

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200796Orig1s000**

**CHEMISTRY REVIEW(S)**

ONDQA Division Director's Memo  
NDA 200-796, Edarbi (Azilsartan Medoxomil) Tablets  
Immediate release tablet strengths of (b) (4) 40 mg, and 80 mg are proposed  
Date: 22-FEB-2011

## Introduction

Edarbi (Azilsartan Medoxomil) is an angiotensin II receptor blocker indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents. The recommended dose is 40 mg taken once daily. Dose escalation to 80 mg per day as necessary is proposed. Immediate release tablet strengths of (b) (4) 40 mg, and 80 mg are proposed. (b) (4)  
Biopharm review issues regarding the dissolution specification were resolved 18-JAN-2011. In this review, the applicant agreed to a dissolution specification of Q (b) (4) (b) (4) for all strengths. **ONDQA recommends approval of this NDA.**

## Administrative

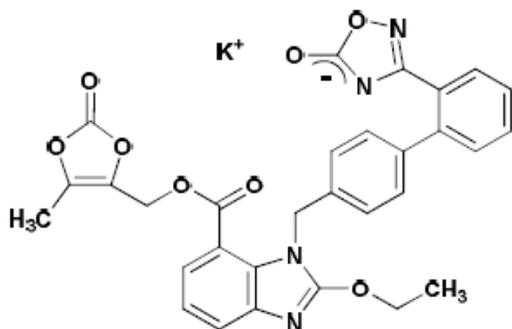
The original submission of this 505(b)(1) NDA was received 28-APR-2010 from Takeda Pharmaceuticals North America. This was a team CMC review. During the review cycle, the CMC team-reviewed two CMC amendments dated 18-OCT-2010 and 20-OCT-2010. Eight Drug Master Files (DMFs) were referenced in support of the NDA. All of them are adequate.

Consults for EES (09-JUN-2010), DMEPA (for Edarbi as trade name, 19-OCT-2010), EA (for categorical exclusion 30-NOV-2010) are all acceptable.

**This NDA is recommended for approval from a Chemistry, Manufacturing and Controls perspective.**

## Drug Substance (azilsartan medoxomil, potassium salt)

The drug substance is the medoxomil ester and potassium salt of azilsartan,



**Molecular Formula:** C<sub>30</sub>H<sub>23</sub>KN<sub>4</sub>O<sub>8</sub>

**Molecular Weight:** 606.62

The complete name is: (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]-1*H*-benzimidazole-7-carboxylate monopotassium salt. The active moiety is revealed by hydrolysis of the medoxomil ester.

The drug substance is a hygroscopic, white (b) (4) powder which melts at (b) (4). It is poorly soluble in aqueous solutions, but becomes slightly soluble at pH 9 and above, conditions where it is readily susceptible to aqueous hydrolysis. It is fully characterized by a combination of quantitative elemental analysis, UV spectroscopy, IR spectroscopy, NMR spectroscopy and mass spectroscopy. (b) (4)

Controls and specifications are adequate.

**A (b) (4) retest period is allowed for the drug substance.**

### **Drug Product:**

**Edarbi (b) (4) Tablets 20 mg, 40 mg, and 80 mg.**

These three strengths are differentiated by size and debossing codes (b) (4). (b) (4). The drug substance belongs to BCS Class 4, i.e. low solubility and low permeability and is unstable in aqueous solution between pH 1 and pH 7; but is relatively stable from pH 3 to pH 5. (b) (4)

(b) (4) Controls and specifications are adequate. Because the tablets are moisture sensitive, the aluminum blisters and the HDPE bottle presentations contain desiccant systems. The aluminum blisters are integrated with desiccant and the HDPE bottles (30 and 90 count) have a desiccant sachet in addition to a desiccant canister mounted on the closure. A 24-month controlled room temperature expiry period is recommended to be approved.

