

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202331Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-331

Edarbyclor

(azilsartan medoxomil plus chlorthalidone) tablets

(b) (4) 40/12.5 mg, (b) (4) 40/25 mg

Takeda Global Research & Development Center, Inc

CMC Review # 2

Prafull Shiromani Ph.D.

**Division of Pre-Marketing Assessment 1
Division of Cardiovascular and Renal Products
Office of New Drug Quality Assessment**

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Chemistry Review Data Sheet

1. NDA 202-331
2. REVIEW #: 2
3. REVIEW DATE: 26-Oct-2011
4. REVIEWER: Prafull Shiromani Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA and its Amendments (0004/0014)	21-Feb-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0019-Complete Responses to CMC IR Letter dated 27-Jun-2011	7/13/2011
Quality Response to ONDQA Biopharm IR Letter; Supplement No, 25	10/18/2011

7. NAME & ADDRESS OF APPLICANT:

Name: Takeda Pharmaceuticals North America
Address: One Takeda Parkway, Deerfield, Illinois
Representative: Beth-Ann Knapp, Manager, Regulatory Affairs,
Takeda
Telephone: (224) 554-2187

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: EDARBYCLOR (azilsartan medoxomil plus chlorthalidone) tablets
- b) Non-Proprietary Name (USAN): Azilsartan kamedoxomil plus chlorthalidone
- c) Code Name/# (ONDC only): TAK-491CLD
- d) Chem. Type/Submission Priority (ONDC only):
 - i. Chem. Type: 4
 - ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Treatment of Hypertension

11. DOSAGE FORM: Tablets

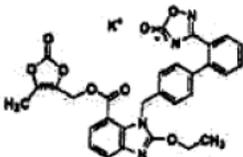
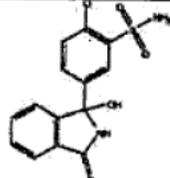
12. STRENGTH/POTENCY: (b) (4) 40/12.5 mg, (b) (4) 40/25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [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

	TAK-491	Chlorthalidone
Structure		
Chemical Name	(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate potassium salt	2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)-benzenesulfonamide
Molecular Formula	$C_{30}H_{23}KN_4O_8$	$C_{14}H_{11}ClN_2O_4S$
Molecular Weight	606.62	338.77

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	01-AUG-2011	LOA: 15-Oct-2010
	IV		4	Adequate		LOA: 30-Sep-2010	
	III		4	Adequate		LOA: 02-Feb-2010	
	III		4	Adequate		LOA: 28-Jan-2010	
			4	Adequate		LOA: 15-Dec-2009	
	III		4	Adequate		LOA: 27-Jan-2010.	
			4	Adequate		LOA: 17-Feb-2010	

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	Adequate		LOA: 12-Feb-2010
			4	Adequate		LOA: 23-Feb-2010
	III		4	Adequate		LOA: 28-Jan-2011
	III		4	Adequate		LOA: 11-feb-2010

¹ 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")

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	Overall Recommendation: Acceptable.	20-May-2011	D. Smith
Pharm/Tox	Approvable	18-Jul-2011	P. Gatti

Chemistry Review Data Sheet

Biopharm	Recommendation for Approval with a Post Marketing Commitment	24-Oct-2011	T. Chen
LNC			
Methods Validation	Samples of the DS, DP and reference compounds are available.		Validation is not required since the analytical methods are conventional.
DMEPA	Acceptable	12-Jul-2011	C. Holquist
EA	Their submission of a categorical exclusion from preparation of an environmental assessment is granted	25-May-2011	P. Shiromani
Microbiology	N/A		

The Chemistry Review for NDA 202-331

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the FDA CMC IR letter sent on 27-Jun-2011. Additionally, the ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS (10-24-2011); revised drug product dissolution specifications are recommended therein. They conclude that this NDA is recommended for approval with a Post Marketing Commitment to be included in the Approval Letter, which the applicant has agreed to in their Supplement # 25; this PMC is included in their review. There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective with the inclusion of the above PMC.

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

N/A

II. Summary of Chemistry Assessments

This is an e-CTD NDA application for a fixed dose combination drug product of azilsartan medoxomil, which is a prodrug of an antagonist of the Angiotensin II subtype 1 receptor (i.e. an AII receptor blocker or ARB) and chlorthalidone, a diuretic. Azilsartan medoxomil, to be marketed under the trade name Edarbi, was recently approved for the treatment of hypertension. The primary objective of the azilsartan medoxomil/chlorthalidone clinical program was to develop a fixed dose combination treatment for hypertension that is more effective than either drug alone.

