CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20738

ADMINISTRATIVE DOCUMENTS

698

REQUEST FOR TRADEMARK REVIEW

NOV 18 1996

TO: Labeling and Nomenclature Committee
Attention: Dan Boring HFD-530

FROM: Division of: Cardio-Renal Drug Products HFD-110
Attention: Robert Wolters Phone: 594-5376

DATE: October 16, 1996

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Teveten NDA/ANDA 20-738

Company Name: Smithkline Beecham

Established name, including dosage form:
Eprosartan Mesylate Tablets 300 & 400 mg

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy):
Angiotensin II receptor antagonist Hypertension

Initial comments from the submitter: (concerns, observations, etc.)

This name was previously reviewed under the IND at the May meeting. See Consult # 625

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. Dec.95

APPEARS THIS WAY
ON ORIGINAL

Consult #698 (HFD-110)

TEVETEN eprosarten mesylate tablets, 300, and 400 mg

There were no look-alike/sound-alike conflicts or misleading aspects noted with the proposed proprietary name.

The Committee has no reason to find the proposed proprietary name unacceptable

W C Boring 11/18/96, Chair
CDER Labeling and Nomenclature Committee

EXCLUSIVITY SUMMARY for NDA # 20-738 **SUPPL #** _____

Trade Name Teveten **Generic Name** eprosartan mesylate
Applicant Name SmithKline Beecham Pharmaceuticals **HFD-** 110

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Diana M Willard August 13, 1997

Signature Date

Title: Regulatory Health Project Manager

Robert L Temple for RJL Apicella 12/23/97

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

8/8/95

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-738 Trade (generic) names Teveten Tablets (eprosartan mesylate)

Check any of the following that apply and explain, as necessary, on the next page:

__✓__ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__✓__ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

9/10/97
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

NDA 20-738

Teveten™

Eprosartan Mesylate Tablets

DEBARMENT STATEMENT

SMITHKLINE BEECHAM PHARMACEUTICALS HEREBY CERTIFIES THAT SAID APPLICANT DID NOT USE IN ANY CAPACITY THE SERVICES OF ANY PERSON DEBARRED UNDER SUBSECTION (A) OR (B) [SECTION 306(A) OR (B) OF THE ACT], IN CONNECTION WITH THE NEW DRUG APPLICATION FOR TEVETEN™ (EPROSARTAN MESYLATE) TABLETS. THE APPLICANT FURTHER CERTIFIES THAT NO SUCH PERSON DEBARRED BY THE FOOD AND DRUG ADMINISTRATION WILL BE USED IN ANY CAPACITY IN FUTURE INVESTIGATIONS INVOLVING THIS DRUG PRODUCT, AT SUCH TIME AS SAID DEBARMENT BECOMES KNOWN TO THE SPONSOR.

DEC 11 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Final Safety Update of Teveten™

NDA #20,738 Teveten™ (eprosartan)
Date of submission: November 7, 1997
Reviewer: Maryann Gordon, MD 12-11-97

Summary

No new concerns regarding the safety of eprosartan in hypertension have been brought forth by the final safety update. The summary statements presented in the safety review dated July 30, 1997 remain unchanged.

Introduction

This final safety update includes data from a total of 17 Phase II/III hypertension trials (up from 15) collected through May 30, 1997. The number of eprosartan patients has been increased by 375 (16%) to a total of 2709 (2346 received monotherapy and 1157 received combination with HCTZ), and includes 256 new patients who participated in a controlled, randomized hypertension trial (protocol 061) and 71 new patients who enrolled into an open label, long term study (protocol 105, an extension of protocol 061).

The update was limited to reporting new deaths, serious adverse events, withdrawals for adverse events, and routine safety for all hypertension studies. Safety from clinical pharmacology studies was not updated.

New studies

The studies added to the final safety update include 061, a double blind, randomized, placebo controlled trial with HCTZ background therapy and 105, an open label long term extension trial of 061 with HCTZ combination. Only study 061 has been completed.

