

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200175

CHEMISTRY REVIEW(S)



NDA # 200175

CMC Review No. 2

CS-8635 Tablets

**(olmesartan medoximil, amlodipine and hydrochlorothiazide)
(20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg and 40/10/25 mg)**

Daiichi Sankyo, Inc.

Prafull Shiromani Ph.D.

**Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA # 200175
2. REVIEW #: 2
3. REVIEW DATE: 14-Jul-2010
4. REVIEWER: Prafull Shiromani Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 200175	30-Sep-2009
CMC Amendment (Stability Update)	17-Mar-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Applicant's Response to FDA IR Letter	28-Apr-2010
CMC Amendment (0016) – Revised DP Specification	01-Jul-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Daiichi Sankyo, Inc.

Address: 399 Thornall Street, Edison, NJ 08837

Representative: Manini Patel, Associate Director, Regulatory Affairs

Telephone: 732-906-6652

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Under negotiation with Agency
- b) Non-Proprietary Name (USAN): CS-8635
- c) Code Name/# (ONDC only):

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Hypertension

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: Olmesartan medoximil, Amodipine and Hydrochlorothiazide
20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg and 40/10/25 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:

Olmesartan Medoxomil – CS-866

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

Amlodipine

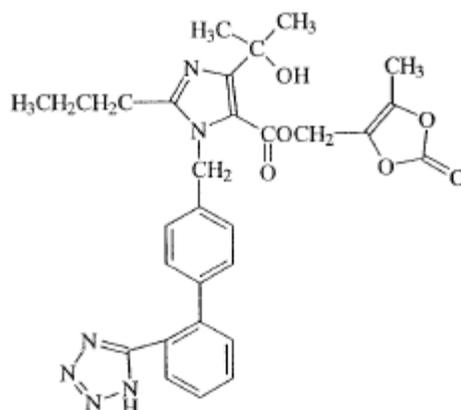
3-Ethyl 5-methyl (+)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate

Hydrochlorothiazide

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

Olmesartan Medoxomil

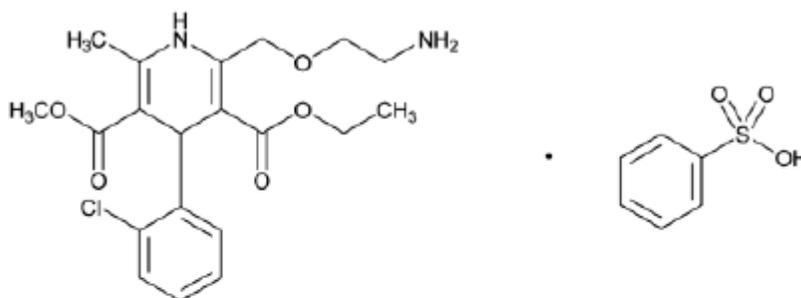
Chemistry Review Data Sheet



Chemical Formula: C₂₉H₃₀N₆O₆

Molecular Weight: 558.59

Chirality: None

Amlodipine

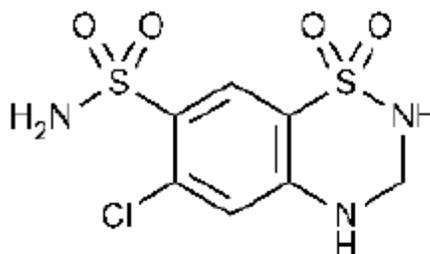
Chemical Formula: C₂₀H₂₅ClN₂O₅ · C₆H₆O₃S

Molecular Weight: 567.1

Chirality: Amlodipine besylate drug substance is a racemic mixture; the asymmetric carbon is noted in the structure below.

Hydrochlorothiazide

Chemistry Review Data Sheet



Chemical Formula: C₇H₈ClN₃O₄S₂

Molecular Weight: 297.7

Chirality: None

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	25-Sep-2009	LOA date 15-Dec-2008
				3	Adequate	10-Sep-2009	LOA date 19-Feb-2009
	II			3	Adequate	24-Aug-2009	LOA date 19-May-2009
	II			3	Adequate	20-Feb-2010	LOA date 13-Mar-2009
14953	II	Daiichi Sankyo Propharma Co., Ltd.	Olmesartan Medoxomil	1	Adequate	20-Oct-2009	LOA date 13-Mar-2009
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	31-Jan-2008	LOA date 21-May-2009
	IV			4			LOA date 05-Mar-2009

¹ Action codes for DMF Table:
1 – DMF Reviewed.