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

Drug Substance

One of the drug substances in this combination drug product is the potassium salt of azilsartan medoxomil. Chlorthalidone is the second drug substance in this combination product. An authorization to DMF (b)(4) was provided for CMC information on chlorthalidone. The initial review of this DMF by this reviewer determined that the DMF was inadequate to support this NDA and the deficiencies were conveyed to the DMF holder. The DMF holder responded adequately to this deficiency letter and the DMF was subsequently reviewed to be supportive for this NDA-DMF Review #4.

Executive Summary Section

Drug Product

(b) (4) strengths of the fixed dose combination drug product were developed as potential commercial formulations – (b) (4) 40/12.5 mg, 40/25 mg, (b) (4) of azilsartan medoxomil and chlorthalidone. However, (b) (4) these strengths are being proposed for marketing – (b) (4) 40/12.5 mg, 40/25 mg (b) (4). The different strengths of these immediate release tablets are distinguished by size, film color and dose specific imprinted markings on one side.

The details of the drug substances and the drug product are presented in CMC Review #1 of this NDA.

This CMC Review # 2 pertains to FDA CMC evaluation of the applicant's responses to the FDA IR Letter of 27-Jun-2011. Their responses are satisfactory, a few of which are summarized below:

(b) (4)

-In response to the FDA comment to include a test for the residual solvents (b) (4) in the drug product specification so as to be in compliant with USP <467>, they have provided data to conclude that the amounts of (b) (4) are reduced (b) (4) to levels well below ICH Q3C (R5) limits. Therefore, their proposal not to include a test for residual solvents in the drug product specification is justified and hence, acceptable.

-They have agreed to the proposed assay limit of 92.0-108.0% for the chlorthalidone component of the TAK-491CLD tablets, so as to be in tandem with the USP monograph assay limits for chlorthalidone tablets. This revision is reflected in the provided updated drug product specification.

-They have agreed to include the 30-month test time point in the stability protocol for the product packaged in bottles for which they are requesting a 30-month expiration dating period; the latter based on satisfactory real time 18 months stability data.

The ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS (10-24-2011); the following revised drug product dissolution acceptance criteria are recommended therein:

a. Azilsartan medoxomil:

Q= (b) (4) at 30 min for (b) (4) 40/12.5, 40/25 mg strengths.
(b) (4)

Executive Summary Section

b. Chlorthalidone:

Q= (b) (4) at 15 min for (b) (4) 40/12.5, 40/25 mg strengths.
(b) (4)

The revised drug product specifications are included in the applicant's supplement 25, dated 10/18/2011.

The applicant has agreed to the PMC as per their following statement in Supplement # 25/3.2.P.5.1 'Specifications'

"After one year from NDA approval, Takeda commits to provide justification for a revised specification (Q and timepoint) for all strengths of TAK-491CLD for which dissolution testing for TAK-491 or chlorthalidone during that year proceeds to Stage 2 testing at a rate of (b) (4). Any revised dissolution specification will be submitted to the NDA as a post approval supplement."

ONDQA Biopharm therefore states that this NDA is recommended for approval with a Post Marketing Commitment to be included in the Approval Letter.

B. Description of How the Drug Product is Intended to be Used**1. Indications and Usage**

Edarbyclor is an angiotensin II receptor blocker (ARB) and a thiazide like diuretic combination product indicated for the treatment of hypertension, to lower blood pressure. Edarbyclor may be used as initial therapy if a patient is likely to need multiple drugs to achieve blood pressure control. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

2. Dosage and Administration

- The usual starting dose of Edarbyclor in adults is (b) (4) 40/12.5 mg taken orally once daily. The dose may be increased after 2-4 weeks as needed to control blood pressure. The maximally effective dose is 40/25 mg.
- Edarbyclor may be administered with or without food.
- Edarbyclor may be administered with other antihypertensive agents. Patients who experience dose-limiting adverse reactions with chlorthalidone may be switched to Edarbyclor tablets containing a lower dose of chlorthalidone.

-----DOSAGE FORMS AND STRENGTHS-----
Tablets: (b) (4) 40/12.5 mg, (b) (4) 40/25 mg

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

C. Basis for Approvability or Not-Approval Recommendation

Executive Summary Section

The applicant has provided adequate responses to the FDA CMC IR letter sent on 27-Jun-2011. Additionally, the ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS (10-24-2011); revised drug product dissolution specifications are recommended therein. They conclude that this NDA is recommended for approval with a Post Marketing Commitment to be included in the Approval Letter; this PMC is included in their review. There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective with the inclusion of the above PMC.

