# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number: NDA 20738/S004**

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-738/S-004

SmithKline Beecham Pharmaceuticals
Attention: Ms. Deborah E. Zuber
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

MAY 27 1999

Dear Ms. Zuber:

Please refer to your supplemental new drug application dated January 25, 1999, received January 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Teveten (eprosartan mesylate) 300, 400 and 600 mg Tablets.

We acknowledge receipt of your submissions dated March 9 and 10 and April 2, 1999.

This supplemental new drug application provides for a new 600 mg strength tablet.

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 draft labeling included with your April 2, 1999 submission with the following revisions:

1. Please correct the following inconsistencies in the listing of the inactive ingredients:

2. "Polysorbate 80" should be listed as an inactive ingredient for the 300 and 400 mg tablets, and not listed in the "may contain" section, since the white and pink colorants for these two tablets both contain polysorbate 80.

3. The components of the colorant, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and polysorbate 80, should be included in the inactive ingredient list for the 600 mg tablet.

4. The list of inactive ingredients for the 600 mg tablet concludes with,"... and magnesium stearate." "And" should be deleted to be consistent with the list of inactive ingredients for the 300 and 400 mg tablet, and magnesium stearate should be listed in alphabetical order in the inactive ingredients list for the 600 mg tablet. Also, if please list this ingredient by its common name.

5. The fourth paragraph in the DESCRIPTION section should be changed to state that

Accordingly, the supplemental application is approved effective on the date of this letter.

These revisions are terms of the approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-738/S-004." Approval of this submission by FDA is not required before the labeling is used.

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. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Sincerely yours,

/S/ 5/27/99

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

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER:NDA 20738/S004

## FINAL PRINTED LABELING

Labeling: original
NDA No. 20-738 Rec'd. 10-28-99
Reviewed by: [signature] 11/30/99

TEVETEN
50186US2

# TEVETEN

brand of
eprosartan mesylate
tablets
400 mg and 600 mg

50186US2

**PRESCRIBING INFORMATION**

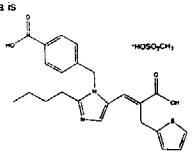
**1E Rev 7/99**

**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, TEVETEN® Tablets should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

## DESCRIPTION

TEVETEN® (eprosartan mesylate) Tablet is a non-biphenyl non-tetrazole angiotensin II receptor ($AT_1$) antagonist. A selective non-peptide molecule, TEVETEN® Tablets are chemically described as the monomethanesulfonate of (*E*)-2-butyl-1-(*p*-carboxybenzyl)-α-2-thienylmethylimidazole-5-acrylic acid.

Its empirical formula is $C_{23}H_{24}N_2O_4S{\cdot}CH_4O_3S$ and molecular weight is 520.625. Its structural formula is




Eprosartan mesylate is a white to off-white free-flowing crystalline powder that is insoluble in water, freely soluble in ethanol, and melts between 248°C and 250°C.

TEVETEN® Tablets are available as aqueous film-coated tablets containing eprosartan mesylate equivalent to 400 mg or 600 mg eprosartan zwitterion (pink, scored Tiltab®, oval or white capsule-shaped tablets, respectively). **Inactive Ingredients:** The 400 mg tablet contains the following: croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide. The 600 mg tablet contains crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [kininase II]), a potent vasoconstrictor, is the principal pressor agent of the renin-angiotensin system. Angiotensin II also stimulates aldosterone synthesis and secretion by the adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Eprosartan blocks 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. Eprosartan does not exhibit any partial agonist activity at the $AT_1$ receptor. Its affinity for the $AT_1$ receptor is 1,000 times greater than for the $AT_2$ receptor. *In vitro* binding studies indicate that eprosartan is a reversible, competitive inhibitor of the $AT_1$ receptor.

Blockade of the $AT_1$ receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effect of eprosartan on blood pressure.

TEVETEN® (eprosartan mesylate) Tablets do not inhibit kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin; whether this has clinical relevance is not known. It does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

### Pharmacokinetics

***General***

Absolute bioavailability following a single 300 mg oral dose of eprosartan is approximately 13%. Eprosartan plasma concentrations peak at 1 to 2 hours after an oral dose in the fasted state. Administering eprosartan with food delays absorption, and causes variable changes (<25%) in $C_{max}$ and AUC values which do not appear clinically important. Plasma concentrations of eprosartan increase in a slightly less than dose-proportional manner over the 100 mg to 800 mg dose range. The terminal elimination half-life of eprosartan following oral administration is typically 5 to 9 hours. Eprosartan does not significantly accumulate with chronic use.

***Metabolism and Excretion***

Eprosartan is eliminated by biliary and renal excretion, primarily as unchanged compound. Less than 2% of an oral dose is excreted in the urine as a glucuronide. There are no active metabolites following oral and intravenous dosing with [$^{14}$C] eprosartan in human subjects. Eprosartan was the only drug-related compound found in the plasma and feces. Following intravenous [$^{14}$C] eprosartan, about 61% of the material is recovered in the feces and about 37% in the urine. Following an oral dose of [$^{14}$C] eprosartan, about 90% is recovered in the feces and about 7% in the urine. Approximately 20% of the radioactivity excreted in the urine was an acyl glucuronide of eprosartan with the remaining 80% being unchanged eprosartan.

***Distribution***

Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses.

The pooled population pharmacokinetic analysis from two Phase 3 trials of 299 men and 172 women with mild to moderate hypertension (aged 20 to 93 years) showed that eprosartan exhibited a population mean oral clearance (CL/F) for an average 60-year-old patient of 48.5 L/hr. The population mean steady-state volume of distribution (Vss/F) was 308 liters. Eprosartan pharmacokinetics were not influenced by weight, race, gender or severity of hypertension at baseline. Oral clearance was shown to be a linear function of age with CL/F decreasing 0.62 L/hr. for every year increase.