Chemistry Review Data Sheet

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")

² 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		
EES	Acceptable	15-Mar-2010	E. Johnson
Pharm/Tox	Approvable	20-Apr-2010	G. Jagadeesh
Biopharm	Acceptable	01-Jul-2010	T. Ghosh
LNC	N/A		
Methods Validation	Samples of DS, DP and Reference Standards are available		Validation is not required since the analytical methods are conventional.
OPDRA			
EA	Acceptable-Qualifies for a categorical exclusion under 21 CFR 25.31(b)	14-May-2010	R. Bloom
Microbiology	N/A		

Executive Summary Section

The Chemistry Review for NDA 200175**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The applicant has provided adequate responses to the FDA IR letter sent on 28-Apr-2010. Additionally, the ONDQA Biopharm and Environmental Assessment reviews have been satisfactorily completed with no pending issues and are submitted into DARRTS. Accordingly, this NDA is recommended for approval from a CMC perspective.

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

N/A

II. Summary of Chemistry Assessments

The drug product is a combination of three FDA approved active pharmaceutical ingredients (API), olmesartan medoxomil (OM) (prodrug form of active olmesartan-angiotensin II antagonist), amlodipine besylate (AML) (calcium channel receptor blocker) and hydrochlorothiazide (HCTZ) (thiazide diuretic) formulated as a once a day (QD) tablet for oral use in five strengths combinations (20mg OM/5mg AML/12.5mg HCTZ, 40mg OM/5mg AML/12.5mg HCTZ, 40mg OM/5mg AML/25mg HCTZ, 40mg OM/10mg AML/12.5mg HCTZ, 40mg OM/10mg AML/25 mg HCTZ). The three APIs are already registered in drug products on the US market and are consequently considered “existing”. Olmesartan medoxomil (OM) is an active ingredient in Benicar® approved in April 2002 (NDA 21-286), in Benicar HCT® approved in June 2003 (NDA 21-532) and in Azor® approved in September 2007 (NDA 22-100).

A. Description of the Drug Product(s) and Drug Substance(s)**DRUG SUBSTANCES**

Refer to CMC Review # 1 of this NDA dated 25-Mar-2010.

DRUG PRODUCT

CS-8635 Tablets are conventional film-coated tablet for immediate release. Each tablet strength can be distinguished by color and size, as well as by the debossing code, which is specific to each strength. For further details refer to CMC Review # 1.

The sponsor has provided adequate responses to FDA CMC comments delineated in the CMC IR letters; three of which are summarized below:

- i. They have provided details of the experimental design and statistical analysis employed on the 40/10/25 mg strength tablets in investigating the concentration of the (b) (4) pregelatinized starch and croscarmellose sodium. These details include the mathematical model (which contains the values of the regression coefficients for the main and interaction terms and

Executive Summary Section

the statistical analyses (p- and t- values to determine the significance of the regression coefficients obtained via Factorial ANOVA). (b) (4)

ii. The revised bracketing design and the stability plan are identical to those of the primary registration stability batches for the post-approval commitment batches and hence, acceptable.

ii. Dissolution and new DP specification: Following an ONDQA Biopharm IR letter, there was a teleconference between the sponsor's representatives and the Division of New Drug Quality Assessment and the Biopharmaceutics representatives on June 24, 2010, where finalization of the dissolution acceptance criteria was mutually agreed upon; the mutually agreed upon dissolution specifications at release and on shelf life are: Dissolution in 0.05 M phosphate buffer pH 6.8, 30 minutes at 50 rpm are $Q =$ (b) (4) label claim for olmesartan medoxomil, $Q =$ (b) (4) of label claim for amlodipine and $Q =$ (b) (4) of label claim for hydrochlorothiazide. Accordingly, a revised acceptable product specification has been provided in Supplement 0016 and is included in this review. Additionally, a *biowaiver* is granted for the three intermediate strengths; OM/AML/HCTZ 40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg (reference: Dr. T. Ghosh's Biopharm review of 01-Jul-2010).

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

1 INDICATIONS AND USAGE

The product is indicated for the treatment of hypertension.
This fixed combination drug is not indicated for the initial therapy of hypertension.