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

ChemistName/Date: Prafull Shiromani Ph.D.
ChemistryTeamLeaderName/Date: Ramesh Sood Ph.D.
ProjectManagerName/Date: Quynh Nguyen

C. CC Block

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/s/

PRAFULL K SHIROMANI

10/31/2011

Smitap47^

RAMESH K SOOD

11/01/2011

NDA 202-331

Edarbyclor

(azilsartan medoxomil plus chlorthalidone) tablets

(b) (4) 40/12.5 mg, (b) (4) 40/25 mg

Takeda Global Research & Development Center, Inc

Prafull Shiromani Ph.D.

**Division of Pre-Marketing Assessment 1
Division of Cardiovascular and Renal Products
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Chemistry Review Data Sheet

1. NDA 202-331
2. REVIEW #: 1
3. REVIEW DATE: 07-Jul-2011
4. REVIEWER: Prafull Shiromani Ph.D.
5. PREVIOUS DOCUMENTS: N/A

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA 202331
Amendment 0004
Amendment 0014

21-Feb-2011
06-Apr-2011
31-May-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Takeda Pharmaceuticals North America
Address: One Takeda Parkway, Deerfield, Illinois
Representative: Beth-Ann Knapp, Manager, Regulatory Affairs,
Takeda
Telephone: (224) 554-2187

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: EDARBYCLOR (azilsartan medoxomil plus chlorthalidone) tablets
- b) Non-Proprietary Name (USAN): Azilsartan kamedoxomil plus chlorthalidone
- c) Code Name/# (ONDC only): TAK-491CLD
- d) Chem. Type/Submission Priority (ONDC only):
 - i. Chem. Type: 4
 - ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Treatment of Hypertension

11. DOSAGE FORM: Tablets

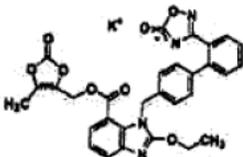
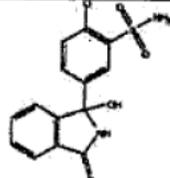
12. STRENGTH/POTENCY: (b) (4) 40/12.5 mg, (b) (4) 40/25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [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

	TAK-491	Chlorthalidone
Structure		
Chemical Name	(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate potassium salt	2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)-benzenesulfonamide
Molecular Formula	$C_{30}H_{23}KN_4O_8$	$C_{14}H_{11}ClN_2O_4S$
Molecular Weight	606.62	338.77

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)	1	Inadequate	13-Apr-2011	LOA: 15-Oct-2010
	IV			4	Adequate		LOA: 30-Sep-2010
	III			4	Adequate		LOA: 02-Feb-2010
	III			4	Adequate		LOA: 28-Jan-2010
				4	Adequate		LOA: 15-Dec-2009
	III			4	Adequate		LOA: 27-Jan-2010.
				4	Adequate		LOA: 17-Feb-2010

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	Adequate		LOA: 12-Feb-2010
			4	Adequate		LOA: 23-Feb-2010
	III		4	Adequate		LOA: 28-Jan-2011
	III		4	Adequate		LOA: 11-feb-2010

¹ 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")

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	Overall Recommendation: Acceptable.	20-May-2011	D. Smith
Pharm/Tox	Pending		

Chemistry Review Data Sheet

Biopharm	Pending		
LNC			
Methods Validation	Samples of the DS, DP and reference compounds are available.		Validation is not required since the analytical methods are conventional.
DMEPA	Pending		
EA	Their submission of a categorical exclusion from preparation of an environmental assessment is granted	25-May-2011	P. Shiromani
Microbiology	N/A		

The Chemistry Review for NDA 202-331

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The 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 IR Letter.

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

N/A

II. Summary of Chemistry Assessments

This is an e-CTD NDA application for a fixed dose combination drug product of azilsartan medoxomil, which is a prodrug of an antagonist of the Angiotensin II subtype 1 receptor (i.e. an AII receptor blocker or ARB) and chlorthalidone, a diuretic. Azilsartan medoxomil, to be marketed under the trade name Edarbi, was recently approved for the treatment of hypertension. The primary objective of the azilsartan medoxomil/chlorthalidone clinical program was to develop a fixed dose combination treatment for hypertension that is more effective than either drug alone.