Rik Lostritto, Director, ONDQA Division I

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/s/  
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RICHARD T LOSTRITTO  
02/22/2011

**TO:** MEMO-TO-FILE

**FROM:** Prafull Shiromani, Ph.D. – CMC Reviewer for the Drug Product

**SUBJECT:** NDA 200796 – Recommendation For Approval From a CMC Perspective

**DATE:** 19-Jan-2011

The sponsor has provided adequate responses, briefly described below, to the FDA IR Letters sent out on 17-Dec-2010 and 21-Dec-2010. Accordingly, this NDA is recommended for approval from a CMC perspective.

- i. In response to the IR letter of 17-Dec-2010, where-in the applicant was requested to provide a detailed manufacturing process description, in accordance with 21CFR 314.50 d(1)(ii)(c), they have modified the eCTD Section 3.2.P.3.3 (Description of Manufacturing Process and Process Control) in the 0013 Amendment dated 22-Dec-2010. They have now included all process parameters with their operating ranges and not just those deemed to be critical presented in the original NDA, as indicated in their table below:

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/s/  
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PRAFULL K SHIROMANI  
01/19/2011

RAMESH K SOOD  
01/20/2011



**NDA 200796**

**Edarbi (Azilsartan Medoxomil) Tablets**

**Takeda Global Research & Development Center, Inc**

**Prafull Shiromani Ph.D. and Charles Jewell 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

**Chemistry Review Data Sheet**

1. NDA 200,796
2. REVIEW #: 1
3. REVIEW DATE: 21-Dec-2010
4. REVIEWER: Prafull Shiromani Ph.D. and Charles Jewell Ph.D.
5. PREVIOUS DOCUMENTS: N/A

Previous DocumentsDocument Date

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA 200796

4/28/2010

Amendment 007 – Responses to IR Letter of  
9/3/10 and 9/30/10 and Revised Drug Product  
Specification

10/18/2010

Amendment 0008 – Revised Container Label

10/20/2010

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Takeda Pharmaceuticals North America

Address: One Takeda Parkway, Deerfield, IL 60015

Representative:

Telephone: 847-582-3511

## 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA

## Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Azilsartan kamedoxomil

c) Code Name/# (ONDC only): TAK-491

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

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antihypertensive

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: (b) (4) 40, 80 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

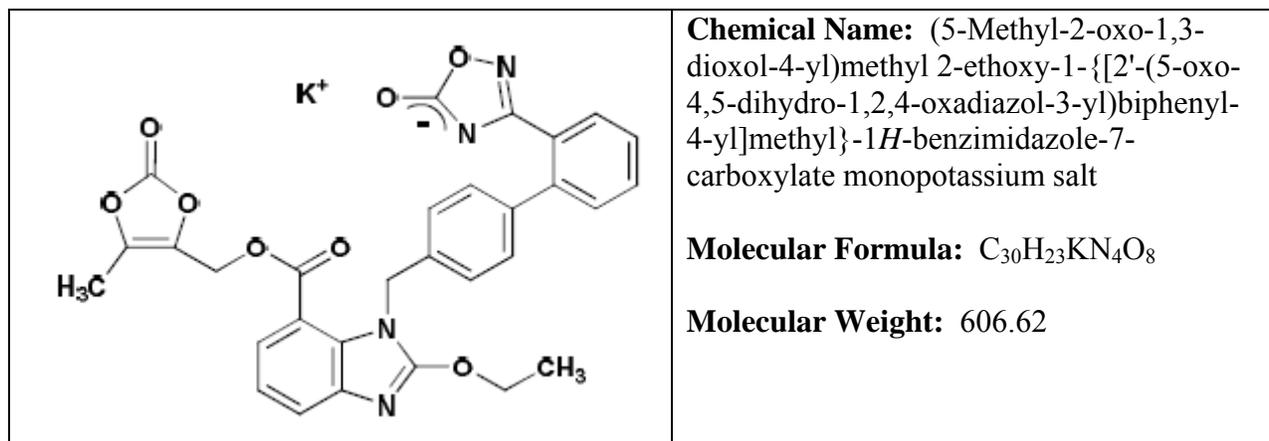
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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