New hypertension studies

protocol no.	doses	duration of treatment	no. of patients enrolled: epro/placebo
061	400 mg epro qd plus 12.5 or 25 mg HCTZ	8 weeks	256/126

appendix 2.0 vol 24.2

Phase II/II Hypertension

Patient characteristics

The demographics for the eprosartan patients are shown below.

	eprosartan	
	safety update N=2334	final safety update N=2709
mean age	56.8 years	56.4 years
age range	20-93 years	20-93 years
≥ 65 years	29.2 %	27.6%
males/females	60.5/39.5 %	60.1/39.9
white/black/other	81.6/10.9/7.5 %	81.1/11.0/7.9
mean duration on drug	145.0 days	268.0 days

appendix 4.1.1 vol 5

There were only minor changes to the demographics with the addition of the new patients. The mean duration on eprosartan, however, was increased to 268 days.

Routine adverse events

All trials

Adverse events by body system reported by at least 2% of patients who received eprosartan in 1 of the 17 Phase II/III hypertension trials are shown below.

Number and (percent) of patients

	eprosartan^	
body system	safety update N=2334	final safety update N=2709
at least 1 event	1488 (63.8)	2004 (74.0)
Respiratory system	460 (19.7)	688 (25.4)
Central and peripheral nervous system	428 (18.3)	636 (23.5)
Body as a whole	423 (18.1)	671 (24.8)
Resistance mechanism	361 (15.5)	554 (20.5)
Musculoskeletal system	324 (13.9)	562 (20.7)
Gastrointestinal system	312 (13.4)	520 (19.2)
Metabolic and nutritional	208 (8.9)	338 (12.5)
Psychiatric	131 (5.6)	205 (7.6)
Urinary system	114 (4.9)	209 (7.7)
Skin and appendages	94 (4.0)	181 (6.7)
Cardiovascular, general/Heart rate, rhythm	72 (3.1)/ 83 (3.6)	171(6.3)+/ 125 (4.6)
Vision	62 (2.7)	107 (3.9)
Vascular, extra cardiac	36 (1.5)	74 (2.7)
Hearing and vestibular	33 (1.4)	59 (2.2)
Liver and biliary system	29 (1.2)	53 (2.0)

^patients with multiple adverse experiences may appear in more than one body system.
+includes cardiovascular events related to myocardium, endocardium, pericardium, valves (these were not included in the previous column)
Appendix 5.1 vol 24.5

There were more patients reporting events, mostly likely the result of the increase in the number of patients and the increase in the duration of treatment.

Specific adverse events reported by 3% or more of the 2709 eprosartan patients are shown below.

Number and (percent) of patients

	Eprosartan	
Adverse event	safety update N=2334	final safety update N=2709
Headache	289 (12.4)	395 (14.6)
Upper respiratory tract infection	254 (10.9)	385 (14.2)
Myalgia	157 (6.7)	238 (8.8)
Injury	101 (4.3)	202 (7.5)
Coughing	129 (5.5)	192 (7.1)
Dizziness	112 (4.8)	184 (6.8)
Pharyngitis	123 (5.3)	172 (6.3)
Rhinitis	121 (5.2)	170 (6.3)
Sinusitis	97 (4.2)	167 (6.2)
Bronchitis	69 (3.0)	137 (5.1)
Back pain	67 (2.9)	139 (5.1)
Viral Infection	86 (3.7)	136 (5.0)
Arthralgia	64 (2.7)	123 (4.5)
Fatigue	71 (3.0)	115 (4.2)
Diarrhea	65 (2.8)	115 (4.2)
Chest pain	61 (2.6)	96 (3.5)
Pain	58 (2.5)	96 (3.5)
Dyspepsia	50 (2.1)	82 (3.0)

Table 5.1.1 vol 24.5

Although the percent of patients reporting events in the final safety update increased in most categories, the 5 most commonly reported events were nearly the same as before (headache, upper respiratory infection, myalgia, coughing, and pharyngitis vs. headache, upper respiratory tract infection, myalgia, injury, and coughing). Face edema was reported by 5 patients (0.2%).

