

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-100**

**CHEMISTRY REVIEW(S)**

**MEMORANDUM**

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

---

**DATE:** September 18, 2007

**FROM:** Prafull Shiromani, Ph. D.  
Reviewing Chemist  
Division of Cardiovascular and Renal Products HFD-110

**TO:** File NDA 22-100

**SUBJECT:** Approval recommendation for Azor<sup>®</sup> (olmesartan medoxomil-amlodipine besylate combination product, (NDA 22-100, Daichii Sankyo Pharm)

This memo recommends the approval of Azor (olmesartan medoxomil and amlodipine besylate) for the treatment of hypertension from CMC perspective based on the receipt of the overall acceptable establishment report from Office of Compliance, summary of which is attached. All other CMC related issues had been resolved as per earlier CMC reviews.

-----  
Prafull Shiromani  
Chemist

**Appears This Way  
On Original**

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22100/000      Sponsor: DAIICHI SANKYO  
Org Code : 110      399 THORNALL ST  
Priority : 4S      EDISON, NJ 08837

Stamp Date : 27-NOV-2006      Brand Name : AZOR  
PDUFA Date : 27-SEP-2007      Estab. Name:  
Action Goal :      Generic Name: AMLODIPINE  
District Goal: 29-JUL-2007      BESYLATE/OLMESARTAN MEDOXOMIL  
Dosage Form: (TABLET)  
Strength : 5/20 5/40 10/20 10/40 M

FDA Contacts:      S. GOLDIE      Project Manager      301-796-2055  
                    K. SRINIVASACHAR      Review Chemist      301-796-1760  
                    K. SRINIVASACHAR      Team Leader      301-796-1760

Overall Recommendation:      ACCEPTABLE on 13-SEP-2007 by S. ADAMS (HPD-322) 301-827-905

Establishment :      FEI :

DMF No:      AADA:

b(4)

Responsibilities:

Profile : TCM      OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 13-DEC-06

Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

---

Establishment :

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 13-DEC-06  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

---

Establishment : CFN : 9617684 FEI : 3003282622  
DAIICHI SANKYO EUROPE GMBH  
D 85276  
PFAFFENHOFEN, , GM

DMF No:

AADA:

Appears This Way  
On Original

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: FINISHED DOSAGE MANUFACTURER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE  
 Last Milestone: QC RECOMMENDATION  
 Milestone Date: 02-AUG-07  
 Decision : ACCEPTABLE  
 Reason : DISTRICT RECOMMENDATION

Establishment :

F

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE  
 Last Milestone: QC RECOMMENDATION  
 Milestone Date: 28-DEC-06  
 Decision : ACCEPTABLE  
 Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9611913 FEI : 3002808056  
 SANKYO COMPANY LTD  
 ODAWARA (KANAGAWA), , JA

Appears This Way  
On Original

DMF No: 14953

AADA

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 13-SEP-07  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

---

Appears This Way  
On Original

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Prafull Shiromani  
9/18/2007 02:46:04 PM  
CHEMIST

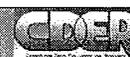


**NDA 22-100  
Amendment**

**AZOR (Amlodipine besylate and Olmesartan medoxomil)  
5/20, 5/40, 10/20, 10/40 mg Tablets**

**Daiichi Sankyo Inc.**

**Prafull Shiromani Ph. D.  
Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment**



# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>8</b>
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s).....	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	10
C. CC Block .....	10
<b>Chemistry Assessment.....</b>	<b>11</b>

Appears This Way  
On Original



# Chemistry Review Data Sheet

1. NDA 22-100
2. REVIEW #: 2
3. REVIEW DATE: 06-Sep-2007
4. REVIEWER: Prafull Shiromani Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

CMC Review 1

Document Date

10-Aug-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Daiichi Sankyo Amendment

Document Date

30-Aug-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Daiichi Sankyo Inc.  
Address: 399 Thornall Street, Edison, NJ 08837  
Representative: Ms. Paulette F. Kosmoski  
Telephone: 732-590-4875

8. DRUG PRODUCT NAME/CODE/TYPE:



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

- a) Proprietary Name: AZOR
- b) Non-Proprietary Name (USAN): amlodipine besylate and olmesartan medoxomil
- c) Code Name/# (ONDC only): CS-8663
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Antihypertensive