2 DOSAGE AND ADMINISTRATION

General Considerations

Dose once daily.

Dosage may be increased after 2 weeks. The full blood pressure lowering effects are attained within 2 weeks after a change in dose. The maximum recommended dose of the product is 40/10/25 mg. It may be taken with or without food. (b) (4)

All proposed doses can be achieved using the proposed commercial strengths.

Renal impairment: The usual regimens of therapy with the product may be followed if the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so avoid use of this product

Replacement Therapy

The product may be substituted for its individually titrated components. (b) (4)

Executive Summary Section

Add-on/Switch Therapy

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate responses to the FDA IR letter, accordingly this NDA is recommended for approval from a CMC perspective.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review: Prafull Shiromani, Ph.D.
Chemistry Branch Chief Name/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Russell Fortney

C. CC Block

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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

/s/

PRAFULL K SHIROMANI
07/15/2010

RAMESH K SOOD
07/16/2010



NDA # 200175

CMC Review No. 1

CS-8635 Tablets

**(olmesartan medoximil, amlodipine and hydrochlorothiazide)
(20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg and 40/10/25 mg)**

Daiichi Sankyo, Inc.

Prafull Shiromani Ph.D.

**Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA # 200175
2. REVIEW #: 1
3. REVIEW DATE: 25-Mar-2010
4. REVIEWER: Prafull Shiromani Ph.D.
5. PREVIOUS DOCUMENTS: N/A

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

NDA 200175

30-Sep-2009

CMC Amendment (Stability Update)

17-Mar-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Daiichi Sankyo, Inc.

Address: 399 Thornall Street, Edison, NJ 08837

Representative: Manini Patel, Associate Director, Regulatory Affairs

Telephone: 732-906-6652

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Under negotiation with Agency
- b) Non-Proprietary Name (USAN): CS-8635
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):

Chemistry Review Data Sheet

- Chem. Type: 4
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Hypertension

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: Olmesartan medoximil, Amodipine and Hydrochlorothiazide
20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg and 40/10/25 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:

Olmesartan Medoxomil – CS-866

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

Amlodipine

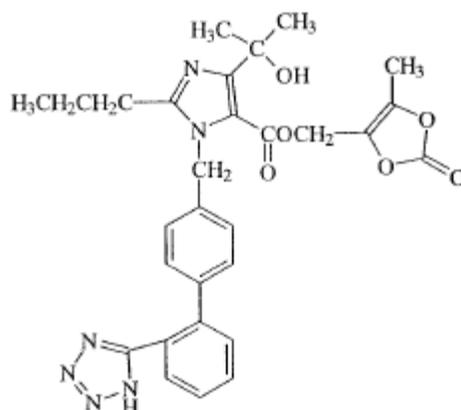
3-Ethyl 5-methyl (+)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate

Hydrochlorothiazide

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

Olmesartan Medoxomil

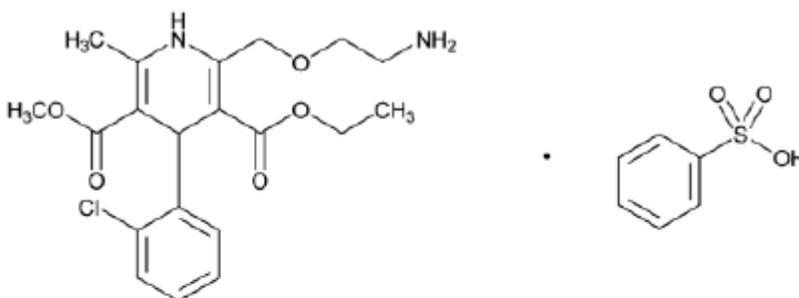
Chemistry Review Data Sheet



Chemical Formula: C₂₉H₃₀N₆O₆

Molecular Weight: 558.59

Chirality: None

Amlodipine

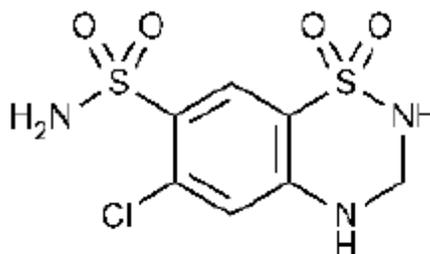
Chemical Formula: C₂₀H₂₅ClN₂O₅ · C₆H₆O₃S

Molecular Weight: 567.1

Chirality: Amlodipine besylate drug substance is a racemic mixture; the asymmetric carbon is noted in the structure below.

