CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20738

CHEMISTRY REVIEW(S)

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

NDA #: 20-738 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 28 Jan 97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11 Oct 96	11 Oct 96	16 Oct 96
AMENDMENT	10 Jan 97	15 Jan 97	16 Jan 97

NAME & ADDRESS OF APPLICANT: SmithKline Beecham
PO Box 7929
Philadelphia, PA 19101

DRUG PRODUCT NAME:

Proprietary:	Teveten Tablets
Nonproprietary/USAN:	Eprosartan Mesylate (USAN, BAN)
Code Name/#:	SK&F 108566-J
Chem.Type/Ther.Class:	1S

PATENT STATUS: US 5,185,351, which expires 9 Feb 10, is owned by the applicant. It covers the composition of matter and method of use of eprosartan for the treatment of hypertension.

PHARMACOL.CATEGORY/INDICATION: Angiotensin II receptor antagonist

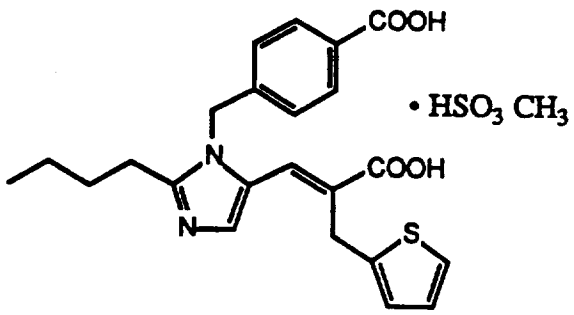
DOSAGE FORM: TCM

STRENGTHS: 300, 400 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(E)-α-[(2-Butyl-1-(4-carboxyphenyl)methyl)-1*H*-imidazol-5-yl)methylene)-2-thiophenepropionic acid monomethanesulfonate

$C_{23}H_{24}N_2O_4S \cdot CH_3SO_3H$

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Environmental Assessment

REMARKS/COMMENTS:

The applicant is requesting approval only for the 300 and 400 mg tablets.

A Request for Trademark Review, dated 16 Oct 96, was sent to the Labeling and Nomenclature Committee. A response was received, dated 18 Nov 96, stating that the committee has no reason to find the proposed proprietary name unacceptable.

The amendment of 10 Jan 97 provides copies of the cover letters from which accompanied the annual reports submitted to their DMFs. The amendment also includes a revised version of the applicant's Flow Diagram for manufacture of the drug substance. This revised version corrects errors that had occurred in the original submission.

CONCLUSIONS & RECOMMENDATIONS:

NOT APPROVABLE

The deficiencies noted during the review of this application are minor and should be easily corrected. None are of such a nature as to impede approval as far as the manufacturing and controls portion of the application is concerned.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/11/5/96
HFD-110/CSO
District
HFD-810/CHoiberg
R/D Init by: RWolters/2/4/97

James H. Short, Ph.D., Review Chemist
filename: **N20-738.CR1**

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MAY 20 1997

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

NDA #: 20-738 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 9 May 97

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		11 Oct 96		
AMENDMENT	BC	4 Mar 97	5 Mar 97	6 Mar 97
	BC	22 Apr 97	23 Apr 97	24 Apr 97

NAME & ADDRESS OF APPLICANT: SmithKline Beecham
PO Box 7929
Philadelphia, PA 19101

DRUG PRODUCT NAME:

Proprietary: Teveten Tablets
Nonproprietary/USAN: Eprosartan Mesylate (USAN, BAN)
Code Name/#: SK&F 108566-J
Chem.Type/Ther.Class: 1S

PATENT STATUS: US 5,185,351, which expires 9 Feb 10, is owned by the applicant. It covers the composition of matter and method of use of eprosartan for the treatment of hypertension.

PHARMACOL.CATEGORY/INDICATION: Angiotensin II receptor antagonist

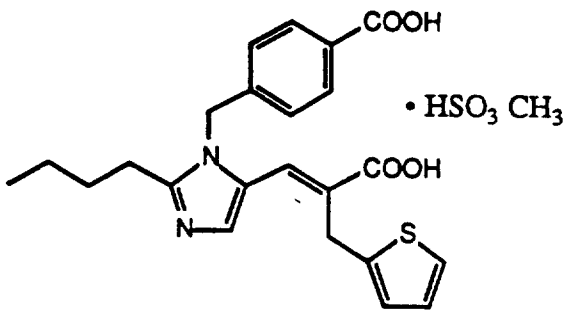
DOSAGE FORM: TCM

STRENGTHS: 300, 400 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(E)-α-((2-Butyl-1-(4-carboxyphenyl)methyl)-1*H*-imidazol-5-yl)methylene)-2-thiophene-propionic acid monomethanesulfonate

$C_{23}H_{24}N_2O_4S \cdot CH_3SO_3H$

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Environmental Assessment
Division of Biopharmaceutics

REMARKS/COMMENTS:

The applicant is requesting approval only for the 300 and 400 mg tablets.