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5/20, 5/40, 10/20, 10/40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

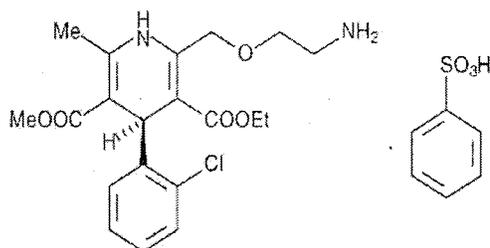
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

## Chemistry Review Data Sheet

Amlodipine Besylate

and enantiomer

Chemical Name: 3-ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate,

Established Name : Amlodipine Besylate

Molecular Formula :  $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

Molecular Weight : 567.1

CAS : [111470-99-6]

Olmesartan Medoxomil

NAME:

CHEMICAL NAME:

CAS NUMBER:

MOLECULAR WEIGHT:

STRUCTURAL FORMULA:

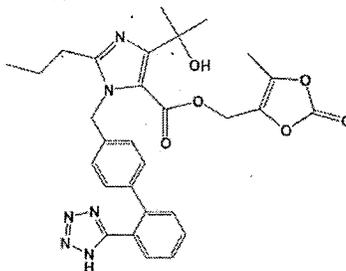
*CS-866 Drug Substance* (olmesartan medoxomil)

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

144689-63-4

558.59

$C_{29}H_{30}N_6O_6$



Appears This Way  
On Original



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs: N/A

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	Pending	N/A	
Pharm/Tox	N/A	N/A	None
Biopharm	Acceptable	25-Jul-2007	Lydia Velazquez
DMETS	Comments with regard to matching Established Name to Strength	16-May-2007	Judy Park



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

Methods Validation	Samples not sent to the laboratory, since conventional methods.	N/A	None
OPDRA	N/A	N/A	None
EA	Acceptable	20-Jun-2007	Prafull Shiromani
Microbiology	N/A	N/A	None

Appears This Way  
On Original



# The Chemistry Review for NDA 22-100

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA is recommended as "Approvable" from a CMC perspective.

The applicant has provided adequate responses to deficiencies delineated in CMC Review 1.

The approval of this application, from a CMC perspective, depends on the overall acceptable Compliance recommendation, which has not been received at this time.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s) Drug Product

Products containing amlodipine besylate (Norvasc<sup>®</sup> - Pfizer, NDA 19-787) and olmesartan medoxomil (Benicar<sup>®</sup> - Sankyo, NDA 21-286) are currently registered and marketed as separate drug products. The sponsor has now developed a fixed combination immediate release formulation for oral use containing both these actives.

AZOR tablets are formulated for oral administration and in the following strength (mg) combinations of amlodipine besylate (expressed as free base), a calcium channel receptor blocker and olmesartan medoxomil, an angiotensin II receptor blocker: 5/20, 10/20, 5/40, and 10/40. Olmesartan medoxomil is a prodrug, which is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. The tablets are packaged in both HDPE bottles, with child resistant closures, and aluminum/aluminum blister. The four strengths are differentiated by color (5/20 mg-white colored tablets, 10/20 mg-greyish orange, 5/40 mg-cream, and 10/40 mg-brownish red) and intagliation.

b(4)

b(4)

The applicant has developed a single dissolution test method for the product selecting the dissolution medium and test conditions appropriate for monitoring both active ingredients simultaneously, which is based on knowledge of the dissolution methodologies of the mono-



## CHEMISTRY REVIEW



### Executive Summary Section

therapy products. The dissolution method proposed by the sponsor is considered to be acceptable, on review. However, after evaluation of all of the dissolution data submitted it appears that Azor tablets can meet a tighter specification. Accordingly, FDA is recommending a higher Q value, \_\_\_\_\_ for olmesartan medoxomil and \_\_\_\_\_ for amlodipine besylate at 50 rpm/30 minutes. This comment will be provided in the FDA Action Letter. **b(4)**

With regard to the primary stability study, there were no significant changes in any of the product attributes in any packages both at long term (18 months) and accelerated (6 months) storage conditions. Accordingly, the applicant's shelf life proposal of 24 months is acceptable as it conforms to ICH guideline Q1E.