Hydrochlorothiazide

Chemistry Review Data Sheet



Chemical Formula: C₇H₈ClN₃O₄S₂

Molecular Weight: 297.7

Chirality: None

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	25-Sep-2009	LOA date 15-Dec-2008
				3	Adequate	10-Sep-2009	LOA date 19-Feb-2009
	II			3	Adequate	24-Aug-2009	LOA date 19-May-2009
	II			3	Adequate	20-Feb-2010	LOA date 13-Mar-2009
14953	II	Daiichi Sankyo Propharma Co., Ltd.	Olmesartan Medoxomil	1	Adequate	20-Oct-2009	LOA date 13-Mar-2009
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	31-Jan-2008	LOA date 21-May-2009
	IV			4			LOA date 05-Mar-2009

¹ Action codes for DMF Table:
1 – DMF Reviewed.

Chemistry Review Data Sheet

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")

² 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		
EES	Acceptable		E. Johnson; 15-Mar-2010
Pharm/Tox	pending		
Biopharm	pending		
LNC	N/A		
Methods Validation	Samples of DS, DP and Reference Standards are available		Validation is not required since the analytical methods are conventional.
OPDRA			
EA	pending		
Microbiology	N/A		

Executive Summary Section

The Chemistry Review for NDA 200175**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

This NDA in its present form cannot be recommended for approval from a CMC perspective. The approval of this application, from a CMC perspective, depends on the applicant's response to the FDA CMC letter. Additionally, the environmental assessment and biowaiver/dissolution assessments have 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

The drug product is a combination of three FDA approved active pharmaceutical ingredients (API), olmesartan medoxomil (OM) (prodrug form of active olmesartan-angiotensin II antagonist), amlodipine besylate (AML) (calcium channel receptor blocker) and hydrochlorothiazide (HCTZ) (thiazide diuretic) formulated as a once a day (QD) tablet for oral use in five strengths combinations (20mg OM/5mg AML/12.5mg HCTZ, 40mg OM/5mg AML/12.5mg HCTZ, 40mg OM/5mg AML/25mg HCTZ, 40mg OM/10mg AML/12.5mg HCTZ, 40mg OM/10mg AML/25 mg HCTZ). The three APIs are already registered in drug products on the US market and are consequently considered "existing". Olmesartan medoxomil (OM) is an active ingredient in Benicar® approved in April 2002 (NDA 21-286), in Benicar HCT® approved in June 2003 (NDA 21-532) and in Azor® approved in September 2007 (NDA 22-100).

A. Description of the Drug Product(s) and Drug Substance(s)**DRUG SUBSTANCES**

OM is a white to pale yellowish white crystalline powder with a characteristic odor. There are no chiral centers. Its dissociation constant (pKa) when measured at 20°C in Britton Robinson buffer solution is 4.3. No evidence of polymorphism has been observed nor is it hygroscopic. OM is practically insoluble in aqueous solution over the physiological pH range (pH 2 to 6) with increasing solubility at pH>6 and <2. Consequently the pH-dependent solubility and other additional studies have demonstrated that particle size control is an important parameter for OM and the applicant has established an appropriate specification.

AML is a white or almost white powder. AML has one chiral center and the drug substance is presented as a racemic mixture. Its dissociation constant (pKa) is 9.02 at 23.5°C. Amlodipine besylate is found to crystallize as an anhydrate from organic solvents and as a monohydrate from aqueous solutions. Both forms were considered to be stable. It is not hygroscopic and does not exhibit polymorphism. Since AML is more soluble than OM, the particle size of the AML drug substance is less critical. Nevertheless, the particle size distribution is controlled by an appropriate specification by the applicant.

Executive Summary Section

HCTZ is a white or almost white crystalline powder and has no chiral centers. Its pKa is 7.9 and 9.2. Although different polymorphs of HCTZ exist, the drug substance batches provided did not exhibit polymorphism. Since HCTZ is more soluble than OM, the particle size of HCTZ drug substance is less critical. Nevertheless, the particle size distribution is controlled by an appropriate specification by the applicant.