### Special Populations

***Pediatric:*** Eprosartan pharmacokinetics have not been investigated in patients younger than 18 years of age.

***Geriatric:*** Following single oral dose administration of eprosartan to healthy elderly men (aged 68 to 78 years), AUC, $C_{max}$, and $T_{max}$ eprosartan values increased, on average by approximately twofold, compared to healthy young men (aged 20 to 39 years) who received the same dose. The extent of plasma protein binding was not influenced by age.

***Gender:*** There was no difference in the pharmacokinetics and plasma protein binding between men and women following single oral dose administration of eprosartan.

***Race:*** A pooled population pharmacokinetic analysis of 442 Caucasian and 29 non-Caucasian hypertensive patients showed that oral clearance and steady-state volume of distribution were not influenced by race.

***Renal Insufficiency:*** Following administration of eprosartan 200 mg b.i.d. for 7 days, patients with mild renal impairment ($CL_{cr}$ 60 to 80 mL/min.) showed mean eprosartan $C_{max}$ and AUC values similar to subjects with normal renal function. Compared to patients with normal renal function, mean AUC and $C_{max}$ values were approximately 30% higher in patients with moderate renal impairment ($CL_{cr}$ 30 to 59 mL/min.) and 50% higher in patients with severe renal impairment ($CL_{cr}$ 5 to 29 mL/min.). The unbound eprosartan fraction was not influenced by mild to moderate renal impairment but increased approximately twofold in a few patients with severe renal impairment. No dosage adjustment is necessary for patients with renal impairment. Eprosartan was poorly removed by hemodialysis ($CL_{HD}$ <1 L/hr.) (see DOSAGE AND ADMINISTRATION).

***Hepatic Insufficiency:*** Eprosartan AUC (but not $C_{max}$) values increased, on average, by approximately 40% in men with decreased hepatic function compared to healthy men after a single 100 mg oral dose of eprosartan. Hepatic disease was defined as a documented clinical history of chronic hepatic abnormality diagnosed by liver biopsy, liver/spleen scan or clinical laboratory tests. The extent of eprosartan plasma protein binding was not influenced by hepatic dysfunction. No dosage adjustment is necessary for patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

### Drug Interactions

Concomitant administration of eprosartan and digoxin had no effect on single oral-dose digoxin pharmacokinetics. Concomitant administration of eprosartan and warfarin had no effect on steady-state prothrombin time ratios (INR) in healthy volunteers. Concomitant administration of eprosartan and glyburide in diabetic patients did not affect 24-hour plasma glucose profiles. Eprosartan pharmacokinetics were not affected by concomitant administration of ranitidine. Eprosartan did not inhibit human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E and 3A *in vitro*. Eprosartan is not metabolized by the cytochrome P450 system; eprosartan steady-state concentrations were not affected by concomitant administration of ketoconazole or fluconazole, potent inhibitors of CYP3A and 2C9, respectively.

### Pharmacodynamics and Clinical Effects

Eprosartan inhibits the pharmacologic effects of angiotensin II infusions in healthy adult men. Single oral doses of eprosartan from 10 mg to 400 mg have been shown to inhibit the vasopressor, renal vasoconstrictive and aldosterone secretory effects of infused angiotensin II with complete inhibition evident at doses of 350 mg and above. Eprosartan inhibits the pressor effects of angiotensin II infusions. A single oral dose of 350 mg of eprosartan inhibits pressor effects by approximately 100% at peak, with approximately 30% inhibition persisting for 24 hours. The absence of angiotensin II $AT_1$ agonist activity has been demonstrated in healthy adult men. In hypertensive patients treated chronically with eprosartan, there was a twofold rise in angiotensin II plasma concentration and a twofold rise in plasma renin activity, while plasma aldosterone levels remained unchanged. Serum potassium levels also remained unchanged in these patients.

Achievement of maximal blood pressure response to a given dose in most patients may take 2 to 3 weeks of treatment. Onset of blood pressure reduction is seen within 1 to 2 hours of dosing with few instances of orthostatic hypotension. Blood pressure control is maintained with once- or twice-daily dosing over a 24-hour period. Discontinuing treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

There was no change in mean heart rate in patients treated with eprosartan in controlled clinical trials.

Eprosartan increases mean effective renal plasma flow (ERPF) in salt-replete and salt-restricted normal subjects. A dose-related increase in ERPF of 25% to 30% occurred in salt-restricted normal subjects, with the effect plateauing between 200 mg and 400 mg doses. There was no change in ERPF in hypertensive patients and patients with renal insufficiency on normal salt diets. Eprosartan did not reduce glomerular filtration rate in patients with renal insufficiency or in patients with hypertension, after 7 days and 28 days of dosing, respectively. In hypertensive patients and patients with chronic renal insufficiency, eprosartan did not change fractional excretion of sodium and potassium.

Eprosartan (1200 mg once daily for 7 days or 300 mg twice daily for 28 days) had no effect on the excretion of uric acid in healthy men; patients with essential hypertension or those with varying degrees of renal insufficiency.

There were no effects on mean levels of fasting triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol or fasting glucose.

### Clinical Trials

The safety and efficacy of TEVETEN® (eprosartan mesylate) Tablets have been evaluated in controlled clinical trials worldwide that enrolled predominantly hypertensive patients with sitting DBP ranging from 95 mmHg to ≤115 mmHg. There is also some experience with use of eprosartan together with other antihypertensive drugs in more severe hypertension.

The antihypertensive effects of TEVETEN® Tablets were demonstrated principally in five placebo-controlled trials (4 to 13 weeks duration) including dosages of 400 mg to 1200 mg given once daily (two studies), 25 mg to 400 mg twice daily (two studies), and one study comparing total daily doses of 400 mg to 800 mg given once daily or twice daily. The five studies included 1,111 patients randomized to eprosartan and 395 patients randomized to placebo. The studies showed dose-related antihypertensive responses.

