CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 20386/S8

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 13 1998

NDA 20-386/S-008

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.

We acknowledge receipt of your submissions dated July 8 and September 3, 1998. Your submission of September 3, 1998 constituted a full response to our June 11, 1998 action letter.

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,

R 4 10/13/98

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

K Bong 9-28-98

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20386/S8

APPROVABLE LETTER

NDA 20-386/ S-008

JUN 11 1998

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:

[ ]

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 [ ] 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

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

COZAAR®
(LOSARTAN POTASSIUM TABLETS)

USE IN PREGNANCY

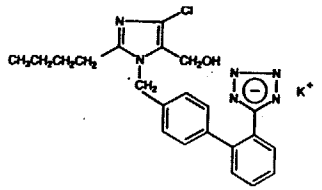
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: *Fetal/Neonatal Morbidity and Mortality.*

DESCRIPTION

COZAAR® (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT_1) antagonist.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg, 50 mg or 100 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, 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 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.

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 block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 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 hormone receptors 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 carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric: Losartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, *Hypotension — Volume-Depleted Patients* and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

Pharmacodynamics and Clinical Effects

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persist-

ing for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 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 prostaglandin 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 comparisons of two doses (50-100 mg/day) as 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 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 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 moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 60-90%, 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 present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average 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 challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1†	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2††	**Placebo**	**Losartan**	**Lisinopril**
Cough	35%	29%	62%

† Demographics = (89% caucasian, 64% female)
†† Demographics = (90% caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all 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 angiotensin 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 administered to pregnant women. Several dozen cases have been

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reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAAR 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 COZAAR as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist 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 intraamniotic environment.

If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress 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.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m^2 basis). These findings are 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.

Hypotension — 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. These conditions should be corrected prior to administration of COZAAR, or 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/or 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 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.

COZAAR® (Losartan Potassium Tablets)

Drug Interactions

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, *Drug Interactions.*) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. In humans, ketoconazole, an inhibitor of P450 3A4, did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan. Inhibitors of cytochrome P450 2C9 have not been studied clinically. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

As with other drugs that block angiotensin II or its effects, concomitant use of 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 (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *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 dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p<0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with COZAAR was well-tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6-12 week placebo controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 1% of

patients treated with losartan and that were more frequent on losartan than placebo.

	Losartan (n=1075) Incidence	Placebo (n=334) Incidence
Digestive		
Diarrhea	2.4	2.1
Dyspepsia	1.3	1.2
Musculoskeletal		
Cramp, muscle	1.1	0.3
Myalgia	1.0	0.9
Pain, back	1.8	1.2
Pain, leg	1.0	0.0
Nervous System/Psychiatric		
Dizziness	3.5	2.1
Insomnia	1.4	0.6
Respiratory		
Congestion, nasal	2.0	1.2
Cough	3.4	3.3
Infection, upper respiratory	7.9	6.9
Sinus disorder	1.5	1.2
Sinusitis	1.0	0.3

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

Adverse events occurred at about 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 5 days after therapy was discontinued.

Superficial peeling of palms and hemolysis was reported in one subject.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to 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:* facial edema, fever, orthostatic effects, syncope; *Cardiovascular:* angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; *Digestive:* anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; *Hematologic:* anemia; *Metabolic:* gout; *Musculoskeletal:* arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; *Nervous System/Psychiatric:* anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; *Respiratory:* dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; *Skin:* alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria; *Special Senses:* blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; *Urogenital:* impotence, nocturia, urinary frequency, urinary tract infection.

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 previously experienced angioedema with other drugs including ACE inhibitors; *Digestive:* Hepatitis (reported rarely).

Hyperkalemia 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 percent 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 (<0.1%) was discontinued due to these laboratory adverse experiences.

OVERDOSAGE

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/m^2 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.

DOSAGE AND ADMINISTRATION

The usual starting dose of COZAAR is 50 mg once daily, with 25 mg used in patients with possible depletion 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 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 PHARMACOLOGY, *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, teardrop-shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:
NDC 0006-0951-54 unit of use bottles of 90
(6505-01-414-4064, 25 mg 90's)
NDC 0006-0951-58 unit of use bottles of 100
(6505-01-414-4059, 25 mg 100's)
NDC 0006-0951-28 unit dose packages of 100
(6505-01-414-4063, 25 mg individually sealed 100's).