The percent of patients reporting adverse events was similar for those who received eprosartan alone and those who received eprosartan plus HCTZ (appendix 5.1.5 vol 24.5)

Deaths, serious safety, and withdrawals for adverse events

Deaths

4.1.1 Hypertension

Of the 2334 patients who received eprosartan in the Phase II/III hypertension trials and were reported in the NDA, a total of 16 deaths either during treatment or within 30 days of the last dose were reported (1 death that occurred 42 days after last dose of study drug is included). There was only 1 death in the placebo group. There were 3 additional patients reported in the NDA who died while receiving eprosartan: 1 in a study of type II diabetics, 1 in a study of left ventricular hypertension, and 1 in a study of congestive heart failure (section 4.1.2 Safety review).

The Safety Update added 33 new patients (all enrolled into open label study 050) to the data base for a total of 2367 patients in the Phase II/III hypertension trials.

The Final safety update included reports of 3 deaths since the previous update. There were no additional deaths in non hypertension trials.

Number of eprosartan hypertension patients who died

safety update N=2367	final safety update N=2709
16	19

The mortality rate for hypertensive patients who received eprosartan and died during or shortly after treatment in a clinical trial remains at less than 1%.

Eprosartan patients

The table below displays the 3 newly reported deaths; all patients had been on drug for over 1 year. A narrative for each death follows the table.

Deaths while on eprosartan

protocol. center. pt no. Study design	age/sex	total daily dose of eprosartan (mg)	days on drug	cause of death
017.414.00198	85/f	200	381	sudden death^
014.302.01899+	86/m	400	440	pulmonary embolism
047.433.00551	74/f	400	440	cerebrovascular accident

^listed as "unknown" in the submission
+received enalapril for the first 187 days

Narratives

Patient 017.414.00198, an 85 year old female in France, had been receiving eprosartan for more than 1 year when she developed epistaxis and died 5 minutes later. The death occurred at home. Medical history included acute bronchitis, atrial fibrillation, bronchospasm, chronic leg ulcer, and left nephrectomy. She experienced "bronchitis superinfection about 1 week before dying." There was an extensive list of concomitant medications including digoxin and amiodarone. There was no mention of an autopsy having been performed.

Patient 014.302.01899, an 86 year old male in Belgium, was hospitalized for acute respiratory distress, dyspnea and collapse more than 1 year after starting eprosartan. One day later he died of a pulmonary embolism. No autopsy was performed. Medical history was noncontributory. No concomitant medications were listed.

Patient 047.433.00551, a 74 year old female, experienced a CVA while on eprosartan which left her with hemiplegia. She stopped study drug and died 3 days later of respiratory complications. Medical history and concomitant medications, if any, were not discussed.

Two additional deaths, both resulting from cancer, were also submitted by the sponsor. Both patients had been discontinued from eprosartan and died much later. Patient 049.067. 03684, a 68 year old female, died of liver and pancreatic cancer 493 days after stopping eprosartan because of thrombocytopenia. Patient 061.272.00273, a 60 year old male, died of adenocarcinoma, 119 days after stopping eprosartan because of esophageal carcinoma.

In summary, the 19 reported deaths in the 2709 eprosartan patients now include 5 sudden deaths, 4 acute MIs, 3 cerebrovascular accidents, and 2 pulmonary embolism; the other 5 deaths were suicide, gastric ulcer, carcinomatosis, acute leukemia, and possible pneumonia. There is no obvious link between eprosartan and any of the deaths.

Serious safety (that did not lead to withdrawal from study or death)

Serious, nonfatal adverse experiences that did not lead to withdrawal were reported by 147 (5.4%) of more than 2709 hypertensive patients who received eprosartan as of July 15, 1997. The previous reporting rate was 4.0% (95/2367).