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

Drug Substance

One of the drug substances in this combination drug product is the potassium salt of azilsartan medoxomil. It is a white crystalline powder which is practically insoluble in acidic and neutral aqueous solutions. The solubility increases slightly at (b) (4). The specifications for the drug substance include limits for particle size in addition to the customary attributes of assay, impurities, identification tests and water content. A retest period of (b) (4) is currently approved. Full details on the characterization, manufacture and control strategy for this drug substance have been submitted in NDA 200-796 which is cross-referenced for this information.

Chlorthalidone, the second drug substance in this combination product, is a creamish to slightly yellow (b) (4). It is practically insoluble in water, ether or chloroform and soluble to slightly soluble in methanol or ethanol. An authorization to

Executive Summary Section

DMF (b) (4) has been provided for CMC information on chlorthalidone. The original DMF was reviewed in support of Takeda's initial IND application for this combination drug product on Apr 30, 2008 and found adequate. Subsequently, an annual report was reviewed by OGD on Sep 18, 2009 and the conclusion was that the DMF remained adequate. A quality amendment and an annual report have been submitted more recently and have not been reviewed. A 'Justification for Re-review' of this DMF was submitted as a memo-to-file into DARRTS by this reviewer as major issues in the original DMF submission were not addressed in previous CMC reviews. The DMF holder (b) (4)

The review of this DMF by this reviewer determined that the DMF was inadequate to support this NDA; the deficiencies were conveyed to the DMF holder. In addition to the DMF reference, the applicant has submitted in the NDA the sites responsible for the manufacture of chlorthalidone, specifications, analytical procedures with validation data for residual solvents and particle size and COAs for multiple lots of this drug substance used in clinical and stability studies of the combination product. The specification for this drug substance is as that described in USP 33 chlorthalidone monograph with the exception for test for particle size and residual solvents.

Drug Product

(b) (4) strengths of the fixed dose combination drug product were developed as potential commercial formulations – (b) (4) 40/12.5 mg, 40/25 mg, (b) (4) of azilsartan medoxomil and chlorthalidone. However, (b) (4) these strengths are being proposed for marketing – (b) (4) 40/12.5 mg, 40/25 mg (b) (4). The different strengths of these immediate release tablets are distinguished by size, film color and dose specific imprinted markings on one side. The excipients used in the formulation are standard compendial ingredients

Both drug substances belong to BCS Class 4 i.e. low solubility and low permeability. Consequently their particle size distribution can potentially affect dissolution of the product. Experiments were carried out to show that azilsartan medoxomil particle size does not significantly influence dissolution characteristics of the finished product whereas chlorthalidone particle size has a somewhat greater effect.

(b) (4)

Based on pharmaceutical and bioavailability studies, (b) (4) (u) (4) was chosen for further development in phase 3 clinical studies. The commercial formulation differs from the phase 3 formulation only in colorants and printing ink.

The manufacturing process development (b) (4)

Executive Summary Section

(b) (4)
The basic formulation factors that were deemed to be potentially important are:

(b) (4)
It was established by experimentation that the use of (b) (4) for azilsartan medoxomil and chlorthalidone improved the stability of the former as shown by the amounts of related substances derived from azilsartan medoxomil. The basic commercial manufacturing process chosen consists of the following unit operations: (b) (4)

All unit operations were assessed for their potential impact on quality attributes of the finished product and it was concluded that the following parameters required experimental investigation to define their statistical significance:

(b) (4)
Based on a number of studies including two large studies executed using DOE, and the verification of performance at commercial scale, no critical process parameters were identified within the ranges studied and all manufacturing processes were shown to be controllable within these ranges. The results of the DOE studies have been systematically presented in terms of ANOVA (analysis of variance) and Pareto analysis. Acceptable process ranges have been provided for the operating parameters and in-process controls at commercial scale for each of the processes – (b) (4)

The acceptable process ranges include the set points used for the experimental design at commercial scale and account for inherent process variability observed during manufacturing. To further ensure high quality of product, two key control parameters (b) (4)

were defined in the production of the product tablets.

The regulatory specifications for (b) (4) strengths of the drug product include the customary test items for solid oral dosage forms-- appearance, identification, assay, related substances, content uniformity and dissolution. Batch analysis data for product used in clinical trials and primary stability studies have been submitted. The applicant has provided several reasons for excluding the microbial limit test in the specification. (b) (4)

The packaging systems proposed for the product consist of HDPE bottles that contain desiccant packets or canisters (b) (4)

Executive Summary Section

(b) (4)

These container/closures were chosen to minimize the exposure of the product to moisture.