#### Drug Substance

Information on amlodipine besylate is given in the \_\_\_\_\_ information on olmesartan medoxomil is given in the Sankyo DMF # 14953. **b(4)**

#### B. Description of How the Drug Product is Intended to be Used

AZOR may be used as initial therapy in selected patients requiring blood pressure reduction \_\_\_\_\_ or may be used as add on therapy for patients not adequately controlled on amlodipine (or another dihydropyridine) or omlesartan (or another angiotension receptor blocker). The recommended starting dose is 5/20 mg once daily. The dose may be increased after 2 weeks in patients requiring further reduction in blood pressure to goal, to a maximum dose of 10/40 mg once daily. **b(4)**

#### C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-100) is recommended as APPROVABLE at this time since the overall Compliance recommendation has not been received at this time.

### III. Administrative

#### A. Reviewer's Signature

Appears This Way  
On Original



Executive Summary Section

**B. Endorsement Block**

ChemistName/Date: Prafull Shiromani, Ph.D.  
ChemistryTeamLeaderName/Date Ramesh Sood, Ph.D.  
ProjectManagerName/Date Denise Hinton

**C. CC Block**

Appears This Way  
On Original

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

8/9/07



**CHEMISTRY REVIEW**



**NDA 22-100**

**AZOR (Amlodipine besylate and Olmesartan medoxomil)  
5/20, 5/40, 10/20, 10/40 mg Tablets**

**Daiichi Sankyo Inc.**

**Prafull Shiromani Ph. D.  
Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>8</b>
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability .....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s) .....	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block .....	10
<b>Chemistry Assessment.....</b>	<b>11</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S DRUG SUBSTANCE [Name, Manufacturer].....	11
P DRUG PRODUCT [Name, Dosage form].....	42
A APPENDICES .....	140
R REGIONAL INFORMATION.....	141
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	142
A. Labeling & Package Insert .....	142
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	147
III. List Of Deficiencies To Be Communicated.....	148

**Appears This Way  
On Original**



# Chemistry Review Data Sheet

1. NDA 22-100
2. REVIEW #: 1
3. REVIEW DATE: 06-Aug-2007
4. REVIEWER: Prafull Shiromani Ph.D.
5. PREVIOUS DOCUMENTS: N/A

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

NDA 22-100

27-Nov-2006

Amendment to NDA 22-100

21-Mar-2007

Daiichi Sankyo Response/Amendment to FDA's  
IR Letter of 29-Jun-2007

02-Aug-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Daiichi Sankyo Inc.

Address: 399 Thornall Street, Edison, NJ 08837

Representative: Ms. Paulette F. Kosmoski



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Telephone: 732-590-4875

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: AZOR
- b) Non-Proprietary Name (USAN): amlodipine besylate and olmesartan medoxomil
- c) Code Name/# (ONDC only): CS-8663
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Antihypertensive

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5/20, 5/40, 10/20, 10/40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

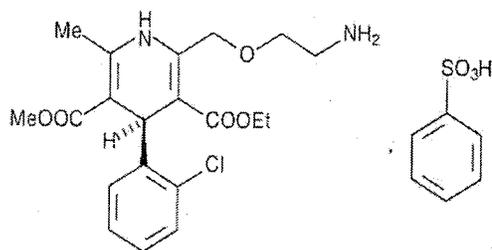
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

**Appears This Way  
On Original**

## Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**
Amlodipine Besylate


and enantiomer

Chemical Name: 3-ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate,

Established Name : Amlodipine Besylate

Molecular Formula :  $C_{20}H_{25}ClN_2O_5, C_6H_6O_3S$

Molecular Weight : 567.1

CAS : [111470-99-6]

Olmesartan Medoxomil

NAME:

CHEMICAL NAME:

CAS NUMBER:

MOLECULAR WEIGHT:

STRUCTURAL FORMULA:

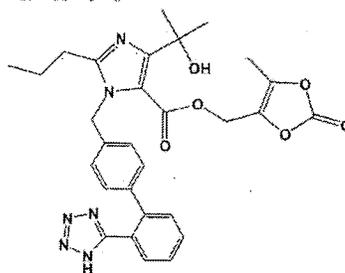
*CS-866 Drug Substance* (olmesartan medoxomil)