At study endpoint, patients treated with TEVETEN® Tablets at doses of 600 mg to 1200 mg given once daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough, with differences from placebo of approximately 5-10/3-6 mmHg. Limited experience is available with the dose of 1200 mg administered once daily. In a direct comparison of 200 mg to 400 mg b.i.d. with 400 mg to 800 mg q.d. of TEVETEN® Tablets, effects at trough were similar. Patients treated with TEVETEN® Tablets at doses of 200 mg to 400 mg given twice daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough, with differences from placebo of approximately 7-10/4-6 mmHg.

Peak (1 to 3 hours) effects were uniformly, but moderately, larger than trough effects with b.i.d. dosing, with the trough-to-peak ratio for diastolic blood pressure 65% to 80%. In the once-daily dose-response study, trough-to-peak response of ≤50% were observed at some doses (including 1200 mg), suggesting attenuation of effect at the end of the dosing interval.

The antihypertensive effect of TEVETEN® Tablets was similar in men and women, but was somewhat smaller in patients over 65. There were too few black subjects to determine whether their response was similar to Caucasians. In general, blacks (usually a low renin population) have had smaller responses to ACE inhibitors and angiotensin II inhibitors than Caucasian populations.

Angiotensin-converting enzyme (ACE) inhibitor-induced cough (a dry, persistent cough) can lead to discontinuation of ACE inhibitor therapy. In one study, patients who had previously coughed while taking an ACE inhibitor were treated with eprosartan, an ACE inhibitor (enalapril) or placebo for six weeks. The incidence of dry, persistent cough was 2.2% on eprosartan, 4.4% on placebo, and 20.5% on the ACE inhibitor; $P=0.008$ for the comparison of eprosartan with enalapril. In a second study comparing the incidence of cough in 259 patients treated with eprosartan to 261 patients treated with the ACE inhibitor enalapril, the incidence of dry, persistent cough in eprosartan-treated patients (1.5%) was significantly lower ($P=0.018$) than that observed in patients treated with the ACE inhibitor (5.4%). In addition, analysis of overall data from six double-blind clinical trials involving 1,554 patients showed an incidence of spontaneously reported cough in patients treated with eprosartan of 3.5%, similar to placebo (2.6%).

## INDICATIONS AND USAGE

TEVETEN® Tablets are indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensives such as diuretics and calcium channel blockers.

## CONTRAINDICATIONS

TEVETEN® Tablets are contraindicated in patients who are hypersensitive to this product or any of its components.

## WARNINGS

### Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, TEVETEN® (eprosartan mesylate) Tablets 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 advise the patient to discontinue the use of eprosartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, TEVETEN® Tablets should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate.

depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Eprosartan mesylate has been shown to produce maternal and fetal toxicities (maternal and fetal mortality, low maternal body weight and food consumption, resorptions, abortions and litter loss) in pregnant rabbits given oral doses as low as 10 mg eprosartan/kg/day. No maternal or fetal adverse effects were observed at 3 mg/kg/day; this oral dose yielded a systemic exposure (AUC) to unbound eprosartan 0.8 times that achieved in humans given 400 mg b.i.d. No adverse effects on *in utero* or postnatal development and maturation of offspring were observed when eprosartan mesylate was administered to pregnant rats at oral doses up to 1000 mg eprosartan/kg/day (the 1000 mg eprosartan/kg/day dose in non-pregnant rats yielded systemic exposure to unbound eprosartan approximately 0.6 times the exposure achieved in humans given 400 mg b.i.d.).

**Hypotension in Volume- and/or Salt-Depleted Patients**
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of TEVETEN® Tablets, or the treatment should start under close medical supervision. If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

## PRECAUTIONS

**Risk of Renal Impairment**
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with angiotensin II antagonists; 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 and angiotensin II receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. TEVETEN® (eprosartan mesylate) Tablets would be expected to behave similarly.

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 angiotensin II antagonists; 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 so that treatment may be discontinued under medical supervision.

**Drug Interactions**
Eprosartan has been shown to have no effect on the pharmacokinetics of digoxin and the pharmacodynamics of warfarin and glyburide. Thus, no dosing adjustments are necessary during concomitant use with these agents. Because eprosartan is not metabolized by the cytochrome P450 system, inhibitors of CYP450 enzyme would not be expected to affect its metabolism, and ketoconazole and fluconazole, potent inhibitors of CYP3A and 2C9, respectively, have been shown to have no effect on eprosartan pharmacokinetics. Ranitidine also has no effect on eprosartan pharmacokinetics.

Eprosartan (up to 400 mg b.i.d. or 800 mg q.d.) doses have been safely used concomitantly with a thiazide diuretic (hydrochlorothiazide). Eprosartan doses of up to 300 mg b.i.d. have been safely used concomitantly with sustained-release calcium channel blockers (sustained-release nifedipine) with no clinically significant adverse interactions.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Eprosartan mesylate was not carcinogenic in dietary restricted rats or *ad libitum* fed mice dosed at 600 mg and 2000 mg eprosartan/kg/day, respectively, for up to 2 years. In male and female rats, the systemic exposure (AUC) to unbound eprosartan at the dose evaluated was only approximately 20% of the exposure achieved in humans given 400 mg b.i.d. In mice, the systemic exposure (AUC) to unbound eprosartan was approximately 25 times the exposure achieved in humans given 400 mg b.i.d.

Eprosartan mesylate was not mutagenic *in vitro* in bacteria or mammalian cells (mouse lymphoma assay). Eprosartan mesylate also did not cause structural chromosomal damage *in vivo* (mouse micronucleus assay). In human peripheral lymphocytes *in vitro*, eprosartan mesylate was equivocal for clastogenicity with metabolic activation, and was negative without metabolic activation. In the same assay, eprosartan mesylate was positive for polyploidy with metabolic activation and equivocal for polyploidy without metabolic activation.