Primary stability studies have been carried out on 3 pilot scale batches of each strength proposed for marketing in commercial packaging configurations. In the original submission 12 months of long term data for the bottles and 18 months of data for the blisters, together with 6 months of data at accelerated conditions for both bottles and blisters were presented. In the 0014 Amendment of 31-May-2011, six months of additional long-term stability data were submitted. Moisture content, as measured by LOD, and tablet hardness were monitored at each test interval in the primary stability studies for information purposes and microbiological testing was carried out at the 6 month time point under accelerated conditions and annually under long term storage conditions. Since the dissolution method was changed from the original procedure to the proposed commercial procedure, blister stability data represents both methods and a bridging study has been performed. However, for 30 and 90 count HDPE bottles, only the proposed commercial procedure has been used. Statistical evaluation of the data for assay and related substances has been performed. An initial expiration dating period of 30 months for 30 and 90 count bottles (b) (4) is proposed. The proposed shelf lives are in conformance to ICH Q1E - extrapolation up to twice the length of available long-term data, but not exceeding it by more than 12 months. Based on the stability data presented their proposal is justified and hence, acceptable.

The applicant has also provided data from a bulk stability study for one lot of each strength of the product, packaged in an (b) (4). The tablets demonstrated satisfactory stability through 24 months storage at 25°C/60% RH and three months at 40°C/75% RH. The tablets were also found to be stable in a photostability study conducted in accordance with ICH Q1B Option 2 (cool white fluorescent light and near UV light). In a severe humidity stress study, where tablets were exposed to 25°C/60% RH in open amber glass bottles, the amount of TAK-491 total related substances increased due to increase in the amount of (b) (4) but still below the acceptance criterion of (b) (4). This study may be considered to be analogous to a simulated 90-day patient in-use study.

Claim Of Categorical Exclusion

The applicant states that this application meets the requirements for categorical exclusion from the preparation of an environmental assessment as stated in 21 CFR 25.31(b). They base their request on calculations performed to confirm that the estimated concentration of the new drug substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). Recalculations performed by this reviewer based on a 2000 EPA update of (<http://www.epa.gov/owm/mtb/cwns/2000rtc/toc.htm>) arrived at the same conclusion and hence, their request for Categorical Exclusion is granted. The monotherapy product of azilsartan medoxomil, was also granted a Categorical Exclusion by the OPS reviewer.

Executive Summary Section

EES

The Office of Compliance issued an 'Overall Recommendation of Acceptability' on 02-May-2011; their summary report is included in this review.

B. Description of How the Drug Product is Intended to be Used**1. Indications and Usage**

Edarbyclor is an angiotensin II receptor blocker (ARB) and a thiazide like diuretic combination product indicated for the treatment of hypertension, to lower blood pressure. Edarbyclor may be used as initial therapy if a patient is likely to need multiple drugs to achieve blood pressure control. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

2. Dosage and Administration

- The usual starting dose of Edarbyclor in adults is (b) (4) 40/12.5 mg taken orally once daily. The dose may be increased after 2-4 weeks as needed to control blood pressure. The maximally effective dose is 40/25 mg.
- Edarbyclor may be administered with or without food.
- Edarbyclor may be administered with other antihypertensive agents. Patients who experience dose-limiting adverse reactions with chlorthalidone may be switched to Edarbyclor tablets containing a lower dose of chlorthalidone.

-----DOSAGE FORMS AND STRENGTHS-----
Tablets: (b) (4) 40/12.5 mg, (b) (4) 40/25 mg

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

C. Basis for Approvability or Not-Approval Recommendation

Approvability will depend on the applicant's response to the following CMC comments on the Drug Product:

1. DMF # (b) (4) for Chlorthalidone drug substance

This DMF was determined to be inadequate on review to support this NDA and hence, a deficiency letter has been sent to the DMF holder.

2. P.2.3 Manufacturing Process Development –Tablet Content Uniformity

You propose a control strategy, to ensure uniformity of CLD in tablets, by (b) (4)

Executive Summary Section

(b) (4) however, you did not provide any explanation of this control strategy adopted on commercial scale; accordingly, provide details of this strategy.

3. P.2.3 Manufacturing Process Development - Dissolution of CLD at (b) (4) minutes

(b) (4)

b. During your comprehensive study of factors affecting tablet dissolution, have you studied the combined effect (interaction) (b) (4) on tablet dissolution. If so, provide details. Your 'Prediction Profiler' plots show opposite effects of these independent variables on CLD dissolution (b) (4) minutes, as expected.