A Request for Trademark Review, dated 16 Oct 96, was sent to the Labeling and Nomenclature Committee. A response was received, dated 18 Nov 96, stating that the committee has no reason to find the proposed proprietary name unacceptable.

An EER was sent to HFD-320, dated 13 Jan 97, requesting inspection of SB's plant in County Cork, Ireland for manufacture of the drug substance, and inspection of their plant in Sussex, England for manufacture of the drug product. An acceptable response was received dated 2 May 97.

The amendment of 4 Mar 97 provides responses to the Agency's letter of 4 Feb 97 identifying deficiencies in the Environmental Assessment section of the original submission. This information has been reviewed, and found acceptable. The review was dated 12 Mar 97, and a FONSI has been recommended.

The amendment of 22 Apr 97 provides responses to the Agency's letter of 25 Feb 97 citing deficiencies in the CMC section of the application. The deficiencies are repeated, followed by the applicant's responses and my comments.

Methods validation will be requested.

CONCLUSIONS & RECOMMENDATIONS:

NOT APPROVABLE

A FAX will be sent to the applicant requesting additional information about their photostability studies on the drug substance and drug product.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/5/7/97
HFD-110/CSO
HFD-810/CHoiberg
District

R/D Init by: Rwolters/5/12/97

James H. Short, Ph.D., Review Chemist
filename: **N20-738.CR2**

5/20/97

SEP 30 1997

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

NDA #: 20-738 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 24 Sep 97

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		11 Oct 96		
AMENDMENT	BL	28 Jul 97	30 Jul 97	1 Aug 97
	BL	31 Jul 97	1 Aug 97	7 Aug 97
	BC	15 Aug 97	22 Aug 97	22 Aug 97
	BC	10 Sep 97	15 Sep 97	17 Sep 97

NAME & ADDRESS OF APPLICANT: SmithKline Beecham Pharmaceuticals
1250 Collegeville Road
Collegeville, PA 19426-0989

DRUG PRODUCT NAME:

Proprietary: Teveten Tablets
Nonproprietary/USAN: Eprosartan Mesylate (USAN, BAN)
Code Name/#: SK&F 108566-J
Chem.Type/Ther.Class: 1S

PATENT STATUS: US 5,185,351, which expires 9 Feb 10, is owned by the applicant. It covers the composition of matter and method of use of eprosartan for the treatment of hypertension.

PHARMACOL.CATEGORY/INDICATION: Angiotensin II receptor antagonist

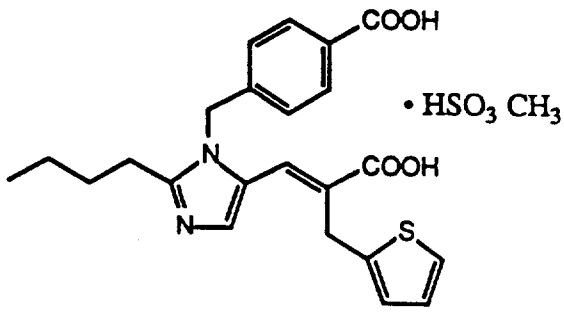
DOSAGE FORM: TCM

STRENGTHS: 300, 400 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(E)-α-((2-Butyl-1-((4-carboxyphenyl)methyl)-1*H*-imidazol-5-yl)methylene)-2-thiophene-propionic acid monomethanesulfonate

$C_{23}H_{24}N_2O_4S \cdot CH_3SO_3H$

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Environmental Assessment
Division of Biopharmaceutics

REMARKS/COMMENTS:

The applicant is requesting approval only for the 300 and 400 mg tablets.

A Request for Trademark Review, dated 16 Oct 96, was sent to the Labeling and Nomenclature Committee. A response was received, dated 18 Nov 96, stating that the committee has no reason to find the proposed proprietary name unacceptable.

An EER was sent to HFD-320, dated 13 Jan 97, requesting inspection of SB's plant in County Cork, Ireland for manufacture of the drug substance, and inspection of their plant in Sussex, England for manufacture of the drug product. An acceptable response was received dated 2 May 97.

The amendment of 28 Jul 97 provides draft copies of the carton and container labels for the 300 and 400 mg tablets.

The amendment of 31 Jul 97 provides a revised version of the Package Insert (PI).

The amendment of 15 Aug 97 provides for used in the manufacture of the drug substance.

The amendment of 10 Sep 97 provides responses to the Agency's letter of 2 Jul 97.

Methods validation will be requested as soon as the package is received from the applicant.

CONCLUSIONS & RECOMMENDATIONS:

APPROVABLE as far as the CMC section of the application is concerned.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/9/17/97
HFD-110/CSO
HFD-810/CHoiberg
District

R/D Init by: RWolters/9/25/97

James H. Short

James H. Short, Ph.D., Review Chemist
filename: **N20-738.CR3**

9/30/97

APPEARS THIS WAY

DEC 4 1997

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

NDA #: 20-738 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 3 Dec 97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11 Oct 96		
AMENDMENT ~~AtB~~	5 Nov 97	7 Nov 97	12 Nov 97
AMENDMENT BB	31 Oct 97	Did not receive	

NAME & ADDRESS OF APPLICANT: SmithKline Beecham Pharmaceuticals
1250 Collegeville Road
Collegeville, PA 19426-0989

DRUG PRODUCT NAME:

Proprietary: Teveten Tablets
Nonproprietary/USAN: Eprosartan Mesylate (USAN, BAN)
Code Name/#: SK&F 108566-J
Chem.Type/Ther.Class: 1S

PATENT STATUS: US 5,185,351, which expires 9 Feb 10, is owned by the applicant. It covers the composition of matter and method of use of eprosartan for the treatment of hypertension.