## Chemistry Review Data Sheet



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	adequate		LOA: 2/2/2010
	III			4	adequate		LOA: 1/28/2010
				4	adequate		LOA: 12/15/2009
	III			4	adequate		LOA: 1-27-2010
				4	adequate		LAO: 2/12/2010
	III			4	adequate		LOA: 2-12-2010
				4	adequate		LOA: 2-23-2010
	III			4	adequate		LOA: 2-11-2010

Chemistry Review Data Sheet

			(b) (4)				
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<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			
EES	Overall Recommendation: Acceptable	09-Jun-2010	A. Inyard
Pharm/Tox			
Biopharm	Pending	12/20/2010	Approvable based on acceptance by applicant of FDA recommended dissolution specification change.
LNC			
Methods Validation	Samples of the DS, DP and reference compounds are available.		Validation is not required since the analytical methods are conventional.
DMEPA	Proposed name Edarbi is acceptable.	10/19/2010	J. Abdus-Samad
EA	Completed/Categorical Exclusion granted.	11/30/2010	R. Bloom
Microbiology	N/A		

## Chemistry Review Data Sheet

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## Executive Summary Section

## The Chemistry Review for NDA 200796

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

The applicant has provided adequate responses to the FDA IR letters sent 03-Sep-2010 and 30-Sep-2010. The application is approvable pending acceptance of the biopharm recommended dissolution specification change by the applicant and upon receipt from the applicant of either a master production record or a detailed manufacturing process description in section P.3.3 (drug product) of the application, in accordance with 21CFR 314.50 d(1)(ii)(c).

**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 NME, azilsartan medoxomil, which is a prodrug of an antagonist of the Angiotensin II subtype 1 receptor (i.e. an AII receptor blocker or ARB). Like other ARBs currently on the market, TAK 491 is indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents. After oral administration, TAK 491 is rapidly converted to the active moiety, TAK 536, by ester hydrolysis in the gut and/or during the process of absorption.

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

The company code name for this drug substance is TAK-491 and its chemistry abstracts registry number is 863031-24-7. It is the medoxomil ester and potassium salt of azilsartan. Its complete chemical name is (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}-1*H*-benzimidazole-7-carboxylate monopotassium salt. It is a potassium salt of the pro-drug azilsartan medoxomil, the active moiety is known as TAK-536 (Azilsartan). The active moiety is revealed by hydrolysis of the medoxomil ester and probably occurs before and during the absorption process, since TAK-491 is not detected in the plasma during *in vivo* experiments in many animals, including man.

(b) (4)

## Executive Summary Section

(b) (4)

(b) (4) For

further reference, another drug known as olmesartan medoxomil, an anti-hypertensive (angiotensin II receptor blocker), analogous to azilsartan medoxomil, is currently a marketed drug (NDA 21286).

TAK-491 is a hygroscopic, white (b) (4) powder which melts at (b) (4). It is poorly soluble in aqueous solutions, but becomes somewhat soluble at pH 9 and above, conditions where it is readily susceptible to aqueous hydrolysis. It is fully characterized by a combination of quantitative elemental analysis, UV spectroscopy, IR spectroscopy, NMR spectroscopy and mass spectroscopy. (b) (4) (b) (4) (b) (4)

(b) (4)

The controls for all raw materials used in the manufacture, including starting materials, solvents, and reagents are adequately described and shown to produce consistent batches of drug substance within the proposed specifications of the applicant. Experiments to support the proposed potential and actual impurity profile were also found to be adequate. In-process controls and the monitoring of critical parameters in the intermediate processes are also used to control impurity levels throughout the manufacturing process. (b) (4)

The applicant developed high resolution assays to detect these potentially genotoxic impurities at levels well below the calculated threshold of toxicological concern (TTC) and have demonstrated that these materials are not present (b) (4) TAK-491 drug substance.

