CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-268

Chemistry Review(s)

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

NDA #: 21-268 **DATE REVIEWED:** June 25, 2001

REVIEW #: 4 **REVIEWER:** Ramsharan D. Mittal

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N-000-C	20-JUN-01	21-JUN-01	25-JUNE-01
N-000-C	22-JUN-01	25-JUN-01	25-JUNE-01

NAME & ADDRESS OF SPONSOR: Unimed Pharmaceutical, Inc.
Four Parkway North
Deerfield, IL 60015-2544

DRUG PRODUCT NAME

Proprietary: TEVETEN HCT
Established: eprosartan mesylate and hydrochlorothiazide
Code Name/#:
Chem.Type/Ther.Class: **4/S**

PHARMACOL. CATEGORY/INDICATION: angiotensin II receptor antagonist and a diuretic

DOSAGE FORM: Tablet
STRENGTHS: 600 mg[1]/12.5 mg and 600 mg[1]/25 mg
ROUTE OF ADMINISTRATION: Oral

Rx/OTC: __x__ **Rx** _____ **OTC**

SPECIAL PRODUCTS: _____ **Yes** __x__ **No**

(If yes, fill out the form for special products and deliver to TIA through Team leader for data entry)

CHEMICAL NAME: (E)-2-butyl-1-(p-carboxybenyle)-2-thienylmethylimidazole-5-acrylic acid, monosulfonate

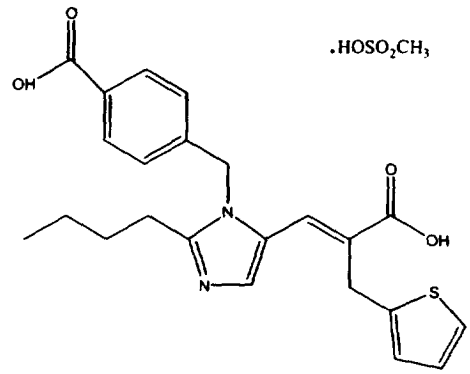
and

6-chloro-3,4-dihydro-2H-1,2,4-benzothiadizine-7-sulfonamide -1,1-dioxide

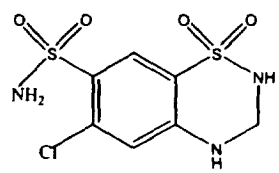
MOLECULAR FORMULA $C_{23}H_{24}N_2O_4S \bullet CH_4O_3S$ and $C_7H_8ClN_3O_4S$

MOLECULAR WEIGHT 520.625 and 297.74

STRUCTURAL FORMULA



Eprosaratan Mesylate



Hydrochlorothiazide

[1] The amount 600 mg is for eprosartan free base and not for eprosartan mesylate.

RELATED DOCUMENTS (if applicable):

IND[ ]and NDA 20-738.

CONSULTS:

None

REMARKS/COMMENTS:

This review covers the response to deficiencies noted in review # 2 and review # 3 sent to the applicant on June 15, 2001 by a FAX.

CONCLUSIONS & RECOMMENDATIONS:

The application may be approved from CMC standpoint. The following labeling and other comments should be conveyed to the applicant in the action letter for this application:

The dosage strengths as printed on **all container labels** misrepresent the amount of eprosartan mesylate as 600 mg. The strength should not appear on same line after established names or generic names. It is recommended that the strength of 600 mg be placed with an asterisk (600*)on same line after the trade name or on a separate line after trade name or established names. The asterisk is to be used for a note on the label to state that Each tablet contains 735.8 mg of eprosartan mesylate equivalent to 600 mg of eprosartan and 12.5 or 25 mg as appropriate of hydrochlorothiazide. An example is given below:

TEVETEN HCT
(Eprosartan mesylate/hydrochlorothiazide)
600* mg/12.5 mg
*Each tablet contains 735.8 mg of eprosartan mesylate equivalent to 600 mg of eprosartan and 12.5 mg of hydrochlorothiazide.

In the package insert, the positions of the double bonds in imidazole ring of eprosartan mesylate structure should be corrected.

