

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-286**

Chemistry Review(s)

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

NDA 21-286

Review # 2

Complete: July 16, 2001

<u>Submission Type</u>	<u>Document Date</u>	<u>CDER Date</u>	<u>Topic</u>
N-BB	May 7, 2001	May 8, 2001	Revised dissolution specification
N-BC	May 15, 2001	May 16, 2001	Response to FDA Letter dated 4/12/2001
N-BC	May 16, 2001	May 17, 2001	Stability protocol for full scale commercial lots

Name and Address of Applicant

Sankyo Pharma Inc
780 Third Avenue, 47th Floor
New York, NY 10017
(212) 753-3172

Agent

Albert Yehaskel
Associate Director, Regulatory Affairs
AYehaskel@SANKYO-USA.com
(212) 753-8207

Drug Product Name

Proprietary: **BENICAR**
Code Name: CS-866

Nonproprietary: Olmesartan Medoxomil
Chemical type/Therapeutic Class: 1S

Patent Status: Sankyo Co. Ltd. (Tokyo, Japan) owns Patent 5,616,599 (expires April 1, 2014) for the API, composition & use and Patent 5,925,664 (expires March 16, 2015) for the Method of Use.

Pharmacological Category and Indication: The in-vivo reaction of the pro-drug gives a selective AT₁ subtype angiotensin II receptor antagonist intended for treatment of essential hypertension.

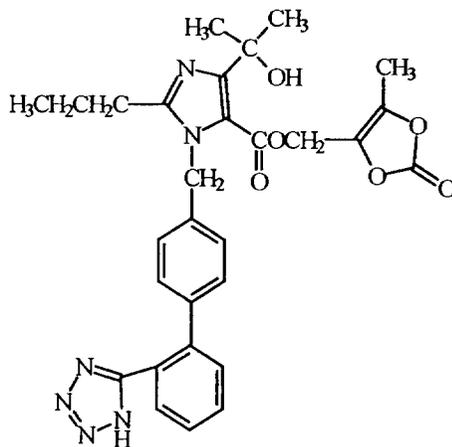
Dosage Form: Film Coated Tablet for oral administration Strengths: 5, 20 and 40 mg

Dispensed: Rx only SPOTS: NO

Related Documents: IND 

Drug substance chemical name, structure & CAS Number:

CS-866 is (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl-4- (hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylate

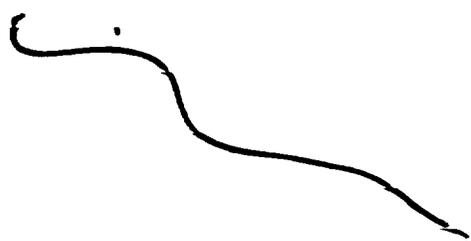


CAS # 144689-63-4

The biologically active compound is RNH-6270, specifically 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic acid.

Drug Master Files:

DMF	Type
█	II
█	II
█	II
█	III



- (a) The DMF █ for preparing CS-866 at laboratory and development scale was not reviewed because the information in it forms the basis for the full-scale synthesis described in DMF █.
- (b) * DMF █ refers to █. The █ bottles used by Sankyo are the subject of Don Klein's DMF review dated September 26, 2000.
- (c) The Letter of Authorization for the █ DMF is in DMF █ Volume 1.1, page C-25. It refers to DMF █ pages 4121 and 4122. Examination of the DMF confirmed that all components are stated to be USP or NF quality.

Remarks and Comments:

- (1) The overall establishment evaluation for CGMP compliance is acceptable (EES report May 24, 2001)
- (2) Analytical methods validations by █ will be requested shortly.
- (3) The proposed trade name, Benicar is acceptable to OPDRA. (Report dated March 21, 2001)
- (4) The nonproprietary names, olmesartan for RNH-5270 and olmesartan medoxomil for CS-866 were adopted by USAN (USAN Letter to Sankyo Pharma dated March 28, 2001).
- (5) The drug substance and/or its metabolites will not be introduced into the environment at a concentration greater than 1 ppb in any of the 5 years following approval of the NDA. Therefore, categorical exclusion from the requirement to prepare an EA is granted according to 21 CFR 25.31 (b).
- (6) The dissolution specification was revised as requested (Sankyo amendment N-BB dated May 7, 2001)
- (7) The stability data reported to date is consistent with a 24-month expiration period for all packaging configurations.
- (8) DMFs █ were inadequate at the completion of CMC Review 1 (4/20/01). These DMFs are adequate now. All the scientific deficiencies were addressed in a satisfactory manner in identical amendments submitted to the NDA and DMFs.