## Executive Summary Section

Experiments and data adequately justified the specification for the TAK-491 drug substance that has been proposed. Batch analysis data from 38 development lots ranging in scale (b) (4) and 4 commercial scale lots (b) (4) were presented and discussed in the context of setting specifications. It includes tests for appearance (visual inspection), identification (IR and LC comparison of retention time with a reference standard), heavy metals (USP<231>Method II), related substances (HPLC or UPLC with 3 specified impurities), residual solvents ((b) (4) by GC), (b) (4)), assay (HPLC or UPLC), particle size (light diffraction), and (b) (4) (HPLC). The assays were validated to support their use for release testing.

(b) (4)

Primary stability studies are in progress on three lots of TAK-491 produced at pilot scale according to the proposed commercial process. Long term data completed for 12 months and accelerated data complete for 6 months support a re-test period of (b) (4). The long term studies will continue for 36 months. Four additional batches produced at commercial scale have also been placed on stability studies, with 9 months complete at long term conditions and 6 months complete at accelerated conditions. Results demonstrate that drug substance will stay within specification for the duration of the re-test period. Stability studies included tests for appearance, identification, related substances, (b) (4) assay, particle size and microbiological examination. The applicant also performed adequate stability experiments under various stressed conditions, including heat, humidity and light. Also aqueous solution based experiments were done at various pH levels. This led to significant understanding of degradation pathways. The drug substance is determined to be humidity and light sensitive. So packaging requires protection from both light and moisture. The applicant commits to putting at least one commercial batch per year on long term stability monitoring for 36 months.

The drug substance is currently manufactured at (b) (4). Takeda Pharmaceutical Company Limited manufactures the drug substance at their Hikari Plant.

(b) (4)

## Executive Summary Section

(b) (4)

**Drug Product**

Data are provided for 3 strengths, 20, 40, and 80 mg of azilsartan medoxomil tablets. The three different strengths are differentiated by size and debossing codes (b) (4)

(b) (4) The drug substance belongs to BCS Class 4, i.e. low solubility and low permeability and is unstable in aqueous solution of pH 1 and pH 7 and relatively stable from pH 3 to pH 5. (b) (4)

The Phase 2 (capsule) and Phase 3 (commercial) formulations have been bridged by a bioequivalence study.

(b) (4)

Some process parameters had impact on product quality, for example, (b) (4). No significant effects from the process parameters were observed for other tablet qualities. Optimization studies were conducted on individual unit operations at commercial scale to develop appropriate manufacturing conditions. The results of these studies have been systematically presented in terms of ANOVA (analysis of variance) and Pareto analysis; these statistical analyses indicate the significance of the effect of an independent variable, e.g. (b) (4) process conditions on a dependent variable, e.g. degradation content or dissolution. Based on the results of all the studies described in 3.2.P.2.3

## Executive Summary Section

and the verification of performance at commercial scale, no critical process parameters were identified in the manufacture of TAK-491 tablets. All manufacturing processes were shown to be controllable within the acceptable process ranges. No design space has been proposed.

The product specification is what is expected for a solid oral dosage form; the only unusual feature is the rather high limit for the (b) (4) (b) (4)

(b) (4) Based on the satisfactory stability data, a comment has been forwarded to the applicant to reduce the acceptance criterion of this degradant from the current (b) (4). A comment has also been forwarded to the applicant to include the microbial limit testing in the specification of the drug product, since they have not provided any scientific evidence for demonstrating the growth inhibitory properties of the drug product as stated in ICH Q6A Decision Tree #8. The dissolution test is performed with USP apparatus 2 at 50 rpm in phosphate buffer at pH 7.8. A consult has been sent to ONDQA Biopharm to review the dissolution method and its specification ( $Q =$  (b) (4)) and determine their acceptability.