Please include moisture specifications and test methods in the stability protocol along with other revisions to be provided by August 29, 2001 as stated in your submission dated June 22, 2001.

Based on the stability data an expiration date of 2 years may be granted for 600/12.5 mg tablets. For 600/25 mg tablets, a tentative expiry date of 1 year may be granted with the understanding that satisfactory data for ( ) months at room temperature and accelerated conditions will be provided by August 29, 2001.

/S/ 6/25/01

Ramsharan D. Mittal Ph.D.,
Review Chemist

/S/ 6/25/01

Kasturi Srinivasachar, Ph.D.,
Chemistry, Team Leader

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

NDA #: 21-268 **DATE REVIEWED:** June 20, 2001

REVIEW #: 3 **REVIEWER:** Ramsharan D. Mittal

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N-BL(Vol 4.1, and 4.2)	15-MAY-01	15-MAY-01	20-JUNE-01

NAME & ADDRESS OF SPONSOR: Unimed Pharmaceutical, Inc.
Four Parkway North
Deerfield, IL 60015-2544

DRUG PRODUCT NAME

Proprietary: TEVETEN HCT
Established: eprosartan mesylate and hydrochlorothiazide
Code Name/#:
Chem.Type/Ther.Class: **4/S**

PHARMACOL. CATEGORY/INDICATION: angiotensin II receptor antagonist and a diuretic
DOSAGE FORM: Tablet
STRENGTHS: 600 mg[1]/12.5 mg and 600 mg[1]/25 mg
ROUTE OF ADMINISTRATION: Oral

Rx/OTC: __x__ **Rx** _____ **OTC**

SPECIAL PRODUCTS: _____ **Yes** __x__ **No**

(If yes, fill out the form for special products and deliver to TIA through Team leader for data entry)

CHEMICAL NAME: (E)-2-butyl-1-(p-carboxybenyle)-2-thienylmethylimidazole-5-acrylic acid, monosulfonate

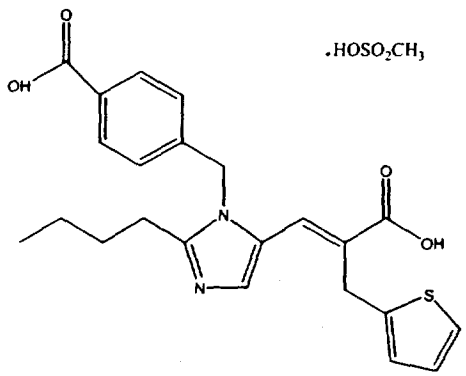
and

6-chloro-3,4-dihydro-2H-1,2,4-benzothiadizine-7-sulfonamide -1,1-dioxide

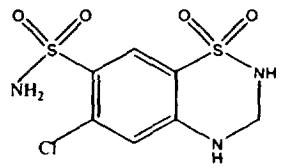
MOLECULAR FORMULA $C_{23}H_{24}N_2O_4S \bullet CH_4O_3S$ and $C_7H_8ClN_3O_4S$

MOLECULAR WEIGHT 520.625 and 297.74

STRUCTURAL FORMULA



Eprosaratan Mesylate



Hydrochlorothiazide

[1] The amount 600 mg is for eprosartan free base and not for eprosartan mesylate.

RELATED DOCUMENTS (if applicable):

IND[ ]and NDA 20-738.

CONSULTS:

Biopharm Division has completed the review and requested the applicant to revise dissolution method and specification.

REMARKS/COMMENTS:

During a phone conversation dated June 15, 2001, deficiencies noted in review # 2 and this review were discussed between Ram Mittal and Kasturi Srinivasachar of Agency and Judy Athley of Unimed. A copy of the FAX sent to applicant is attached at the end of this review.

CONCLUSIONS & RECOMMENDATIONS:

Mostly the CMC information provided for 600 mg/25 mg tablets is satisfactory but stability data is limited and no meaningful expiration date can be approved at this stage. The applicant has been requested to provide additional stability data.