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

144689-63-4

558.59

$C_{29}H_{30}N_6O_6$





# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II		Amlodipine besylate - Drug Substance	3	Adequate	26-Mar-2007	None
	II		Amlodipine - Drug Substance	3	Adequate	29-Mar-2007	None
14953	II	Sankyo Co., Ltd.,	Olmesartan medoxomil - Drug Substance	1	Adequate	06-Aug-2007	None
	IV			3	Adequate	21-09-2003	None
	IV		b(4)	3	Adequate	08-Jan-2007	None

<sup>1</sup> Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

#### 18. STATUS:

##### ONDC:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A	N/A	None
EES	Pending	N/A	
Pharm/Tox	N/A	N/A	None
Biopharm	Acceptable	25-Jul-2007	Lydia Velazquez
DMETS	Comments with regard to matching Established Name to Strength	16-May-2007	Judy Park
Methods Validation	Samples not sent to the laboratory, since conventional methods.	N/A	None
OPDRA	N/A	N/A	None
EA	Acceptable	20-Jun-2007	Prafull Shiromani
Microbiology	N/A	N/A	None

**Appears This Way  
On Original**



# The Chemistry Review for NDA 22-100

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA is recommended as "Approvable: from a CMC perspective.

The approvability of this application, from a CMC perspective, depends on the sponsor's responses to FDA review comments on their second amendment.

Additionally, the overall Compliance recommendation has not been received at this time.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

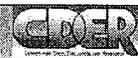
#### A. Description of the Drug Product(s) and Drug Substance(s) Drug Product

Products containing amlodipine besylate (Norvasc<sup>®</sup> - Pfizer, NDA 19-787) and olmesartan medoxomil (Benicar<sup>®</sup> - Sankyo, NDA 21-286) are currently registered and marketed as separate drug products. The sponsor has now developed a fixed combination immediate release formulation for oral use containing both these actives.

AZOR tablets are formulated for oral administration and in the following strength (mg) combinations of amlodipine besylate (expressed as free base), a calcium channel receptor blocker and olmesartan medoxomil, an angiotensin II receptor blocker: 5/20, 10/20, 5/40, and 10/40. Olmesartan medoxomil is a prodrug, which is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. The tablets are packaged in both HDPE bottles, with child resistant closures, and aluminum/aluminum blister. The four strengths are differentiated by color (5/20 mg-white colored tablets, 10/20 mg-greyish orange, 5/40 mg-cream, and 10/40 mg-brownish red) and intagliation.

b(4)

b(4)



Executive Summary Section

The applicant has developed a single dissolution test method for the product selecting the dissolution medium and test conditions appropriate for monitoring both active ingredients simultaneously, which is based on knowledge of the dissolution methodologies of the mono-therapy products. The dissolution method proposed by the sponsor,

USP Apparatus 2, 900 mL, JP 2<sup>nd</sup> Fluid (phosphate buffer solution, pH 6.8), 37°C, is considered to be acceptable, on review. However, after evaluation of all of the dissolution data submitted it appears that Azor tablets can meet a tighter specification. Accordingly, FDA is recommending a higher Q value, v for olmesartan medoxomil and v for amlodipine besylate at 50 rpm/30 minutes. b(4)

With regard to the primary stability study the applicant has employed a bracketing design (approved by FDA at the EOP meeting of July 27, 2006) for the 30 and 90 tablet count HDPE bottles. Based on this design two site specific pilot scale batches of each strength and one laboratory scale batch of the lowest and highest strength of drug product were placed on stability. There were no significant changes in any of the product attributes in any packages both at long term (12 months and 18 months, the latter provided in the second amendment) and accelerated (6 months) storage conditions. Accordingly, the applicant's shelf life proposal of 24 months is acceptable as it conforms to ICH guideline Q1E. Additionally, their statistical analysis of their 12 months stability data, also, supports this proposed shelf life. The applicant has also provided substantial supporting stability data, in the form of stress stability studies, photostability study, bulk holding-time study, and in-use stability testing, indicating that the product is stable in the defined package configurations.