4. P.5.1 Specification(s)

- a. (b) (4)
- b. To comply with USP <467> include a test for the control of residual solvents in the drug product (b) (4)
- c. The USP monograph for chlorthalidone tablets has assay limits of 92-108%; accordingly, these limits should be reflected in your drug product specification.
- d. Provide a revised drug product specification with the above item/s reflected there-in.

5. P.5.2 Analytical Procedures

- a. Since your drug product is a combination product, clarify with explanation which drug substance peak in the chromatogram for related substances is used to calculate the amount of an unspecified impurity?
- b. You have provided two alternative procedures, a primary method and an alternative method, in the product specification for assay, content uniformity, related substances and dissolution; however, no study is presented to demonstrate equivalency and hence, interchangeability between these methods. Provide data to show that the primary and alternative methods are equivalent and hence, interchangeable.

6. P.8.1 Stability

Since you are requesting a 30-month expiration dating period for the product in the bottles, include a 30-month test time period in the stability protocol for the bottles.

7. R1 Executed Batch Records

Clarify the discrepancy between (b) (4)

Executive Summary Section

(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: Quynh Nguyen

C. CC Block

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

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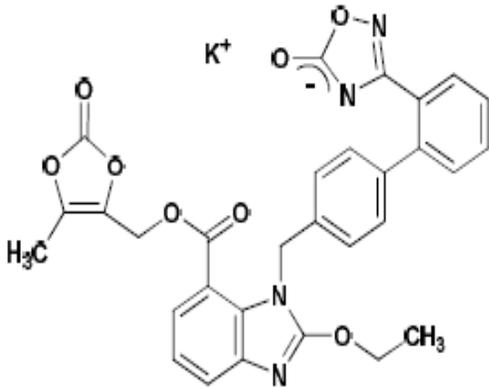
/s/

PRAFULL K SHIROMANI
07/07/2011

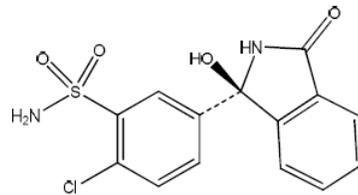
RAMESH K SOOD
07/11/2011

Initial Quality Assessment
Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 202-331
Applicant: Takeda Pharmaceuticals
Letter Date: Feb 21, 2011
Stamp Date: Feb 24, 2011
PDUFA Date: Dec 24, 2011
Tradename: Pending
Established Name: Azilsartan medoxomil and chlorthalidone
Dosage Form: Tablets, (b) (4) 40/12.5 mg, (b) (4) and 40/25 mg
Route of Administration: Oral
Indication: Hypertension
Assessed by: Kasturi Srinivasachar
ONDQA Fileability: Yes



Azilsartan medoxomil



Chlorthalidone

Summary

This is an e-CTD NDA application for a fixed dose combination drug product of azilsartan medoxomil, which is a prodrug of an antagonist of the Angiotensin II subtype 1 receptor (i.e. an AII receptor blocker or ARB) and chlorthalidone, a diuretic. Azilsartan medoxomil, to be marketed under the tradename Edarbi, was recently approved for the treatment of hypertension. An IND (77,278) for the fixed dose combination of azilsartan medoxomil and chlorthalidone was submitted by Takeda on March 24, 2008. The primary objective of the azilsartan medoxomil/chlorthalidone clinical program was to develop a fixed dose combination treatment for hypertension that is more effective than either drug alone.

Only one meeting with CMC issues was scheduled with Takeda – this was a Pre-NDA meeting involving nonclinical and quality reviewers. The meeting, which was to be held on Sep. 9, 2010, was cancelled based on the Agency's preliminary responses to the questions posed by the firm. The CMC issues that Takeda needed clarification on were mostly straightforward – agreement on cross-referencing NDA 200-796 for CMC information on azilsartan medoxomil, providing product stability updates 4 months after NDA submission with a proposal for extension of the expiration date etc. The only significant point raised by Takeda was the observation of an extra peak related to the chlorthalidone drug substance in the drug product HPLC analytical method. This has been identified as a tautomer of chlorthalidone and is claimed to result from sample preparation. Since this is not a degradant or process related impurity Takeda proposed not to assign a limit to this compound and not include it in the calculation of total impurities. They did however, commit to monitor and report the tautomer content in the registration and postapproval stability studies. This was acceptable to the Agency.