/S/ 6/20/01

Ramsharan D. Mittal Ph.D.,
Review Chemist

/S/ 6/20/01

Kasturi Srinivasachar, Ph.D.,
Chemistry, Team Leader

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

NDA #: 21-268 **DATE REVIEWED:** June 20, 2001

REVIEW #: 2 **REVIEWER:** Ramsharan D. Mittal

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BL	19-APR-01	20-APR-01	20-APR-01
N-BC	30-APR-01	01-MAY-01	01-MAY-01
BC	02-MAY-01	03-MAY-01	03-MAY-01
N-BL(Vol 4.3)	15-MAY-01	15-MAY-01	18-MAY-01

NAME & ADDRESS OF SPONSOR: Unimed Pharmaceutical, Inc.
Four Parkway North
Deerfield, IL 60015-2544

DRUG PRODUCT NAME

Proprietary: TEVETEN HCT
Established: Eprosartan Mesylate and Hydrochlorothiazide
Code Name/#:
Chem.Type/Ther.Class: **4/S**

PHARMACOL. CATEGORY/INDICATION: angiotensin II receptor antagonist and diuretic
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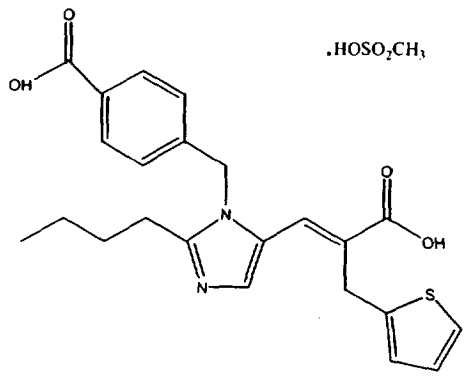
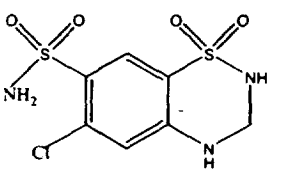


Eprosaratan Mesylate



Hydrochlorothiazide

[1] The amount 600 mg is for eprosartan free base and not for eprosartan mesylate.

RELATED DOCUMENTS (if applicable):

IND[ ] and NDA 20-738.

CONSULTS:

Overall recommendation from Office of Compliance regarding status of facilities is acceptable. A copy of the EER status is attached to this review. Biopharm review has been completed. The alternate trade name "TEVETEN HCT" applicant has been accepted by OPDRA.

REMARKS/COMMENTS:

The two amendments of this review are reply to Agency's letter of deficiencies sent on April 05, 2001 by FAX. The applicant submitted Methods Validation Package which will be initiated after approval of this NDA. The applicant has responded to all of the deficiencies. The CMC information for 600/25 mg tablet is currently under review, which will be completed, in review # 3. Most of the responses in this review are satisfactory except minor issues related to regulatory specification of eprosartan mesylate and drug product, labeling and method validation. These are discussed in the review. A FAX copy of the deficiencies that was sent to the applicant is attached at the end of review # 3.

CONCLUSIONS & RECOMMENDATIONS:

Applicant requested an expiration date of ( ) months but based on the available stability data, an expiration date of ( ) months is recommended for 600/12.5 mg strength. 600/12.5 mg strength is recommended for approval on the basis that applicant will commit to provide the information related to the deficiencies within a reasonable time.

/S/ 6/20/01

Ramsharan D. Mittal Ph.D.,
Review Chemist

/S/ 6/20/01

Kasturi Srinivasachar, Ph.D.,
Chemistry, Team Leader

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

NDA #: 21-268 **DATE REVIEWED:** April 9, 2001

REVIEW #: 1 **REVIEWER:** Ramsharan D. Mittal

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-AUG-99	01-SEP-00	01-SEP-00
BC	02-NOV-00	03-NOV-00	03-NOV-00

NAME & ADDRESS OF SPONSOR: Unimed Pharmaceutical, Inc.
Four Parkway North
Deerfield, IL 60015-2544

DRUG PRODUCT NAME

Proprietary: [redacted] or TEVETEN HCT
Established: eprosartan mesylate and hydrochlorothiazide
Code Name/#:
Chem.Type/Ther.Class: **4/S**

PHARMACOL. CATEGORY/INDICATION: angiotensin II receptor antagonist and a diuretic