Eprosartan mesylate had no adverse effects on the reproductive performance of male or female rats at oral doses up to 1000 mg eprosartan/kg/day. This dose provided systemic exposure (AUC) to unbound eprosartan approximately 0.6 times the exposure achieved in humans given 400 mg b.i.d.

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

**Nursing Mothers**
Eprosartan is excreted in animal milk; it is not known whether eprosartan is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from eprosartan, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**
Of the total number of patients receiving TEVETEN® Tablets in clinical studies, 29% (681 of 2,334) were 65 years and over, while 5% (124 of 2,334) were 75 years and over. Based on the pooled data from randomized trials, the decrease in diastolic blood pressure and systolic blood pressure with TEVETEN® Tablets was slightly less in patients ≥65 years of age compared to younger patients. In a study of only patients over the age of 65, TEVETEN® Tablets at 200 mg twice daily (and increased optionally up to 300 mg twice daily) decreased diastolic blood pressure on average by 3 mmHg (placebo corrected). Adverse experiences were similar in younger and older patients.

## ADVERSE REACTIONS

TEVETEN® Tablets have been evaluated for safety in more than 3,300 healthy volunteers and patients worldwide, including more than 1,460 patients treated for more than 6 months, and more than 980 patients treated for 1 year or longer. TEVETEN® Tablets were well tolerated at doses up to 1200 mg daily. Most adverse events were of mild or moderate severity and did not require discontinuation of therapy. The overall incidence of adverse experiences and the incidences of specific adverse events reported with eprosartan were similar to placebo.

Adverse experiences were similar in patients regardless of age, gender, or race. Adverse experiences were not dose-related.

In placebo-controlled clinical trials, about 4% of 1,202 of patients treated with TEVETEN® Tablets discontinued therapy due to clinical adverse experiences, compared to 6.5% of 352 patients given placebo.

**Adverse Events Occurring at an Incidence of 1% or More Among Eprosartan-treated Patients:** The following table lists adverse events that occurred at an incidence of 1% or more among eprosartan-treated patients who participated in placebo-controlled trials of 8 to 13 weeks' duration, using doses of 25 mg to 400 mg twice daily, and 400 mg to 1200 mg once daily. The overall incidence of adverse events reported with TEVETEN® Tablets (54.4%) was similar to placebo (52.8%).

**Table 1. Adverse Events Reported by ≥1% of Patients Receiving TEVETEN® (eprosartan mesylate) Tablets and Were More Frequent on Eprosartan than Placebo**

| | Incidence | |
|---|---|---|
| **Event** | **Eprosartan (n=1,202) %** | **Placebo (n=352) %** |
| **Body as a Whole** | | |
| Infection viral | 2 | 1 |
| Injury | 2 | 1 |
| Fatigue | 2 | 1 |
| **Gastrointestinal** | | |
| Abdominal pain | 2 | 1 |
| **Metabolic and Nutritional** | | |
| Hypertriglyceridemia | 1 | 0 |
| **Musculoskeletal** | | |
| Arthralgia | 2 | 1 |
| **Nervous System** | | |
| Depression | 1 | 0 |
| **Respiratory** | | |
| Upper respiratory tract infection | 8 | 5 |
| Rhinitis | 4 | 3 |
| Pharyngitis | 4 | 3 |
| Coughing | 4 | 3 |
| **Urogenital** | | |
| Urinary tract infection | 1 | 0 |

The following adverse events were also reported at a rate of 1% or greater in patients treated with eprosartan, but were as, or more, frequent in the placebo group: headache, myalgia, dizziness, sinusitis, diarrhea, bronchitis, dependent edema, dyspepsia, chest pain.

Facial edema was reported in 5 patients receiving eprosartan. Angioedema has been reported with other angiotensin II antagonists.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to eprosartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether events were causally related to eprosartan:

*Body as a Whole:* alcohol intolerance, asthenia, substernal chest pain, peripheral edema, fatigue, fever, hot flushes, influenza-like symptoms, malaise, rigors, pain;

*Cardiovascular:* angina pectoris, bradycardia, abnormal ECG, specific abnormal ECG, extrasystoles, atrial fibrillation, hypotension, tachycardia, palpitations;

*Gastrointestinal:* anorexia, constipation, dry mouth, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, nausea, periodontitis, toothache, vomiting;

*Hematologic:* anemia, purpura;

*Liver and Biliary:* increased SGOT, increased SGPT;

*Metabolic and Nutritional:* increased creatine phosphokinase, diabetes mellitus, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperkalemia, hypokalemia, hyponatremia;

*Musculoskeletal:* arthritis, aggravated arthritis, arthrosis, skeletal pain, tendinitis, back pain;

*Nervous System/Psychiatric:* anxiety, ataxia, insomnia, migraine, neuritis, nervousness, paresthesia, somnolence, tremor, vertigo;

*Resistance Mechanism:* herpes simplex, otitis externa, otitis media, upper respiratory tract infection;

*Respiratory:* asthma, epistaxis;

*Skin and Appendages:* eczema, furunculosis, pruritus, rash, maculopapular rash, increased sweating;

*Special Senses:* conjunctivitis, abnormal vision, xerophthalmia, tinnitus;

*Urinary:* albuminuria, cystitis, hematuria, micturition frequency, polyuria, renal calculus, urinary incontinence;

*Vascular:* leg cramps, peripheral ischemia.

***Laboratory Test Findings:*** In placebo-controlled studies, clinically important changes in standard laboratory parameters were rarely associated with administration of TEVETEN® (eprosartan mesylate) Tablets. Patients were rarely withdrawn from TEVETEN® Tablets because of laboratory test results.

***Creatinine, Blood Urea Nitrogen:*** Minor elevations in creatinine and in BUN occurred in 0.6% and 1.3%, respectively, of patients taking TEVETEN® Tablets and 0.9% and 0.3%, respectively, of patients given placebo in controlled clinical trials. Two patients were withdrawn from clinical trials for elevations in serum creatinine and BUN, and three additional patients were withdrawn for increases in serum creatinine.

