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

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<td>May 7, 2001</td>
<td>May 8, 2001</td>
<td>Revised dissolution specification</td>
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<td>N-BC</td>
<td>May 16, 2001</td>
<td>May 17, 2001</td>
<td>Stability protocol for full scale commercial lots</td>
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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


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
Dispensed: Rx only
Strengths: 5, 20 and 40 mg
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

![Chemical Structure](image)

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
  - III
  - III
  - III
  - III
  - 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. The bottles used by Sankyo are the subject of Don Klein's DMF review dated September 26, 2000.

(b) DMF refers to 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 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, categorization 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.

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

NDA 21-286, CMC Review # 2
25-MAY-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21286/000
Applicant: SANKYO PHARMA INC
780 3RD AVE 4TH FLOOR
NEW YORK, NY 10017

Priority: 15
Org Code: 110
Action Goal: District Goal: 26-MAR-2001
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)
F. ZIELINSKI (HFD-110)
K. SRINIVASACHAR (HFD-110)
301-594-5330, Project Manager
301-594-5348, Review Chemist
301-594-5376, Team Leader

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

Establishment: [Blank]
DMF No: AADA No:

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

Establishment: [Blank]
DMF No: AADA No:

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

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

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

NDA 21-286, CMC Review # 2
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pages of trade secret and/or confidential commercial information
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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

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<td>CMCinfo on floppy discs Stability data update</td>
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<td>Dec 8, 00</td>
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<td>Stability of 5 mg tablets</td>
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<td>Jan 10, 01</td>
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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


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

Dispensed: Rx only

Strengths: 5, — 20 and 40 mg

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

\[
\text{CAS} \ # \ 144689-63-4
\]
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
III
III
III
III
III

(a) The DMF for preparing CS-866 at laboratory and development scale was not reviewed because
the information 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
Redacted 16 pages of trade secret and/or confidential commercial information
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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

Application: NDA 21286/000
Priority: 1S
Org Code: 110

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

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

Establishment: DMF No:

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

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

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

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

Establishment: DMF No:

SANKYO CHEMICAL INDUSTRIES INC
2-58 HIROMACHI 1 CHOME
SHINAGAWA-KU, TOKYO, JA 140-87

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Methods Validation

As of March 20, 2002, the methods validation is pending.
Environmental Assessment (EA)

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