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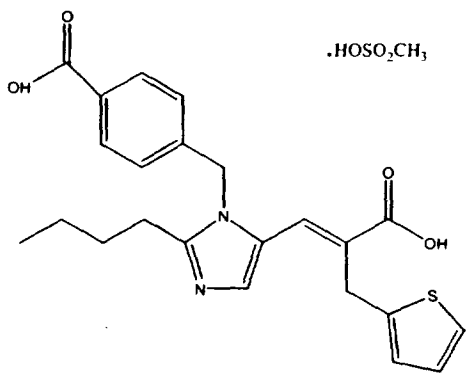
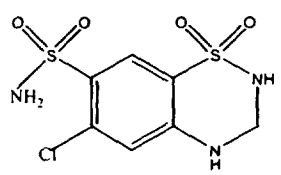


Eprosaratan Mesylate



Hydrochlorothiazide

[1] The amount 600 mg is for eprosartan free base and not for eprosartan mesylate.

Table I. DMF List (Vol. 2, Pages 10-11, 84)

DMF #	Subject	Holder	Status	Review Date	Letter date
	Drug Substance Hydrochlorothiazide		ADEQUATE	08-31-98	N/A
			ADEQUATE	08-06-99	N/A
			ADEQUATE	09-27-00	N/A
			ADEQUATE	10-09-99	N/A
			ADEQUATE	12-03-97	N/A
			ADEQUATE	06-04-00	N/A
			Approved for NDA 20-738	01-28-97	N/A

RELATED DOCUMENTS (if applicable):

IND[ ]nd NDA 20-738.

CONSULTS:

EER for the manufacturer of drug substance hydrochlorothiazide is pending and remaining facilities have been found to be ACCEPTABLE. Biopharm review is pending. The[ ]trade name may not be accepted by OPDRA however, this is not yet final. The applicant submitted an alternate trade name "TEVETEN HCT" that is pending review by OPDRA.

REMARKS/COMMENTS:

This is a combination product for Eprosartan mesylate (NDA 20-738) and hydrochlorothiazide . The applicant has not provided CMC information for 600 mg/25 mg tablet. Method Validation will be initiated after CMC information for the 600/25 mg strength is submitted. A copy of the deficiencies as noted in section H has been sent to the applicant by FAX.

CONCLUSIONS & RECOMMENDATIONS:

Based on various deficiencies as noted in the section H, the application is NOT APPROVABLE until these deficiencies are satisfactorily addressed by the applicant. CMC information for 600 mg/25 mg tablets was not provided and in the absence of this information strength cannot be approved.

/S/ 4/9/01

Ramsharan D. Mittal Ph.D.,
Review Chemist

/S/ 4/9/01

Kasturi Srinivasachar, Ph.D.,
Chemistry, Team Leader

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21268/000**
Stamp: **30-AUG-2000** Regulatory Due: **30-JUN-2001**
Applicant: **UNIMED PHARMS**
4 PKY NORTH
DEERFIELD, IL 600152544

Priority: **4S** Org Code: **110**
Action Goal: District Goal: **01-MAY-2001**
Brand Name: **TEVETEN (EPROSARTAN MESYLATE/HYDROCH**
Established Name:
Generic Name: **EPROSARTAN MESYLATE/HYDROCHLOROTHIAZIDE**
Dosage Form: **TAB (TABLET)**
Strength: **600/12.5 MG; 600/25 MG**

FDA Contacts: **S. BIRDSONG (HFD-110) 301-594-5300 , Project Manager**
R. MITTAL (HFD-110) 301-594-5353 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

ACCEPTABLE on 14-JUN-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted] DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

Establishment: [redacted] DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **07-FEB-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted] DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Responsibilities: [redacted]

Last Milestone: **OC RECOMMENDATION**
Milestone Date **07-FEB-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **16-FEB-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

Establishment: **9610344**
SOLVAY DUPHAR BV

1381 CP WEESP, , NL

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **26-FEB-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment: **9610742**
SOLVAY PHARMACEUTICALS BV

8121 AA OLST, , NL

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **16-FEB-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