No. 3613 — Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:
NDC 0006-0952-31 unit of use bottles of 30
(6505-01-414-4062, 50 mg 30's)
NDC 0006-0952-54 unit of use bottles of 90
(6505-01-414-4060, 50 mg 90's)
NDC 0006-0952-58 unit of use bottles of 100
(6505-01-414-4058, 50 mg 100's)
NDC 0006-0952-28 unit dose packages of 100
(6505-01-414-4061, 50 mg individually sealed 100's)
NDC 0006-0952-82 bottles of 1,000.

No. 6536 — Tablets COZAAR, 100 mg, are dark green, teardrop-shaped, film-coated tablets with code 960 on one side and MRK on the other. They are supplied as follows:
NDC 0006-0960-31 unit of use bottles of 30
NDC 0006-0960-58 unit of use bottles of 100
NDC 0006-0960-28 unit dose packages 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. Protect from light.

Manuf. for:
MERCK & CO., INC., West Point, PA 19486, USA

by:
DU PONT PHARMA Wilmington, DE 19880 USA

Issued August 1998
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20386/S8

CHEMISTRY REVIEW(S)

DF

JUN 5 1998

DIVISION OF CARDIO-RENAL 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

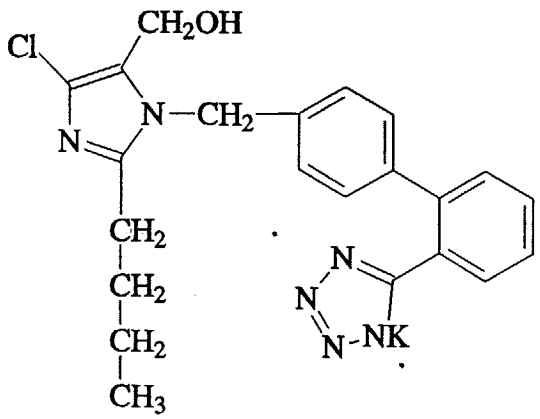
ROUTE OF ADMINISTRATION: ORAL **DISPENSED:** Rx

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: $C_{22}H_{22}ClKN_6O$ **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"

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

R/D Init by: JShort/1S/
6-4-98

/S/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20386\20386SCM.008

OCT 26 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-386 **REVIEW DATE:** 23-OCT-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCS-008(AF) (Amendment)	03-SEP-98	04-SEP-98	04-SEP-98

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 package circular in response to the Agency's approvable letter of June 11, 1998.

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

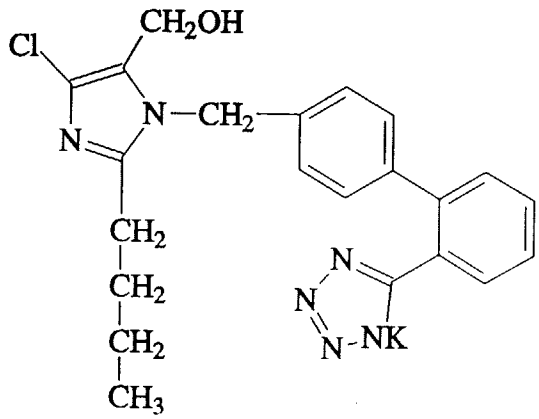
ROUTE OF ADMINISTRATION: ORAL **DISPENSED:** Rx

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: $C_{22}H_{22}ClKN_6O$ **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

/S/
10-23-98

/S/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20386\20386AF.008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20386/S8

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DF

MAY - 4 1998 MAY 1 1998

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 (AT_1) 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 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 [redacted] in the NDA but Agency approved [redacted] 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 [redacted] dissolution testing would be required in two of the ten lots where 6 tablets were tested and [redacted] 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 [redacted] for the 100 mg tablet.

COMMENTS TO BE SENT TO THE FIRM:
Since all the batches are passing at the [redacted] dissolution testing or [redacted] 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: [redacted]
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 [redacted]

/S/ 5/1/98

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. ----------/S/ 5/4/98

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

JUN - 8 1998

DF

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 (AT_1) 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).

/S/ 6/8/98

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. /S/ - 6/8/1998

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

DF

OCT 13 1998

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.

/S/
Kathleen F. Bongiovanni

cc: NDA 20-386/S-008
HFD-110
HF-2/MedWatch
HFD-110/KBongiovanni
HFD-110/SBenton
kb/9/11/98.