**Drug Substance**

Information on amlodipine besylate is given in the information on olmesartan medoxomil is given in the Sankyo DMF # 14953. b(4)

**B. Description of How the Drug Product is Intended to be Used**

AZOR may be used as initial therapy in patients requiring blood pressure reduction or may be used as add on therapy for patients not adequately controlled on amlodipine (or another dihydropyridine) or omlesartan (or another angiotension receptor blocker). The recommended starting dose is 5/20 mg once daily. The dose may be increased after 2 weeks in patients requiring further reduction in blood pressure to goal, to a maximum dose of 10/40 mg once daily. b(4)

**C. Basis for Approvability or Not-Approval Recommendation**

Approvability will be based on the sponsor's responses to FDA review comments on the second amendment. These comments are:



Executive Summary Section

1) P.8.2 Postapproval Stability Protocol and Stability Commitment:

b(4)

2) II Review of Common Technical Document – Quality (CtdQ) Module 1; A. Labeling and Packaging Insert:

Sankyo's response of 02-Aug-2007 to the FDA IR letter directs the reviewer to the label described in the April 9, 2007 amendment. This label does not conform to FDA's recommendation, which is repeated below and should be implemented.

The established name for amlodipine besylate does not match the labeled strength. Revise all labeling using the following format. As an example, for 5 mg/20 mg:

b(4)

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

ChemistName/Date: Prafull Shiromani, Ph.D.  
ChemistryTeamLeaderName/Date Ramesh Sood, Ph.D.  
ProjectManagerName/Date Denise Hinton

#### C. CC Block

Appears This Way  
On Original

140 Page(s) Withheld

X Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Prafull Shiromani  
8/9/2007 01:16:34 PM  
CHEMIST

Kasturi Srinivasachar  
8/9/2007 06:09:13 PM  
CHEMIST

Initial Quality Assessment  
Branch I

<b>OND Division:</b>	Division of Cardiovascular and Renal Products
<b>NDA:</b>	22-100
<b>Applicant:</b>	Daiichi Sankyo Inc.
<b>Letter Date:</b>	27 Nov 2006
<b>Stamp Date:</b>	27 Nov 2006
<b>PDUFA Date:</b>	27 Sep 2007
<b>Tradename:</b>	Azor
<b>Established Name:</b>	Amlodipine besylate/olmesartan medoxomil
<b>Dosage Form:</b>	Tablets, 5mg/20mg, 5mg/40mg, 10mg/20mg, 10mg/40mg
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	Hypertension
<b>Assessed by:</b>	Kasturi Srinivasachar
<b>ONDQA Fileability:</b>	Yes
<b>Comments for 74-Day Letter:</b>	Labeling Issue—see Comments and Recommendations

**Summary**

This is an e-CTD 505(b)(2) NDA application for a fixed dose combination drug product containing 2 active ingredients, amlodipine and olmesartan, as their besylate and medoxomil salts respectively. Amlodipine is a calcium channel receptor blocker and olmesartan is an angiotensin II antagonist and both are currently marketed as monotherapies--- Norvasc, Pfizer, NDA 19-787 and Benicar, Sankyo, NDA 21-286. Both Norvasc and Benicar are available in 3 strengths, 2.5, 5, 10 mg and 5, 20, 40 mg respectively. However, the Applicant proposes to market only 4 strengths of the fixed dose combination drug product. The formulation developed is for immediate release of both actives. This NDA is based on the results from a Phase III clinical trial evaluating safety and efficacy of free combinations of olmesartan and amlodipine compared to monotherapy as well as bioequivalence studies bridging the highest and lowest strengths of the fixed dose combination to the separate entities used in the clinical trial.

A Pre-NDA meeting was held with Sankyo on July 27, 2006 to discuss CMC issues. Agreement was reached on the product stability data package to be submitted at the time of NDA submission with an update in 4 months. There was an extensive discussion of the in vitro dissolution specification -- details are provided in the minutes of this meeting in DFS.

**Drug Substance**

Olmesartan medoxomil:

This drug substance was originally developed by Sankyo for Benicar, NDA 21-286 and has also been used in their combination product, Benicar HCT, NDA 21-532. It is a BCS Class II pro-drug which is bioactivated by ester hydrolysis to olmesartan. Sankyo has incorporated all CMC information for this drug substance into their own DMF # 14,953. There are 4 formal reviews of this DMF and its amendments, the last one dated May 31, 2005. In addition the amendment of

Jan 13, 2006 has been reviewed in conjunction with Annual Report #3 for NDA 21-532. Only amendments subsequent to this need to be reviewed.