The 6 most common serious adverse events for the 2709 patient data base were: injury (17 patients), carcinoma (9 patients), arthritis (8 patients), infection (8 patients), cerebrovascular accident (5 patients), and cholecystitis (5 patients).

There was one report of abnormal hepatic function in a 53 year old black male. He had elevated liver enzymes at baseline that fluctuated throughout the study. The patient remained on study drug.

There were 5 additional reports of serious safety for the diabetic population (studies 091 and 110) including 1 CVA and 1 breast carcinoma.

Withdrawals for adverse events

The withdrawal rate for the 2709 patients in the final safety update was 10.2% (276 patients), similar to the rate of 9.2% (218 patients) for the first safety update.

The table below lists the adverse events that led to patient drop outs, limited to those events with drop out rates of at least 1.0%.

Number and (percent) of patients

	eprosartan	
adverse event	safety update N=2367	final safety update N=2709
withdrew for any adverse event	218 (9.2)	275^ (10.2)
headache	80 (3.4)	91 (3.4)
myalgia	38 (1.6)	48 (1.8)
coughing	33 (1.4)	41 (1.5)
URI	32 (1.4)	41 (1.5)
dizziness	27 (1.1)	38 (1.4)
fatigue	27 (1.1)	29 (1.1)
pharyngitis	26 (1.1)	29 (1.1)
sinusitis	21 (0.9)	30 (1.1)
diarrhea	19 (0.8)	26 (1.0)
nausea	19 (0.8)	25 (1.0)

^data from 1 patient are missing
Appendix 8.3.A vol 24.6

In addition, there were 8 patients withdrawn for anemia, 7 for abnormal ECG, 6 for serum creatinine increase, 5 for thrombocytopenia, 5 for hypokalemia, 4 for hepatic enzymes increase, 2 for syncope, 1 for granulocytopenia, 1 for jaundice, 1 for pancytopenia, and 1 for leukopenia.

The 4 most common events (headache, myalgia, coughing, and URI) in the hypertension trials leading to withdrawal remained unchanged from the first safety update.

There were an additional 8 patients not included in the final safety update but who withdrew from eprosartan because of an adverse event between September 1, 1996 and July 15, 1997. These withdrawals include depression and worsening breathing, MI, CVA, malignant melanoma, asthma, pulmonary edema, progressive pancytopenia (discussed below), and ischemic toes (appendix 8.7 vol 24.6). A newly submitted report (serial 256 dated 11-3-97) relates a case of severe thrombocytopenia in a 55 year old male with Hodgkin's disease and adenocarcinoma of the colon. He had been on eprosartan

for 14 days.

The progressive pancytopenia was reported in a 66 year old male (061.010.00165) who received eprosartan for 314 days when he was noted to have a platelet count of 20,000. A bone marrow biopsy showed normocelluar marrow with reduced numbers of megakaryocytes. A follow up report (serial 256 dated 11-3-97) indicated that the patient remained thrombocytopenic and anemic 3 months after eprosartan had been discontinued and the probable diagnosis is emerging myelodysplasia.

Renal function

A review of renal function abnormalities in patients was performed by the sponsor because of the preliminary results of a 3 month toxicity study in dogs. This study, using 1000 mg/kg eprosartan and 31.25 mg/kg HCTZ, was terminated at 28 days because of azotemia with progression to acute renal failure and uremic gastroenteritis.

The percents of hypertensive patients with increases in BUN and/or serum creatinine are shown below.

Percent of patients

	eprosartan alone n=2346	eprosartan plus HCTZ n=1596
increases in BUN	0.1%	0.3%
increases in serum creatinine	0.4%	0.7%

Appendix 5.1.5 vol 24.5

A total of 25 patients reported adverse events related to renal function. Events reported as moderate or severe and did not lead to study withdrawal include: 1 increase in BUN and serum creatinine and 2 cases of dehydration (1 moderate and 1 severe). Of the 25, 9 were receiving combination therapy with HCTZ (table 11.3 vol 24.1). [Patient 017.414.00197 was erroneously marked as a death in table 11.3. This 80 year old female was participating in open label trial 040 for 25 days when she was hospitalized for supraventricular tachycardia, pulmonary edema, and renal failure (medical history included kidney disease). Eprosartan was withdrawn and she was discharged from the hospital (see fax from sponsor dated 11-26-97). The sponsor states that the patient did not die within 30 days of discontinuing study drug.]