Conclusions and Recommendations: Based on the CMC Review, this application may be approved.

S

Florian Zielinski, Ph.D., Review Chemist, New Drug Chemistry I

Distribution:

- Original NDA 21-286
- HFD 110 Division File
- HFD 110 Florian Zielinski
- HFD 110 Ed Fromm
- HFD-810 John Simmons

Initialed by Kasturi Srinivasachar

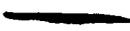
File name: NDA 21286 Benicar Review 2.doc

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21286/000	Priority: 1S	Org Code: 110
Stamp: 25-JUL-2000 Regulatory Due: 25-AUG-2001	Action Goal:	District Goal: 26-MAR-2001
Applicant: SANKYO PHARMA INC 780 3RD AVE 47TH FLOOR NEW YORK, NY 10017	Brand Name: BENICAR(OLMESARTAN MEDOXOMIL)5/10/20/40M	
	Established Name:	
	Generic Name: OLMESARTAN MEDOXOMIL	
	Dosage Form: TAB (TABLET)	
	Strength: 5, 10, 20 AND 40 MG	
FDA Contacts: E. FROMM (HFD-110)	301-594-5300	, Project Manager
F. ZIELINSKI (HFD-110)	301-594-5348	, Review Chemist
K. SRINIVASACHAR (HFD-110)	301-594-5376	, Team Leader

Overall Recommendation:

ACCEPTABLE on 24-MAY-2001 by M. GARCIA (HFD-322) 301-594-0095

Establishment: 	DMF No:
	AADA No:

Profile: TCM	OAI Status: NONE	Responsibilities:
Last Milestone: OC RECOMMENDATION		
Milestone Date: 10-AUG-2000		
Decision: ACCEPTABLE		
Reason: BASED ON PROFILE		

Establishment: 	DMF No:
	AADA No:

Profile: CTL	OAI Status: NONE	Responsibilities:
Last Milestone: OC RECOMMENDATION		
Milestone Date: 07-FEB-2001		
Decision: ACCEPTABLE		
Reason: DISTRICT RECOMMENDATION		

Establishment: 9612181	DMF No:
SANKYO CHEMICAL INDUSTRIES IN	AADA No:
2-58 HIROMACHI 1 CHOME	
SHINAGAWA-KU, TOKYO, JA 140-87	

Profile: CSN	OAI Status: NONE	Responsibilities: }
Last Milestone: OC RECOMMENDATION		
Milestone Date: 24-MAY-2001		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9610288** DMF No:
SANKYO CO LTD AADA No:

HIRATSUKA-SHI, KANAGAWA-KEN,

Profile: **CSN** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9611913** DMF No:
SANKYO CO LTD AADA No:

ODAWARA (KANAGAWA), , JA

Profile: **CSN** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9617684** DMF No:
SANKYO PHARMA INC AADA No:
LUITPOLDSTRASSE 1
PFAFFENHOFEN, , GM D-85276

Profile: **TCM** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

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/s/

Florian Zielinski
8/3/01 02:30:20 PM
CHEMIST

Kasturi Srinivasachar
8/8/01 06:25:24 PM
CHEMIST

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

NDA 21-286 Review # 1 Assigned: July 26, 00 Complete: April 20, 2001

<u>Submission Type</u>	<u>Document Date</u>	<u>CDER Date</u>	<u>Topic</u>
Original NDA	July 25, 00	July 26, 00	Benicar Tablets
T-Con Minutes	Dec 8, 00	Dec 28, 00	Stability of 5 mg tablets
Amendment (BC)	Jan 10, 01	Jan 11, 01	CMC info on floppy discs
Amendment (BC)	Feb 27, 01	Feb 28, 01	Stability data update

Name and Address of Applicant

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780 Third Avenue, 47th Floor
New York, NY 10017
(212) 753-3172

Agent

Albert Yehaskel
Associate Director, Regulatory Affairs
AYehaskel@SANKYO-USA.com
(212) 753-8207