The applicant tested the compatibility of the three drug substances (b) (4)

The mixtures were found to be stable for 6 weeks at 60°C in glass bottles and for 12 weeks at 40°C/75% RH in glass bottles and under open conditions. No novel impurities were detected. Accordingly, they concluded that the three drug substances are compatible with each other.

The specification for each of the drug substances and the COAs of the lots of drug substances used in the registration stability batches are presented in this review. For the rest of the drug substance sections applicant refers the reviewer to the respective DMFs.

DRUG PRODUCT

CS-8635 Tablets are conventional film-coated tablet for immediate release. Each tablet strength can be distinguished by color and size, as well as by the debossing code, which is specific to each strength. (b) (4)

Extensive investigations of bioavailability of prototype formulations were conducted during the development of CS-8635 Tablets. The results of these investigations support the bioequivalence of the proposed fixed-dose combination product with the corresponding reference of the previously approved products Benicar HCT® Tablets and Antacal® (Errekappa/licensed by Pfizer, Inc.). Benicar HCT® Tablets is the fixed-dose combination product containing OM/HCTZ. Antacal® (Errekappa/licensed by Pfizer, Inc.) is a monotherapy product containing AML.

The excipients employed in the final formulation of CS-8635 Tablets are the same ones used for the commercial Azor® Tablets, viz. pregelatinized starch (b) (4), silicified microcrystalline cellulose (b) (4), croscarmellose sodium (b) (4), magnesium stearate (b) (4), and various grades of (b) (4) as film coating systems. The applicant has developed a dissolution test method to be discriminatory, by selecting dissolution test conditions appropriate for monitoring all three active substances simultaneously. The dissolution method is identical to that for the Azor tablets, viz. 900 mL of 0.05 M phosphate buffer solution pH 6.8 with USP apparatus 2 at 50 rpm. ONDQA Biopharm will determine the method and specification acceptability.

The manufacturing process was derived from the well established process for Azor tablets, viz. a (b) (4) manufacturing process. Based on a risk assessment of the process, it was determined that the particle size distributions of the drug substances were considered to be critical for manufacturability

Executive Summary Section

and dissolution behavior. Accordingly, appropriate particle size specifications have been established for the drug substances.

A comprehensive stability program has been initiated by the applicant that encompasses all the CS-8635 Tablet strengths (20/5/12.5 mg, 20/10/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg and 40/10/25 mg) and packaging configurations (7 count-30cc & 90 count-60 cc HDPE bottles with desiccant and induction seal and capped with a CRC closure and aluminum/aluminum blister). The primary stability study employs a bracketing design that uses some of the packaging configurations, thus providing for a reduced stability program. Supporting stability studies are included, which assessed photostability of drug substance and drug product, freeze-thaw stability of the drug product, bulk drug product stability (b) (4), tablet cores and film-coated tablets holding time studies), and in-use stability studies. Supportive stability studies were also conducted to evaluate the drug product packaged in an alternative bottle packaging configuration (7-count-30 cc and 90-count-60 cc HDPE bottles without desiccant). The stability of the drug product packaged in blisters exposed to a high temperature stress condition was also assessed. Updated stability data (24 months at 25°C/60% RH) has been recently provided in the Amendment-Sr. No. 0007 of 17-Mar-2010. Based on the satisfactory stability data and the minimum calculated shelf life (b) (4) months, the applicant proposes a shelf life of 36 months for all dose strengths and all packaging variations (bottles with desiccant and blister) of CS-8635 drug product. Their shelf life proposal is acceptable based on ICH Q1E 2.4.1.1.

The applicant has included a Post Marketing Plan containing a comprehensive Comparability Protocol to support an alternative container closure system: HDPE bottle without desiccant. The Comparability Protocol is acceptable based on the stability plan presented above and that the same release and shelf life specifications will be used as presented in this NDA. Their proposed regulatory category, CBE-0, is acceptable based on the satisfactory supportive stability without the desiccant.

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

1 INDICATIONS AND USAGE

The product is indicated for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension.

2 DOSAGE AND ADMINISTRATION

General Considerations

Dose once daily.

Dosage may be increased after 2 weeks. The full blood pressure lowering effects are attained within 2 weeks after a change in dose. The maximum recommended dose of the product is 40/10/25 mg. It may be taken with or without food (b) (4).