PHARMACOL.CATEGORY/INDICATION: Angiotensin II receptor antagonist

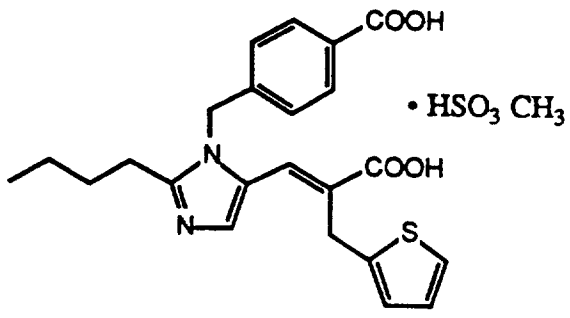
DOSAGE FORM: TCM

STRENGTHS: 300, 400 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(E)-α-[(2-Butyl-1-((4-carboxyphenyl)methyl)-1*H*-imidazol-5-yl)methylene)-2-thiophene-propionic acid monomethanesulfonate

$C_{23}H_{24}N_2O_4S \cdot CH_3SO_3H$

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Environmental Assessment
Division of Biopharmaceutics

REMARKS/COMMENTS:

The applicant is requesting approval only for the 300 and 400 mg tablets.

Methods Validation has been requested.

The comments referenced in the cover letter of the amendment of 31 Oct 97 regarding the dissolution testing procedure and specification were sent to the Division of Biopharmaceutics for review.

CONCLUSIONS & RECOMMENDATIONS:

The structure of the methanesulfonic acid portion of the structure in the DESCRIPTION section of the PI needs to be changed.

The correct package sizes need to be included in the HOW SUPPLIED section of the PI, or labels for the proposed package sizes need to be provided.

The firm should be asked to provide stability data for tablets stored in the approved package configurations.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/12/1/97
HFD-110/CSO
HFD-810/CHoiberg
District

R/D Init by: RWolters/12/4/97

James H. Short

James H. Short, Ph.D., Review Chemist
filename: **N20-738.CR4**

DEC 19 1997

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

NDA #: 20-738 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 19 Dec 97

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		11 Oct 96		
AMENDMENT	BL	16 Dec 97	17 Dec 97	18 Dec 97

NAME & ADDRESS OF APPLICANT: SmithKline Beecham Pharmaceuticals
1250 Collegeville Road
Collegeville, PA 19426-0989

DRUG PRODUCT NAME:

Proprietary: Teveten Tablets
Nonproprietary/USAN: Eprosartan Mesylate (USAN, BAN)
Code Name/#: SK&F 108566-J
Chem.Type/Ther.Class: 1S

PATENT STATUS: US 5,185,351, which expires 9 Feb 10, is owned by the applicant. It covers the composition of matter and method of use of eprosartan for the treatment of hypertension.

PHARMACOL.CATEGORY/INDICATION: Angiotensin II receptor antagonist

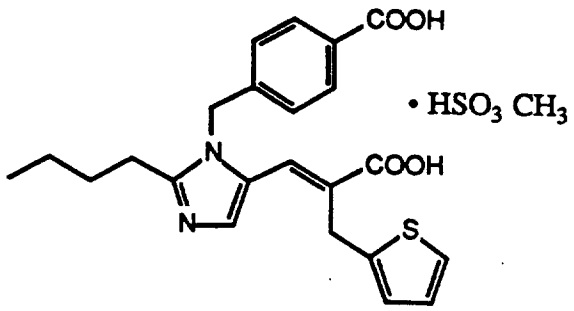
DOSAGE FORM: TCM

STRENGTHS: 300, 400 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(E)-α-((2-Butyl-1-((4-carboxyphenyl)methyl)-1*H*-imidazol-5-yl)methylene)-2-thiophene-propionic acid monomethanesulfonate

$C_{23}H_{24}N_2O_4S \cdot CH_3SO_3H$

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Environmental Assessment
Division of Biopharmaceutics

REMARKS/COMMENTS:

The applicant is requesting approval only for the 300 and 400 mg tablets.

Methods Validation has been requested.

The amendment of 16 Dec 97 provides draft labeling for the container sizes which will be marketed.

CONCLUSIONS & RECOMMENDATIONS:

The labels, as presented, are satisfactory.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/12/19/97
HFD-110/CSO
HFD-810/CHoiberg
District

R/D Init by: RWolters/12/19/97

James H. Short, Ph.D., Review Chemist
filename: **N20-738.CR5**

12-19-97