Two hypertension studies (016 and 061) compared eprosartan to eprosartan plus HCTZ. In study 016, withdrawals for events related to the renal system in patients receiving the combination included hypokalemia (2 patients), UTI (2 patients), albuminuria (1 patient) and hematuria (1 patient). In study 061, patients received either 12.5 or 25 mg of HCTZ with or without eprosartan. Of the reported serious adverse events in patients receiving the combination, there was 1 patient with increased BUN and serum creatinine, 4 patients with hypokalemia and 1 patient with hyperuricemia. None of these patients was withdrawn from drug prematurely.

Of the 1807 patients in long term studies, 4 (0.2%) reported increases in BUN and 16 (0.9%) reported increases in serum creatinine as adverse events (appendix 11.3 vol.24.7). The percent of patients in the long term study with normal BUN at baseline and increases to above normal during study was 3% for both those on eprosartan alone and those on eprosartan plus HCTZ. The percents for elevated serum creatinine were 1% and 2%, respectively.

It is appears that some patients are prone to instances of increased BUN and/or serum creatinine while taking eprosartan, and there is an indication that this may be enhanced with concomitant use of HCTZ.

Other laboratory values

As stated in the safety review, it is likely that eprosartan can cause mildly elevated liver enzymes in rare individuals, perhaps with progression to jaundice, but this is unlikely. Also, there is an indication that mean RBC and hemoglobin are slightly decreased in patients taking this drug.

Concomitant medications

The most commonly used co-mediation was hydrochlorothiazide (76.9% of the 2709 study patients). Eprosartan is not metabolized and, therefore, not expected to affect the metabolism of other medications.

Long term use

As of May 30, 1997, eprosartan with and without HCTZ has been administered to 1807 patients in long term studies. This reflects an increase of 390 patients as of the NDA/Safety update. The mean duration of exposure for these patients increased from 198 to 372 days. The break down by the length of exposure is shown below.

Number and (percent) of patients

	eprosartan	
length of exposure (months)	safety update n=1417	final safety update n=1807
< 6	736 (51.9)	393 (21.7)
6-12	515 (36.3)	432 (23.9)
> 12	166 (11.7)	982 (54.3)

Appendix 17.1.A vol 24.7

The longest exposure was at least 721 days and this was limited to 77 patients. The maximum duration of treatment was 871 days.

Overall, the percent of patients receiving eprosartan longterm and reporting adverse events increased slightly from 67.8% for the safety update to 69.4% for the final safety update. The most frequently reported adverse events were URI (17.7%) and headache (16.5%).

cc
orig. NDA#20,738
HFD-110
HFD-110/C Ganley/DWillard

RHPM Overview of NDA 20-738
Teveten (eprosartan mesylate)
Update December 17, 1997

Background

This NDA was submitted on October 11, 1996 for Teveten (eprosartan mesylate)Tablets for once daily oral use in the management of essential hypertension. The original SmithKline Beecham Pharmaceuticals IND . for eprosartan mesylate was submitted on May 21, 1992.

Update

An approvable letter was signed by Dr. Temple on October 10, 1997 requesting final printed labeling "essentially identical in content to the enclosed marked-up draft." The sponsor submitted revised draft labeling on November 5, 1997. This labeling was discussed with Dr. Temple during a meeting with Dr. Ganley and Ms. Willard on December 5, 1997. On December 8, 1997 proposed labeling was sent by facsimile transmission (FAX) to SmithKline Beecham Pharmaceuticals. During a December 8, 1997 telephone conversation with Ms. Linda Rebar of SmithKline, Ms. Willard indicated that Dr. Temple would be willing to discuss this labeling in a teleconference with SmithKline to "iron out" any differences before a second action letter issued. During a December 15, 1997 telephone conversation with Ms. Willard, Ms. Rebar indicated that SmithKline did not intend to respond to the December 8, 1997 FAX until more data was available from their 600 mg once a day Teveten trial. This would most probably be sometime between late January and mid-February 1998.