***Liver Function Tests:*** Minor elevations of ALAT, ASAT, and alkaline phosphatase occurred for comparable percentages of patients taking TEVETEN® (eprosartan mesylate) Tablets or placebo in controlled clinical trials. An elevated ALAT of >3.5 x ULN occurred in 0.1% of patients taking TEVETEN® Tablets (one patient) and in no patient given placebo in controlled clinical trials. Four patients were withdrawn from clinical trials for an elevation in liver function tests.

***Hemoglobin:*** A greater than 20% decrease in hemoglobin was observed in 0.1% of patients taking TEVETEN® Tablets (one patient) and in no patient given placebo in controlled clinical trials. Two patients were withdrawn from clinical trials for anemia.

***Leukopenia:*** A WBC count of $\leq 3.0 \times 10^3/mm^3$ occurred in 0.3% of patients taking TEVETEN® Tablets and in 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for leukopenia.

***Neutropenia:*** A neutrophil count of $\leq 1.5 \times 10^3/mm^3$ occurred in 1.3% of patients taking TEVETEN® Tablets and in 1.4% of patients given placebo in controlled clinical trials. No patient was withdrawn from any clinical trials for neutropenia.

***Thrombocytopenia:*** A platelet count of $\leq 100 \times 10^9/L$ occurred in 0.3% of patients taking TEVETEN® Tablets (one patient) and in no patient given placebo in controlled clinical trials. Four patients receiving TEVETEN® Tablets in clinical trials were withdrawn for thrombocytopenia. In one case, thrombocytopenia was present prior to dosing with TEVETEN® Tablets.

***Serum Potassium:*** A potassium value of ≥5.6 mmol/L occurred in 0.9% of patients taking TEVETEN® Tablets and 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for hyperkalemia and three for hypokalemia.

## OVERDOSAGE

Limited data are available regarding overdosage. Appropriate symptomatic and supportive therapy should be given if overdosage should occur. There was no mortality in rats and mice receiving oral doses of up to 3000 mg eprosartan/kg and in dogs receiving oral doses of up to 1000 mg eprosartan/kg.

## DOSAGE AND ADMINISTRATION

The usual recommended starting dose of TEVETEN® Tablets is 600 mg once daily when used as monotherapy in patients who are not volume-depleted (see WARNINGS, Hypotension in Volume- and/or Salt-Depleted Patients). TEVETEN® Tablets can be administered once or twice daily with total daily doses ranging from 400 mg to 800 mg. There is limited experience with doses beyond 800 mg/day.

If the antihypertensive effect measured at trough using once-daily 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. Achievement of maximum blood pressure reduction in most patients may take 2 to 3 weeks.

TEVETEN® Tablets may be used in combination with other antihypertensive agents such as thiazide diuretics or calcium channel blockers if additional blood-pressure-lowering effect is required. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

*Elderly, Hepatically Impaired or Renally Impaired Patients:*
No initial dosing adjustment is generally necessary for elderly or hepatically impaired patients or those with renal impairment.

TEVETEN® Tablets may be taken with or without food.

## HOW SUPPLIED

TEVETEN® (eprosartan mesylate) Tablets are available as aqueous film-coated tablets as follows:

400 mg pink, scored Tiltab®, oval tablets debossed with 5044 on both sides of the tablet.
NDC 0051-5044-01 (bottles of 100)
NDC 0051-5044-11 (unit dose box of 100)
600 mg white, capsule-shaped tablets, debossed with "SOLVAY" on one side and 5046 on the other.
NDC 0051-5046-01 (bottles of 100)
NDC 0051-5046-11 (unit dose box of 100)

## STORAGE

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

$R_x$ only



Manufactured by:
SmithKline Beecham Pharmaceuticals
Crawley, UK

Marketed by:
UNIMED Pharmaceuticals, Inc.,
A Solvay Pharmaceuticals, Inc. company,
Buffalo Grove, IL 60089-1862

1E Rev 7/99
Printed in U.S.A.

50186US2

NOV 29 1999

Lot:
Exp.:

**400mg**
NDC 0051-5044-01

**TEVETEN**
(eprosartan mesylate) Tablets
100 Tablets Rx only
UNIMED Pharmaceuticals

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].
Each tablet contains eprosartan as the mesylate, 400 mg.
**Dosage:** See accompanying prescribing information.
**Important:** Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Manufactured by:
SmithKline Beecham Pharmaceuticals
Crawley, UK
Marketed by:
UNIMED Pharmaceuticals, Inc.,
A Solvay Pharmaceuticals, Inc. company,
Buffalo Grove, IL 60089-1862
40194US2 40194US2 40194US2 1E Rev 7/99.

Labeling: original
NDA No. 20-738
Date: 10-28-99
Reviewer: C. Tyson 11/24/99

Lot:
Exp.:

**600mg**
NDC 0051-5046-01

**TEVETEN**
(eprosartan mesylate) Tablets
100 Tablets Rx only
UNIMED Pharmaceuticals

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].
Each tablet contains eprosartan as the mesylate, 600 mg.
**Dosage:** See accompanying prescribing information.
**Important:** Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Manufactured by:
SmithKline Beecham Pharmaceuticals
Crawley, UK
Marketed by:
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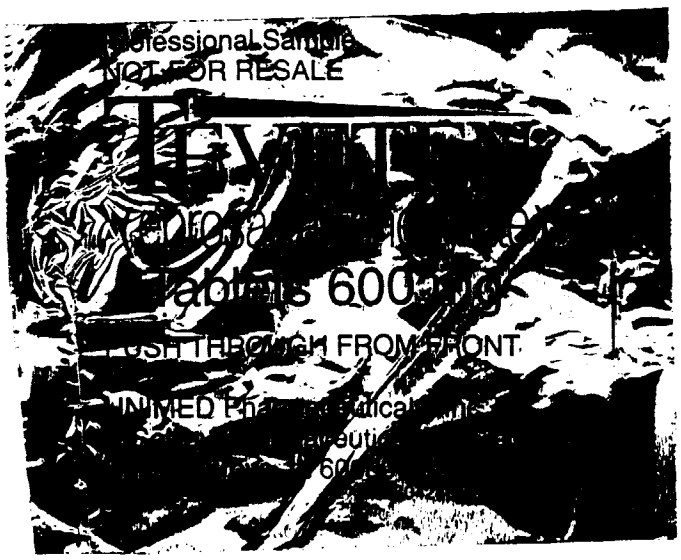
Buffalo Grove, IL 60089-1862
40195US2 40195US2 40195US2 1E Rev 7/99.