Renal impairment: The usual regimens of therapy with the product may be followed if the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so avoid use of this product

Replacement Therapy

Executive Summary Section

The product may be substituted for its individually titrated components. [REDACTED]

(b) (4)

Add-on/Switch Therapy

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

Approvability will be based on the applicant's response to FDA comments submitted through an IR letter. These comments are the following:

1. P.2.2.1 Formulation Development:

Provide details of the experimental design and statistical analysis you employed on the 40/10/25 mg strength tablets in investigating the concentration of the [REDACTED] pregelatinized starch and croscarmellose sodium. The details should include the polynomial model used, the regression coefficients for main and interacting independent variables, the standard error, the statistical method to determine significance [statistical criteria for goodness of fit of model (R²) and p and t-values to determine the significance of the regression coefficients].

2. P.5.1 Specification

a. Provide a single consolidated drug product specification table that includes release and stability limits.

b. Regarding the Degradation Products test in your specification, the unspecified peak amount is attributed to which drug substance? Additionally, provide a justification for the high acceptance criterion of unidentified total on stability (NMT [REDACTED]), considering that actual levels on stability are [REDACTED].

c. Regarding the microbial contamination test, you state in P.5.6, 'Justification of Specification' that the frequency of release testing is consistent with the principles of the Periodic Quality Indicator Test (PQIT) program. Accordingly, this test should not be a part of the drug product specification but as a separate "PQIT" test.

3. P.8.2 Postapproval Stability Protocol and Stability Commitment

Your [REDACTED] is not acceptable, [REDACTED].

[REDACTED] Accordingly, each stability batch in your plan should conform to the testing frequency stated in ICH Q1A(R2) 2.2.6. – “- the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period”. Further, the test for microbial contamination should also be performed at the 12 month time point.

Executive Summary Section

4. Review of Common Technical Document-Quality (Ctd-Q) Module

1A. Labeling& Package Insert

The established names on the container label should be in parenthesis, with the word 'tablets' inserted after the parenthesis.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review: Prafull Shiromani, Ph.D.

ChemistryTeamLeaderName/Date: Kasturi Srinivasachar, Ph.D.

ProjectManagerName/Date: Russell Fortney

C. CC Block

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

PRAFULL K SHIROMANI
03/30/2010

KASTURI SRINIVASACHAR
03/31/2010

Initial Quality Assessment Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	200-175
Applicant:	Daiichi Sankyo Inc.
Letter Date:	30 Sep 2009
Stamp Date:	30 Sep 2009
PDUFA Date:	31 Jul 2010
Tradename:	(b) (4)
Established Name:	Olmesartan medoxomil/ Amlodipine/ hydrochlorothiazide
Dosage Form:	Tablets, 20/5/12.5 mg, 40/5mg/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg
Route of Administration:	Oral
Indication:	Hypertension
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

Summary

This is an e-CTD 505(b)(2) NDA application for a fixed dose combination drug product containing 3 active ingredients, olmesartan, amlodipine and hydrochlorothiazide. Amlodipine is a calcium channel receptor blocker, olmesartan is an angiotensin II antagonist and hydrochlorothiazide is a diuretic. All 3 drugs are currently marketed as monotherapies and dual fixed dose combination products--- Norvasc, Pfizer, NDA 19-787; Benicar, Sankyo, NDA 21-286; Benicar HCT, Sankyo, NDA 21-532; Azor, Sankyo, NDA 22-100. The Applicant proposes to market 5 strengths of the fixed dose combination drug product. The formulation developed is for immediate release of all actives. This NDA is based on the results from a Phase III clinical trial demonstrating that the antihypertensive effect of a triple combination at the highest dose is superior to each double combination at the highest dose, 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 Special Protocol Assessment for Primary Stability Studies incorporating a reduced testing design was submitted on Sep 14, 2007 to IND 77,651. Based on Agency comments and teleconference on Dec 18, 2007, the stability protocol was revised and finalized in an amendment submitted on Jan 31, 2008. A CMC specific EOP2 meeting was held with Sankyo to discuss issues pertaining to an NDA submission such as drug substance particle size distribution and dissolution. It was agreed that a comparability protocol could be submitted for a HDPE bottle packaging system without desiccant.