The October 10, 1997 letter also stated that, before the application could be approved, it would be necessary to submit the following information:

The sponsor submitted a reply to items 1 and 2 on October 31, 1997. Dr. Fadiran's December 2, 1997 review states that:

Based on the additional data submitted, the dissolution method and specification should still be:

This recommendation is based on the observations that formulations that are exactly compositionally proportional were absorbed to different extents (original NDA submission). In addition, the 2-year stability data indicate that the quality of the product deteriorates with time. In order to assure the product quality and meet expected *in vivo* bioavailability, the above dissolution specification and method are justified.

The revised draft labeling submitted by the sponsor November 5, 1997 in response to the draft labeling issued with the October 10, 1997 approvable letter contained revisions in the HOW SUPPLIED section regarding the number of tablets per container. A December 16, 1997 submission contains written justification for the change in the number of tablets per bottle as well as revised container labels to reflect this change. Dr. Short's December 19, 1997 review states that the proposed package configurations are acceptable as the stability data in the original NDA submission support the changes. The container labels were also reviewed by Dr. Short and found to be acceptable.

Summary

1) Exclusivity summary must be signed.

2) Methods validation of the regulatory methods has not been completed. This is reflected in the approval letter.

3) The biopharmaceutists' comments are included in the action letter.

Diana M. Willard
Regulatory Health Project Manager

cc: Original File
HFD-110
HFD-110/Dwillard

RHPM Overview of NDA 20-738
Teveten (eprosartan mesylate)
October 2, 1997

Background

This NDA was submitted on October 11, 1996 for Teveten (eprosartan mesylate)Tablets for once daily oral use in the management of essential hypertension. The original SmithKline Beecham Pharmaceuticals IND [redacted] for eprosartan mesylate was submitted on May 21, 1992.

The User Fee Goal Date is October 11, 1997.

Group Leader Memorandum

Dr. Ganley's September 10, 1997 review states that the information included in the NDA support the approval of eprosartan for the treatment of hypertension. Attached to Dr. Ganley's review is a revised version of the labeling submitted on July 31, 1997 by the sponsor. Dr. Lipicky has endorsed Dr. Ganley's review in lieu of a separate transmittal memo.

Medical Reviews

Efficacy:

In his review dated August 7, 1997, Dr. Hammond states that 200 to 400 mg eprosartan twice daily was effective in decreasing diastolic blood pressure. Some patients, however, responded favorably to eprosartan at the highest dose studied (1200 mg once daily). Eprosartan appeared to be comparably effective in all age groups. The data are unclear whether this is an effective monotherapy for blacks and female patients. Regarding cough, Dr. Hammond's review states that in study 053 there was significantly less cough in the eprosartan group when compared to the enalapril group.

Safety:

Dr. Gordon's July 30, 1997 review states that overall, there are no safety issues for eprosartan that have been documented in the testing of approximately 3000 patients. There is no evidence that the safety of eprosartan is influenced by age, gender, or race. The clearance of eprosartan was reduced in patients with renal impairment. The AUC and median T_{max} were increased in patients with liver impairment. While there was no evidence that a dose reduction in these patients is necessary, it would be prudent to consider such a reduction.

Clinical Pharmacology:

Dr. U's August 8, 1997 review of Protocol 051 (comparison of eprosartan with enalapril on left ventricular hypertrophy) states that at the doses used (200 mg eprosartan titrated up to 300 mg and then to 400 mg: 10 mg enalapril titrated up to 20 mg and then to 40 mg), eprosartan and enalapril showed no differences in clinical and laboratory safety profiles and in ECGs.