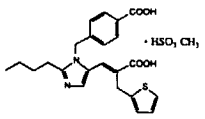


# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20738/S004

## CHEMISTRY REVIEW(S)

MAY 19 1999

| CHEMIST'S REVIEW | 1. ORGANIZATION<br>HFD-110 | 2. NDA Number<br>20-738 |
|---|---|---|
| 3. Name and Address of Applicant (City & State)<br>SmithKline Beecham Pharmaceuticals<br>Collegeville, PA | | 4. Supplement(s)<br>Number(s) Date(s)<br>S-004 25 Jan 99 |
| 5. Drug Name<br>Teveten Tablets | 6. Nonproprietary Name<br>Eprosartan Mesylate | 7. Amendments & Other (reports, etc) - Dates<br>Amendment 9 Mar 99<br>Amendment 10 Mar 99<br>Amendment 2 Apr 99 |
| 8. Supplement Provides For:<br>Manufacture of a 600 mg tablet. | | |
| 9. Pharmacological Category<br>Antihypertensive | 10. How Dispensed<br>[X] Rx [ ] OTC | 11. Related IND(s)/ NDA(s)/DMF(s)<br>DMF DMF<br>DMF DMF<br>DMF DMF<br>DMF DMF<br>DMF |
| 12. Dosage Form(s)<br>TCM | 13. Potency(ies)<br>50, 100, 200, 300, 400 mg | |
| 14. Chemical Name and Structure<br>  <br>(E)-α-[[2-Butyl-1-[(4-carboxyphenyl)methyl]-1*H*-imidazol-5-yl]methylene]-2-thiophenepropionic acid monomethanesulfonate | | 15. Records/Reports Current<br>[X] Yes [ ] No<br>Reviewed<br>[X] Yes [ ] No |

16. Comments

The amendments of 9 Mar and 10 Mar 99 are concerned exclusively with biopharmaceutical issues and are not reviewed herein.

The applicant states that a copy of this supplement has been sent to the San Juan District Office.

The applicant has carried out a bioequivalence study comparing the blood levels of 2 x 300 mg tablets (manufactured at [ ] with the proposed commercial 600 mg tablet (formulation BD), and another 600 mg tablet (formulation BN). Dr. Fadiran reviewed the results of this study and determined that the 600 mg tablets are bioequivalent to 2 x 300 mg tablets. He also determined that the dissolution profile provided for the 300 mg tablets manufactured at [ ] is similar to the profile for the commercial 300 mg tablets manufactured at Crawley, UK.

17. Conclusions and Recommendations

Approval is recommended. However a number of changes need to be made in the DESCRIPTION section of the Package Insert.

18. REVIEWER

Name James H. Short /S/ Date Completed 19 May 99

Distribution: [X] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO

jhs/2/9/99/N20-738.S04

/S/
5-19-99

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER:NDA 20738/S004

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAR 25 1999

# CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

**NDA 20-738 (SCM 004)** **SUBMISSION DATES:** January 25, 1999.
Teveten® (Eprosartan mesylate) Tablets March 9, 1999
March 10, 1999

SMITHKLINE BEECHAM **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

**TYPE OF SUBMISSION:** NDA SUPPLEMENT

**BACKGROUND:**

Eprosartan is a selective non-peptide angiotensin II receptor antagonist ($AT_1$) recently approved (Teveten tablets) for the treatment of hypertension. The original NDA requested approval for the 200, 300 and 400 mg eprosartan tablets. The sponsor now intends to market a 600 mg tablet in order to increase patient compliance and has conducted a clinical study to determine the bioequivalence of two different test tablet formulations (600 mg-BD (proposed commercial formulation) and 600 mg-BN) of eprosartan relative to the 300 mg (2x300 mg) commercial formulation of eprosartan. The 600 mg tablet utilizes crospovidone as the tablet disintegrant, instead of croscarmellose sodium used in the approved 200, 300 and 400 mg tablets. The approved manufacturing site for the Teveten tablets is Crawley, UK but the new 600 mg tablet and 300 mg tablet used for the bioequivalence study were manufactured at the new approved site at [ ]. The sponsor has submitted comparative dissolution data on the 300 mg Tablets manufactured at both sites.

**SYNOPSIS:**

This was a randomized, open-label, three-period, period-balanced crossover study 61 healthy subjects. Each subject received a single 600 mg oral dose of eprosartan, administered as one of three regimens: (A) eprosartan 1x600 mg, test formulation (Formula BD); (B) eprosartan 1x600 mg, test formulation (Formula BN); (c) eprosartan 2x300 mg, commercial formulation. The summary of the review is attached (Appendix). The 600 mg tablet (Formula BD) of eprosartan is bioequivalent to the approved 300 mg commercial tablet formulation (Formula AU).

Comparative dissolution data showed that the 300 mg tablet manufactured at [ ] (used for the bioequivalenc study) has a similar dissolution profile to commercial 300 mg tablet manufactured at Crawley, UK.

The proposed 600 mg tablet formulation meets the approved dissolution specification for Teveten tablets of Q[ ] % at [ ] minutes.