Drug Substance

One of the drug substances in this combination drug product is the potassium salt of azilsartan medoxomil. It is a white crystalline powder which is practically insoluble in acidic and neutral aqueous solutions. The solubility increases slightly at (b) (4)

The specifications for the drug substance include limits for particle size in addition to the customary attributes of assay, impurities, identification tests and water content. A retest period of (b) (4) is currently approved. Full details on the characterization, manufacture and control strategy for this drug substance have been submitted in NDA 200-796 which is cross-referenced for this information.

Chlorthalidone, the second drug substance in this combination product, is a creamish to slightly yellow (b) (4) It is practically insoluble in water, ether or chloroform and soluble to slightly soluble in methanol or ethanol. An authorization to DMF (b) (4) has been provided for CMC information on chlorthalidone. The original DMF was reviewed in support of Takeda's initial IND application for this combination drug product on Apr 30, 2008 and found adequate. Subsequently, an annual report was reviewed by OGD on Sep 18, 2009 and the conclusion was that the DMF remained adequate. A quality amendment and an annual report have been submitted more recently and have not been reviewed. In addition to the DMF reference, the Applicant has submitted in the NDA the sites responsible for the manufacture of chlorthalidone, specifications, analytical procedures with validation data for residual solvents and particle size and COAs for multiple lots of this drug substance used in clinical and stability studies of the combination product.

Drug Product

(b) (4) strengths of the fixed dose combination drug product were developed as potential commercial formulations – (b) (4) 40/12.5 mg, 40/25 mg, (b) (4) of azilsartan medoxomil and chlorthalidone. However, (b) (4) these strengths are being proposed for marketing – (b) (4) 40/12.5 mg, 40/25 mg (b) (4). The different strengths of these immediate release tablets are distinguished by size, film color and dose specific imprinted markings on one side. The excipients used in the formulation are standard compendial ingredients with the exception of the printing ink used for tablet markings.

Both drug substances belong to BCS Class 4 i.e. low solubility and low permeability. Consequently their particle size distribution can potentially affect dissolution of the product. Experiments were carried out to show that azilsartan medoxomil particle size does not significantly influence dissolution characteristics of the finished product whereas chlorthalidone particle size has a somewhat greater effect.

(b) (4)

Based on pharmaceutical and bioavailability studies, (b) (4) was chosen for further development in phase 3 clinical studies. The commercial formulation differs from the phase 3 formulation only in colorants and printing ink.

(b) (4)

The basic formulation factors that were deemed to be potentially important are:

(b) (4)

It was established by experimentation that the use of (b) (4) for azilsartan medoxomil and chlorthalidone improved the stability of the former as shown by the amounts of related substances derived from azilsartan medoxomil. The basic commercial manufacturing process chosen consists of the following unit operations: (b) (4)

All unit operations were assessed for their potential impact on quality attributes of the finished product and it was concluded that the following parameters required experimental investigation to define their statistical significance:

(b) (4)

Based on a number of studies including two large studies executed using DOE, and the verification of performance at commercial scale, no critical process parameters were identified within the ranges studied and all manufacturing processes were shown to be controllable within these ranges. Acceptable process ranges have been provided for the operating parameters and in-process controls at commercial scale for each of the processes – (b) (4)

The acceptable process ranges include the set points used for the experimental design at commercial scale and account for inherent process variability observed during manufacturing. To further ensure high quality of product, two key control parameters, (b) (4) were defined in the production of the product tablets.

The regulatory specifications for (b) (4) strengths of the drug product include the customary test items for solid oral dosage forms-- appearance, identification, assay, related substances, content uniformity and dissolution. Batch analysis data for product used in clinical trials and primary stability studies have been submitted.

The packaging systems proposed for the product consist of HDPE bottles that contain desiccant packets or canisters (b) (4)

Primary stability studies have been carried out on 3 pilot scale batches of each strength proposed for marketing in commercial packaging configurations. 12 months of long term data are available for the bottles whereas 18 months of data have been submitted for the drug product in blisters. 6 months of data at accelerated conditions are available for both bottles and blisters. Moisture content, as measured by LOD, and tablet hardness were monitored at each test interval in the primary stability studies for information purposes and microbiological testing was carried out at the 6 month time point under accelerated conditions and annually under long term storage conditions. Since the dissolution method was changed from the original procedure to the proposed commercial procedure, blister stability data represents both methods and a bridging study has been performed. However, for 30 and 90 count HDPE bottles, only the proposed commercial procedure has been used. Statistical evaluation of the data for assay and related substances has been performed. An initial expiration dating period of (b) (4) for 30 and 90 count bottles and 30 months for blisters is proposed.