In his August 8, 1997 review of Protocol 061, Dr. U states that at the doses used (400 mg eprosartan in combination with 12.5 or 25 mg HCTZ), eprosartan/HCTZ combinations showed no differences from placebo in clinical and laboratory safety profiles. No excessive lowering of blood pressure and no effect on heart rate were found.

Pages 22 to 27 of Dr. U's August 7, 1997 review contain labeling recommendations for eprosartan. Pages 28 and 29 outline several issues raised during the clinical pharmacology review.

DSI Audit

In a June 10, 1997 memo to Drs. Gordon and Hammond and Ms. Willard, Dr. El-Hage states that "All four requested inspections have been completed. No objectionable conditions were found which would preclude the use of the data submitted in support of pending NDA." This memo contains the COMIS printout for the DSI inspections.

Statistical Reviews

Dr. Nuri's July 22, 1997 review states that an eprosartan OD regimen was investigated for 400, 600, 800, and 1200 mg in studies 013, 045, and 049. The results of studies 045 and 049 indicated that there is no significant difference (p-value ≥ 0.121) in the reduction of SiDBP for patients receiving eprosartan 400 mg OD compared to those on placebo. Eprosartan 600 and 1200 mg OD (investigated only in study 049) have resulted in significant ($p \leq 0.010$) reductions in SiDBP over that of placebo. This study shows that there is no significant difference (based on modified Bonferroni procedure, p-value = 0.028) in the reduction of SiDBP for patients receiving eprosartan 800 mg OD and those on placebo. There results were also true, except for the significance for 400 and 800 mg OD in study 049, for the results of the SiSBP.

Eprosartan BID regimen was investigated for 25, 50, 100, 150, 300, and 400 mg strengths in studies 010, 011, 013, and 017. The results of studies 010 and 011 show that eprosartan 50, 100, and 150 mg BID did not cause a significant difference (p-value ≥ 0.0724) in the reduction of SiDBP among patients who received eprosartan compared to those on placebo. The results of studies 010 and 011 indicate that there is a significant difference (p-value ≤ 0.0010) in the reduction of SiDBP among patients who received eprosartan 200 mg BID compared to those who were on placebo. Study 011 shows that eprosartan 300 and 400 mg BID have resulted in significant differences (p-value = 0.0001) in the reduction of SiDBP for patients receiving eprosartan compared to those who were on placebo. There results were also true (except for 200 mg BID in study 010) for the results of the SiSBP.

In his May 5, 1997 review (and May 21, 1997 addendum) of the pre-clinical studies, Dr. Nuri states that the survival analysis for both male and female mice shows significant differences (p-value ≤ 0.00259) in survival distributions among the treatment groups. A significant (p-value ≤ 0.0429) positive trend in mortality in the eprosartan treated groups was seen when compared to the combined control group. The results of analysis for the incidence of tumor show that for all tumor types there is no significant trend in the number of animals that had tumors in the control group compared to the high dose group.

For both male and female rats, there is no significant difference (p-values ≥0.5884) in survival distributions among the treatment groups. There is no significant positive trend (p-value ≥0.4676) in mortality in the eprosartan treated groups when compared to the control group.

Pharmacology Reviews

Pharmacology/Toxicology

In his July 30, 1997 review, Dr. Proakis states that from a pre-clinical safety perspective, this new drug application is approvable.

Genotoxicity/Mutagenicity

Dr. Koerner's July 31, 1997 review states that based on consideration of carcinogenicity and mutagenicity studies, the application is approvable with the recommended changes in labeling.

Biopharmaceutical Review

In his August 22, 1997 review, Dr. Fadiran states that the absolute bioavailability of eprosartan is about 14% and eprosartan plasma concentrations increase with dose in less than a proportional manner. The clinical trial formulations are not bioequivalent to the to-be-marketed formulations.