**RECOMMENDATIONS:**

The Division of Pharmaceutical Evaluation I has completed the review of the sponsor's supplement and recommends the approval of the 600 mg (Formula BD) commercial formulation of Teveten tablets. The approved dissolution method and specification for Teveten tablets of Q[ ] % at [ ] minutes should be used for the proposed 600 mg tablet formulation.

/S/ 3/24/99

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

FT Initialed by P. Marroum, Ph.D. /S/ 3/25/1999

cc: NDA 20-738, HFD-110, HFD-860 (Fadiran), Srinivasachar (Chemistry Team Leader, HFD-110), CDR (Attn: Barbara Murphy).

**BIOAVAILABILITY / BIOEQUIVALENCE STUDY**

**STUDY 108566/ 127**

**INVESTIGATOR AND LOCATION:**

**STUDY DATE**: May to July 1998.

**OBJECTIVE:** (1) To estimate the bioequivalence of two different 600 mg reduced weight tablet formulations (600 mg-BD and 600 mg-BN) relative to the 300 mg (2x300 mg) commercial formulation of eprosartan in healthy vounteers, and (2) To assess the safety and tolerability of eprosartan in healthy male volunteers.

**FORMULATIONS:**
(1) Eprosartan 300 mg tablet, Formula AU, Batch no. U-98057 (commercial formulation)
(2) Eprosartan 600 mg tablet, Formula BD, Batch no. U-98058 (commercial formulation)
(3) Eprosartan 600 mg tablet, Formula BN, Batch no. U-98068

**STUDY DESIGN:**
A randomized, open-label, three-period, period-balanced crossover study 61 healthy subjects. Each subject received a single 600 mg oral dose of eprosartan, administered as one of three regimens: (A) eprosartan 1x600 mg, test formulation (Formula BD); (B) eprosartan 1x600 mg, test formulation (Formula BN); (c) eprosartan 2x300 mg, commercial formulation.
Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24 and 32 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

**ASSAYS:**

**DATA ANALYSIS**: $AUC_{0\text{-}inf}$, Cmax, and Tmax were calculated.

**RESULTS**: Tables 1- 4 and Figures 1- 3 summarize the pharmacokinetic and dissolution data obtained from the study.

**Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers**

| PARAMETER | TREATMENT A | TREATMENT B | TREATMENT C | 90% CI (A/C) |
|---|---|---|---|---|
| Cmax (ng/ml) | 2527 (1208) | 3331 (1311) | 2462 (1223) | 94 - 114 |
| $AUC_{(0\text{-}inf)}$ (ng*h/ml) | 10192 (5111) | - | 10355 (6533) | 93 - 110 |
| $T_{max}$ (h)* | 1.5 (0.5-6.0) | 1.5 (0.5-4.0) | 1.5 (0.9-6.0 | - |

TREATMENT A = 1 x 600 mg tablet (Formula BD)
TREATMENT B = 1 x 600 mg tablet (Formula BN)
TREATMENT C = 1 x 100 mg tablet (Formula AF)
*Median (range)

**Figure 1.**

**Mean Plasma Concentration-Time Profiles for Eprosartan**

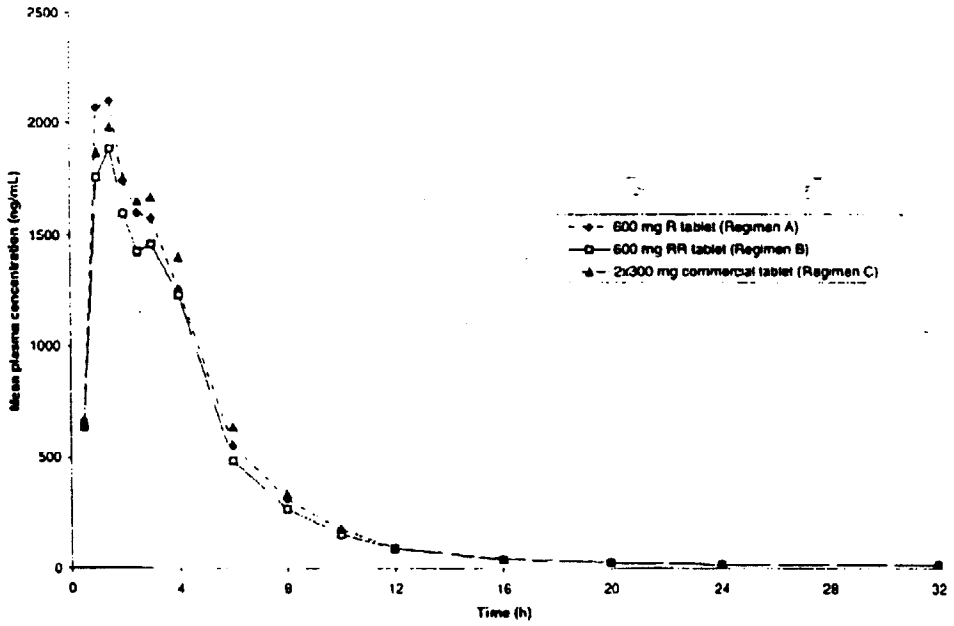


Table 2:

**Comparative In-vitro Dissolution Profiles for the 600 mg Teveten Tablet vs the 300 mg Commercial Formula Teveten Tablet**

**300 mg Commercial Formula, Batch U98057, 0.2M Phosphate Buffer pH 7.5 USP Apparatus 2, 100 RPM**

| Tablet # | 10 min | 20 min | 30 min | 45 min | 60 min |
|---|---|---|---|---|---|
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | | | | | |
| 8 | | | | | |
| 9 | | | | | |
| 10 | | | | | |
| 11 | | | | | |
| 12 | | | | | |
| Average: | 95 | 97 | 98 | 99 | 99 |