Drug Product Name

Proprietary: **BENICAR**
Code Name: CS-866

Nonproprietary: Olmesartan Medoxomil
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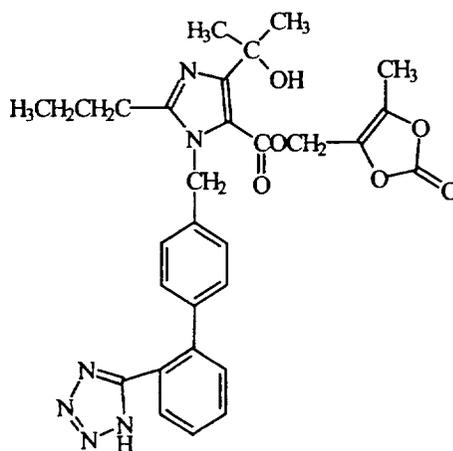
Pharmacological Category and Indication: The in-vivo reaction of the prodrug gives a selective AT₁ subtype angiotensin II receptor antagonist intended for treatment of essential hypertension.

Dosage Form: Film Coated Tablet for oral administration Strengths: 5, — 20 and 40 mg
Dispensed: Rx only SPOTS: NO

Related Documents: IND

Drug substance chemical name, structure & CAS Number:

CS-866 is (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylate

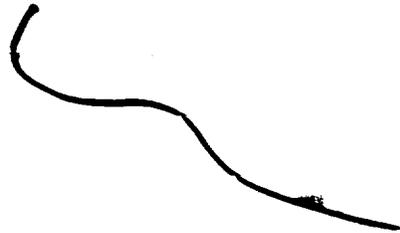


CAS # 144689-63-4

The biologically active compound is RNH-6270, specifically 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic acid.

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█	II
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- (a) The DMF █ for preparing CS-866 at laboratory and development scale was not reviewed because the information in it forms the basis for the full-scale synthesis described in DMF █.
- (b) * DMF █ refers to █. The exact identity of █ bottles used by Sankyo is not known at this time. Sankyo and the DMF holder are aware that additional information (lot numbers) is required. It is not known if the bottles for this NDA are the subject of Don Klein's DMF review dated September 26, 2000.
- (c) The Letter of Authorization for the █ DMF is in DMF █, Volume 1.1, page C-25. It refers to DMF █ pages 4121 and 4122. Examination of the DMF confirmed that all components are stated to be USP or NF quality.

Remarks and Comments:

- (1) The overall establishment evaluation for CGMP compliance is pending.
- (2) Analytical methods validations by █ will be requested shortly.
- (3) The proposed trade name, Benicar is acceptable to OPDRA. (Report dated March 21, 2001)
- (4) It is not known whether the nonproprietary name, Olmesartan Medoxomil is acceptable to USAN.
- (5) The drug substance and/or its metabolites will not be introduced into the environment at a concentration greater than 1 ppb in any of the 5 years following approval of the NDA. Therefore, categorical exclusion from the requirement to prepare an EA is granted according to 21 CFR 25.31 (b).
- (6) The OCPB Review of dissolution testing methodology and specification is in progress.
- (7) The stability data reported to date is consistent with a 24-month expiration period for all packaging configurations.

Conclusions and Recommendations: This application is **not approvable** because CMC topics described in the Draft Letter at the end of this review must be resolved in a satisfactory manner. Office of Compliance recommendation is still pending. DMFs █ and █ pertaining to drug substance and drug product manufacturing are **not adequate**. A list of deficiencies was sent to the DMF holders.

Florian Zielinski, Ph.D., Review Chemist, New Drug Chemistry I

Distribution:

Original NDA 21-286
HFD 110 Division File
HFD 110 Florian Zielinski
HFD 110 Ed Fromm
HFD-810 John Simmons

Initialed by Kasturi Srinivasachar
File name: NDA 21286 Benicar.doc

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/s/

Florian Zielinski
5/1/01 03:12:48 PM
CHEMIST

Kasturi Srinivasachar
5/1/01 04:29:02 PM
CHEMIST

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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	Strength: 5, 10, 20 AND 40 MG	
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F. ZIELINSKI (HFD-110)	301-594-5348	, Review Chemist
K. SRINIVASACHAR (HFD-110)	301-594-5376	, Team Leader

Overall Recommendation:

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	AADA No:

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Profile: **TCM** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Methods Validation

As of March 20, 2002, the methods validation is pending.

**APPEARS THIS WAY
ON ORIGINAL**

Environmental Assessment (EA)

Dr. Zielinski, in his April 20, 2001 review, stated that the firm should be granted exclusion.

**APPEARS THIS WAY
ON ORIGINAL**