Chemistry Review

Minor deficiencies sent to the sponsor in a July 2, 1997 letter (see attached) still need to be addressed. The sponsor stated to Ms. Willard in a telephone conversation on September 10, 1997 that the reply to the July 2, 1997 letter will be submitted on September 15, 1997. Dr. Short states that this material will take less than a day to review.

The CDER Labeling and Nomenclature Committee stated on November 18, 1996 that "The Committee has no reason to find the proposed proprietary name unacceptable."

The EER was signed acceptable on May 2, 1997.

Dr. Short's September 30, 1997 review states that this application is approvable as far as the CMC section of the application is concerned.

Environmental Assessment

A FONSI was signed by Dr. Sager on March 12, 1997 and by Dr. Sheinin on March 13, 1997.

Summary

1) Reply to July 2, 1997 chemistry letter must be submitted and reviewed.

2) Exclusivity summary must be signed.

3) Labeling:

a) Dr. Gordon's statement regarding dose reduction in patients with renal or liver impairment needs to be considered.

b) Dr. U's labeling recommendations can be found on pages 22 to 27 of his August 7, 1997 review under the Clinical Pharmacology section of the Medical Reviews.

c) Dr. Koerner's recommendations can be found on pages 49 and 50 of his review.

d) Labeling recommendations by Dr. Proakis on pages 82 and 83 of his review need to be considered.

e) Page 60 of Dr. Short's Chemistry Review #1 outlines labeling recommendations for the package insert.

f) Dr. Fadiran's recommendations can be found on page 14 of the biopharmaceutics review.

Diana M. Willard
Regulatory Health Project Manager

cc: Original File
HFD-110
HFD-110/DWillard

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 10, 1997

FROM: Director, Office of Drug Evaluation I

SUBJECT: Eposartan NDA 20-738

TO: ✓Dr. Lipicky
Dr. Ganley

Eposartan is plainly another active angiotensin II inhibitor antihypertensive, but there are a few questions:

1. Dose finding has not really been optimal and once daily use is very questionable. Study 11, with top dose of 400 mg bid, gets to a mean response of 8/5, and 200, 300 mg bid give 7/4 and 8/4 mmHg responses. Less than 400 mg/day is plainly not useful, but higher doses merit study. O.D. dosing to 1200 mg has been evaluated but only 1200 mg (not 400-800 mg) gives a response at all worth while (9/4) and even that response is not numerically as good as lower total doses bid. Trough/peak ratio for o.d. dosing is ≤ 0.4 at eight weeks (0.5 at four weeks) and there is very little total experience with this dose (about 70 patients for eight weeks). Given the roughly 5 hour half life of the drug, its marginal effectiveness when used once daily is not surprising. I have real doubt as to whether any o.d. regimen should be approved (conceivably 1200 could be suggested as something to switch to if there were more experience) and suggest the following addition to the letter, following reference to draft labeling:

Please note the following particular aspects of the draft labeling.

1. We have removed most references to once-daily dosing. It is not surprising, given the roughly five-six hour half-life of eposartan, that its antihypertensive effect diminishes at the end of a 24 hour dosing interval. It is clear from your data that twice daily regimens giving 400 mg per day are reasonably effective and represent useful starting doses, but single daily doses even up to 800 mg do not show a useful effect. Only the 1200 mg dose, in a single study, yielded a 24 hour diastolic response of as much as 4 mmHg, and that study showed a much greater peak response (trough/peak ratio about ____), suggesting that twice daily dosing with daily doses of more than 800 mg total dose should be explored.

2. Although it is certainly likely that Eposartan will have the usual effects when combined with diuretics, available placebo-controlled data is minimal, studying doses of only 200 mg/daily and providing no experience at all with the large doses needed for once daily dosing. There is longer term safety experience from the cough study on 300 mg bid so that I did not feel Indications had to contain a reservation but I've added one to D&A. Further data on the diuretic-eposartan combination are needed.

3. Experience with the elderly needs to be described. It appears, from overall analysis and study 17, that the effect may be smaller than in younger persons. In any case, specific data need attention.

Robert Temple, M.D.