**600 mg Formula, Batch U98058, 0.2M Phosphate Buffer pH 7.5, USP Apparatus 2, 100 RPM**

| | 10 min | 20 min | 30 min | 45 min | 60 min |
|---|---|---|---|---|---|
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | | | | | |
| 8 | | | | | |
| 9 | | | | | |
| 10 | | | | | |
| 11 | | | | | |
| 12 | | | | | |
| Average | 84 | 91 | 94 | 95 | 96 |

Figure 2:

**Comparative In-vitro Dissolution Profiles for the 600 mg Teveten Tablet vs the 300 mg Commercial Formula Teveten® Tablet**

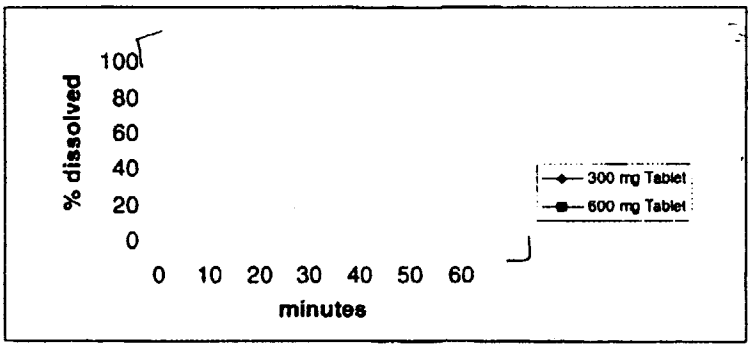


Table 3:

**Dissolution f2 similarity factor**

**300mg Cidra Batch U98057 vs 300mg Crawley Batch 0589590**

| Time | Cidra % Dissolved | Crawley % Dissolved | f2 | (R1-T1)^2 |
|---|---|---|---|---|
| 15 min* | | | | |
| 30 min | | | | |
| 45 min | | | | |

**f2 for the full profile as per SUPAC =**

*Note: The 15 minute value for the Cidra data was extrapolated.

Table 4:

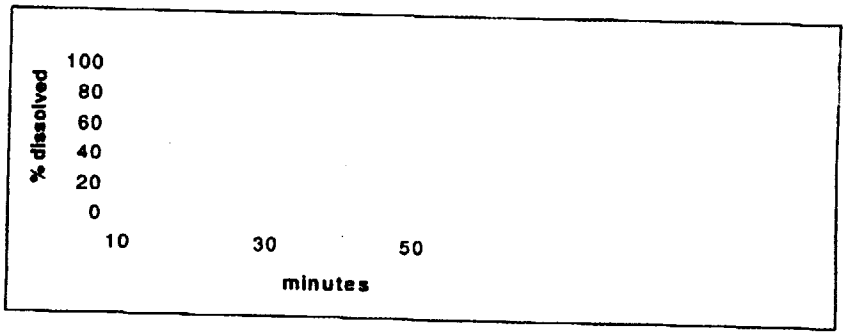
**Comparative In-vitro Dissolution Profiles for the 300 mg Teveten Tablet Manufactured at Crawley, UK vs the 300 mg Teveten Tablet Manufactured at Cidra, PR**

| **300 mg Cidra Tablet, Batch U98057** | | |
|---|---|---|
| Tablet # | 30 min | 45 min |
| 1 | | |
| 2 | | |
| 3 | | |
| 4 | | |
| 5 | | |
| 6 | | |
| Average | 98 | 99 |
| **300 mg Crawley Tablet, Batch 0589590** | | |
| | 30 min | 45 min |
| 1 | | |
| 2 | | |
| 3 | | |
| 4 | | |
| 5 | | |
| 6 | | |
| Average | 104 | 104 |

*0.2M Phosphate Buffer pH 7.5, USP Apparatus 2, 100 RPM

Figure 3:

**Comparative In-vitro Dissolution Profiles for the 300 mg Cidra, PR Tablet vs 300 mg Crawley, UK Tablet**



**CONCLUSIONS:** The results obtained from the study show that the 600 mg tablet (Formula BD) of eprosartan is bioequivalent to the approved 300 mg commercial tablet formulation (Formula AU). Comparative dissolution data showed that the 300 mg tablet manufactured at [redacted] used for the bioequivalenc study) has a similar dissolution profile to commercial 300 mg tablet manufactured at Crawley, UK.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20738/S004

## CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 29 1999

NDA 20-738/S-004

UNIMED Pharmaceuticals, Inc.
Attention: Ms. Judy Athey
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862

Dear Ms. Athey:

We acknowledge the receipt of your October 27, 1999 submission containing final printed labeling in response to our May 27, 1999 letter approving your supplemental new drug application (S-004) for Teveten (eprosartan mesylate) Tablets.

We have reviewed the labeling that you submitted in accordance with our May 27, 1999 approval letter and we find it acceptable.

In a conversation on November 22, 1999 between Ms. Judy Athey of UNIMED and Edward Fromm of DCRDP, it was agreed to change the following paragraphs in the **DESCRIPTION** section at the next printing from:

1.

to:

Teveten® Tablets are available as aqueous film-coated tablets containing eprosartan mesylate equivalent to 400 mg or 600 mg eprosartan zwitterion (pink, oval, scored Tiltab® or white, non-scored, capsule-shaped tablets, respectively).

2.

to:

The 400 mg tablet contains the following: croscarmellose sodium, hydroxpropyl methylcellulose, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide.

It was also agreed to change, at the next printing, the 600 mg Tablet description in the **HOW SUPPLIED** section from:

to:

600 mg white, non-scored, capsule-shaped tablets, debossed with "SOLVAY" on one side and 5046 on the other.

If you have any questions, please contact:

Mr. Edward Fromm
Consumer Safety Officer
(301) 594-5313

Sincerely,

/S/ 11-29-99

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I
Division of Cardio-Renal Drug Products (HFD-110)
Office of New Drug Chemistry
Center for Drug Evaluation and Research