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 products, Benicar HCT, NDA 21-532 and Azor, NDA 22-100. 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 6 formal reviews of this DMF and its amendments. The last review dated Jun 9, 2009 found the DMF adequate.

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 and atorvastatin calcium), NDA 21-540, Exforge (amlodipine and valsartan), NDA 21-990 and Azor (amlodipine and olmesartan medoxomil), NDA 22-100. It belongs to BCS Class III and has an USP monograph. There are 2 suppliers of this drug substance, (b) (4) and both have DMFs on file. DMF # (b) (4) was last reviewed on Mar 3, 2009 and deemed adequate. The (b) (4) DMF # (b) (4) was last reviewed on Sep 4, 2009 and also found adequate.

Hydrochlorothiazide:

This drug substance, which has an USP monograph, has been used in numerous combination drug products including Sankyo's Benicar HCT. There are two suppliers for this NDA, (b) (4) and (b) (4). (b) (4) DMF # (b) (4) and (b) (4) DMF # (b) (4) were last reviewed on Sep 21, 2009 and Sep 29, 2009 respectively and both were determined to be adequate.

Drug Product

Conventional excipients (pregelatinized starch, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate and (b) (4)) are used in the manufacture of the film coated immediate release tablets. (b) (4)

Data are provided for 6 strengths, 20/5/12.5, 20/10/12.5, 40/5/12.5, 40/5/25, 40/10/12.5 and 40/10/25 mg of olmesartan medoxomil/amlodipine/hydrochlorothiazide although the 20/10/12.5 mg strength is not proposed to be marketed in the US. The different strengths will be differentiated by color, shape and debossing codes. (b) (4)

The film coating is used to impart different colors to the different strengths. (b) (4)

The drug product is packaged in HDPE bottles with desiccant and aluminum/aluminum blisters. A comparability protocol for the use of an alternative container closure system, HDPE bottles without desiccant, has been submitted. The specification proposed has all the requisite test attributes for solid oral dosage forms. The protocol for the primary stability studies was discussed and agreed to well in advance of NDA submission. Three batches of the highest and lowest strengths (2 pilot and one laboratory scale) and 2 pilot scale batches of the intermediate strengths are included in the stability studies. A bracketing design has been applied to the bottle presentations of 30^{(b) (4)} and 90 counts. Real time data have been provided for 12 months, in addition to accelerated data for 6 months. Based on statistical evaluation of the data, a ^{(b) (4)} expiration dating period is proposed. An additional 6 months' data will be provided in an update and an extension of the expiration dating period will be proposed.

Critical Review Issues

Drug Substance

- Sankyo has set particle size distribution acceptance criteria for hydrochlorothiazide based on data from both suppliers. Are these criteria sufficient to ensure product performance?
- Sankyo's specification for hydrochlorothiazide, which encompasses both suppliers, ^{(b) (4)} Is this acceptable?
- Issues regarding amlodipine besylate and olmesartan medoxomil (e.g. particle size) which were identified for NDA 22-100 (Azor) are also relevant to this NDA and need to be evaluated.

Drug Product

- Have the compatibility studies between the 3 drug substances and with the excipients been adequately performed?
- ^{(b) (4)}
- ^{(b) (4)}
- Is the proposed manufacturing process suitable for routine full scale production?
- Dissolution testing of the drug product should be consulted to the Biopharmaceutics team in ONDQA. They should also be consulted on the applicability of biowaivers for the 3 intermediate strengths of the drug product.
- The microbial contamination test in the specification is stated to be a non-routine release test with a minimum of one batch tested every 6 months. Is this acceptable?
- Have the stability studies been conducted in conformance with the Agency recommendations?
- ^{(b) (4)}

- The proposed Comparability Protocol for an alternative container closure system consisting of HDPE bottles without desiccant should be carefully evaluated. Is the proposed CBE-0 supplement acceptable?

Comments and Recommendations

The application is fileable. Facilities have been entered into EES and the reviewer should confirm the accuracy and completeness of the entries. It is noted that the labeling accurately reflects the established name and matching strength for amlodipine. 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

Oct. 27, 2009
Date

Ramesh Sood, Ph.D.
Branch Chief

Oct. 27, 2009
Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

KASTURI SRINIVASACHAR
10/27/2009

RAMESH K SOOD
10/27/2009