#### Amlodipine Besylate:

This drug substance was originally developed by Pfizer for Norvasc, NDA 19-787 and has been also been used in combination products such as Caduet (amlodipine besylate and atorvastatin calcium), NDA 21-540, and Exforge (amlodipine and valsartan), NDA 21-990. It belongs to BCS Class III. There are suppliers of this drug substance, and have DMFs on file. has been previously reviewed by the Office of Generic Drugs and currently has an "Inadequate" status. No response to the deficiency identified in the Sep 27, 2006 fax to the DMF holder has been received. The is currently under review by OGD.

b(4)

#### Drug Product

Conventional excipients are used in the manufacture of the film coated immediate release tablets. Data are provided for 6 strengths, 5/10, 10/10, 5/20, 10/20, 5/40 and 10/40 mg of amlodipine besylate/olmesartan medoxomil although only 5/20, 10/20, 5/40 and 10/40 mg strengths are proposed to be marketed in the US.

b(4)

The film coating is used to impart different colors to the different strengths.

Six formulations were initially developed but only one (formulation G) was found to be satisfactory on the basis of manufacturability, bioequivalence to the marketed monotherapy products and dissolution behavior. The drug product is manufactured

b(4)

to adequately protect the tablets from degradation, container closures chosen were HDPE bottles with desiccant or double aluminum blister packs.

#### Critical Review Issues

##### Drug Substance

- Since there are suppliers of amlodipine besylate, it is important to compare impurity profiles and physical properties of this drug substance from to confirm equivalence. In addition, it should be verified whether representative drug product batches were manufactured using drug substance from each supplier and placed on stability.
- In the summary of Biopharmaceutic Studies and Associated Analytical Methods it is stated that amlodipine besylate belongs to BCS Class III (high solubility, low permeability); however in the QOS amlodipine besylate is characterized as slightly water soluble. This discrepancy needs to be sorted out since it has a bearing on whether particle size is critical for this drug substance.

b(4)

- has a particle size specification for amlodipine besylate but does not. Sankyo has set its own specification for particle size and makes the statement that the particle size distribution of amlodipine besylate from suppliers is comparable. Is there adequate justification for Sankyo's limits for particle size? Do they test every batch from both suppliers for particle size as part of their acceptance testing? b(4)
- Does amlodipine besylate from either supplier meet the requirements of the new USP monograph which becomes official in April 2007?
- It is controlled in the specification with fairly broad limits using analysis. It is further part of the product manufacturing operation and tighter acceptance criteria are imposed at this stage. Are these final limits adequately justified? b(4)

#### Drug Product

- Is blend uniformity an in-process test? If not, how is adequacy of mixing assured during routine manufacture?
- Dissolution testing of the drug product needs to be evaluated in depth since the Office of Clinical Pharmacology and Biopharmaceutics will not be involved. Is the method discriminating? Based on discussions at the pre-NDA meeting Sankyo has provided results from testing at both 50 and 75 rpm and included both speeds with different Q values in the specification. The reviewer will need to determine the appropriate method and acceptance criteria using test results from clinical, registration and primary stability batches.
- The limits for water content and degradation products proposed in the specification should be evaluated considering data from release and stability batches. Is there adequate justification for the significantly higher shelf-life limits?

#### Comments and Recommendations

The application is fileable. The following labeling issue is recommended for inclusion in the 74 Day Letter: The established name, amlodipine besylate, and the strength (5 or 10 mg) do not match . The Package Insert and container labels should be revised accordingly. b(4)

Facilities have been entered into EES. A single reviewer is recommended for this NDA since the drug substances are well known and the product manufacturing process is straightforward.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead

Jan. 23, 2007  
Date

Ramesh Sood, Ph.D.  
Branch Chief

Jan 23, 2007  
Date

Appears This Way  
On Original

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Kasturi Srinivasachar  
1/23/2007 01:30:47 PM  
CHEMIST

Ramesh Sood  
1/24/2007 08:35:59 AM  
CHEMIST