White on September 11, 1998, and asked him to include the type of dosage form (tablets) in the DESCRIPTION section of
the package inserts for COZAAR and HYZAAR. He said that it will be added in the next labeling supplements for which they have not already printed labeling.

HOW SUPPLIED:
Information on the 100 mg tablets has been added.

Storage: The storage statement has been revised to now read, “Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F)[see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.”

The submission also contains labels for unit of use bottles of 30 and 100, and unit dose packages of 100 tablets. The storage statement on these labels is “Store at controlled room temperature, 15-30° C (59-86° F). Keep container tightly closed. Protect from light.”

Recommendation: The final printed package insert includes the information that was in the draft labeling in the original submission, along with a revised storage statement. The firm has not revised the storage statements on the bottles yet, but will do so as existing stocks are depleted. The following should be included in the approval letter:

We note that you will change the storage statement on your container labels as existing stock is depleted to read “Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.”

Please describe this change in your next annual report, as provided for under 21 CFR 314.70(d)(3), an editorial or similar minor change in labeling.

The firm has agreed to the dissolution specification in the approvable letter. I recommend that an approval letter issue.

Kathleen F. Bongiovanni

cc: NDA 20-386/S-008
HFD-110
HF-2/MedWatch
HFD-110/KBongiovanni
HFD-110/SBenton

kb/9/11/98.