Critical Review Issues

Drug Substance

- As mentioned earlier, DMF (b) (4) for chlorthalidone has only been reviewed in support of the IND application for the fixed dose combination of azilsartan medoxomil and chlorthalidone. The information in the DMF and the DMF review should be checked to see if it is adequate to support an NDA (e.g. acceptability of starting materials, specifications of starting materials and intermediates, adequacy of drug substance specifications etc.). Updated information submitted in 2010 and 2011 in the form of amendments and annual reports should also be evaluated.
- Have the particle size acceptance criteria for chlorthalidone been adequately justified particularly since it was shown that particle size distribution affects dissolution of this BCS Class 4 drug? Is this drug substance micronized? If so, is this done by the DMF holder or at another facility?
- Has a polymorph screen been performed on chlorthalidone? Is morphic form of this drug substance critical to the performance of the drug product?

Drug Product

- The comprehensive formulation and manufacturing process development sections in 3.2.P.2 should be evaluated. The detailed report in 3.2.P.2 on experimental investigation to define the statistical significance of (b) (4) should also be reviewed to verify the Applicant's contention that no critical process parameters can be identified in the manufacture of azilsartan medoxomil/chlorthalidone tablets.
- Dissolution specifications for the drug product should be consulted to the Biopharmaceutics team in ONDQA. They should also review the dissolution method development in section 3.2.P.2 and the BCS 4 classification of chlorthalidone. Does the change from 2% SDS to 1% Tween 80 improve the discriminatory power of the method as claimed?
- Two analytical procedures, a primary method and an alternative method, are listed in the product specification for assay, content uniformity, related substances and dissolution. Have these alternative methods shown to be equivalent and hence interchangeable with the primary methods?
- It should be noted that the USP monograph for chlorthalidone tablets has assay limits of 92%-108%.
- Has adequate justification been provided for not including the microbial limits test in the release specification of the product?
- Has Takeda convincingly demonstrated that (b) (4)
- Are the stability data in bottles and blisters sufficiently robust to allow the full extrapolation of the expiration dating period recommended in ICH Q1E? Note that Takeda had stated in the pre-NDA communication that stability updates would be

provided within 120 days of the initial NDA submission with a proposal to extend the expiration date.

- Was the bridging dissolution study, between the original and commercial methods, properly designed and executed for the stability of the product in blisters?
- Since the product should be dispensed to the patient in the original containers and not repackaged, has an in-use study been performed to show that its quality is not compromised by repeated opening and closing of the bottles over a period of 90 days? If not, can the results of the open bottle study over 7 days be used to support in-use stability?

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. Currently a “Withhold” overall recommendation has been given by the Office of Compliance but this recommendation should be re-checked before an action on this NDA is taken. It should be noted that all labeling submitted carries the proprietary name, (b) (4) which has been rejected by DMEPA. Other names, (b) (4) and (b) (4) have been submitted for review by Takeda. The labeling (PI and container labels) should be resubmitted to the NDA once a tradename has been approved. This NDA does not qualify as a QbD submission based on the criteria in the ONDQA interim policy (no design space, PAT, RTRT, reduced end-product testing etc.). However, it does contain an extensive formulation and manufacturing process development section (3.2.P.2). A single reviewer is recommended since drug substance information to be reviewed is minimal. Since this application is for a combination drug product of a recently approved NME (azilsartan medoxomil) and a well-established drug (chlorthalidone) with no unique regulatory or scientific issues, a Branch Level Regulatory Briefing is recommended.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 202331

**Applicant: Takeda
Pharmaceuticals North America**

Stamp Date: Feb. 24, 2011

**Established/Proper Name:
Azilsartan medoxomil and
Chlorthalidone**

**NDA Type: 4 New Combination
Standard Review**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		Looks to be in standard eCTD format.
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion is requested.
7	Does the section contain controls for the drug substance?	X		Cross reference to NDA 200796 and DMF (b) (4)
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		DP expiration dating proposed (b) (4) for all strengths in bottles and 30 months for blister pkg
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		Section 3.2.R.
15	Is a separate microbiological section included?		X	Solid oral dosage form. See section 3.2.P.2.5
16	Have all DMF references been identified?	X		DMF (b) (4) for Chlorthalidone Drug Substance Packaging DMFs see Sec. 1.4.2

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter:
None identified so far.

Kasturi Srinivasachar
Pharmaceutical Assessment Lead

Mar 18, 2011
Date

Ramesh Sood, Ph.D.
Branch Chief

Mar 18, 2011
Date

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
03/18/2011

RAMESH K SOOD
03/22/2011