Since the product is sensitive to moisture, the container closure system has been chosen to minimize exposure to humidity. The aluminum blisters are integrated with desiccant and the HDPE bottles have a desiccant sachet in addition to a desiccant canister mounted on the closure.

Primary stability studies have been carried out with 3 pilot scale batches of each strength packaged in the proposed commercial configurations (30 and 90 count HDPE bottles with a CR closure integrated with a desiccant and a desiccant within the bottle; desiccated aluminum blister). Twelve and six months' data at 25°C/60% RH and 40°C/75% RH respectively, have been submitted. Based on the satisfactory data and its statistical analyses an initial expiration dating period of 24 months is proposed for all packaging configurations; their proposal is justified as it conforms to ICH Q1E.

The applicant has also provided data from bulk stability studies for one lot of each strength of the product, packaged in an (b) (4). The tablets demonstrated satisfactory stability through at least 12 months of storage at 25°C/60% RH and 3 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 studies under more severe stress conditions, tablets were susceptible to degradation from light and humidity. Total related substances and LOD was increased in open bottles stored at 25°C/60% RH and irradiated light  $1.2 \times 10^6$  Lx-hr. However, the tablets in the proposed market package configurations were stable and no significant changes at long-term conditions and irradiated light  $1.2 \times 10^6$  Lx-hr were observed.

(b) (4)

Compliance issued an overall recommendation for approval on 09-Jun-2010; their summary report is attached to this review.

**Executive Summary Section**

The environmental assessment review has been completed and their request for a categorical exclusion has been granted.

The biopharm review has been completed and approval is recommended pending acceptance by the applicant of the FDA recommended dissolution specification change; Q= (b) (4) instead of Q= (b) (4).

\*\*\*\*\*

This review also captures the applicant's responses to the CMC review comments in the IR Letters dated 03-Sep-2010 and 30-Sep-2010. These responses have been evaluated to be adequate, with a few of the more pertinent ones presented below:

- Takeda have agreed to test microbial limits for commercial lots at release based on ICH Q6A Decision Tree #8.
- They have reduced the acceptance criterion of the (b) (4) degradate to (b) (4) and consequently, the Total to (b) (4).
- (b) (4)

Revised drug product specifications for all strengths, taken into consideration the first two items above, are provided; they have been reviewed to be adequate.

\*\*\*\*\*

The application is approvable pending acceptance of the biopharm recommended dissolution specification change by the applicant and upon receipt from the applicant of either a master production record or a detailed manufacturing process description in section P.3.3 (drug product) of the application, in accordance with 21CFR 314.50 d(1)(ii)(c). On resolution of these issues, a memo to the file will be submitted into DARRTS by the drug product reviewer.

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

TAK-491 is an angiotensin II receptor blocker indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents.

**2. Dosage and Administration**

The recommended starting dose in adults is 40 mg taken once daily. The dose may be increased to a maximum of 80 mg once daily when additional blood pressure reduction is required. TAK-491 tablets may be administered with or without food. TAK-491 tablets may be administered with other antihypertensive agents.

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

## Executive Summary Section

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

The application is approvable from a CMC perspective pending acceptance of the biopharm recommended dissolution specification change by the applicant and upon receipt from the applicant of either a master production record or a detailed manufacturing process description in section P.3.3 (drug product) of the application, in accordance with 21CFR 314.50 d(1)(ii)(c). On resolution of these issues, a memo to the file will be submitted into DARRTS by the drug product reviewer.

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

Chemist Name/Date: Charles Jewell, Ph.D. and Prafull Shiromani, Ph.D.;  
December 21, 2010

ChemistryTeamLeaderName/Date: Ramesh Sood, Ph.D.; December 21, 2010

ProjectManagerName/Date: Alexis Childers; December 21, 2010

**C. CC Block**

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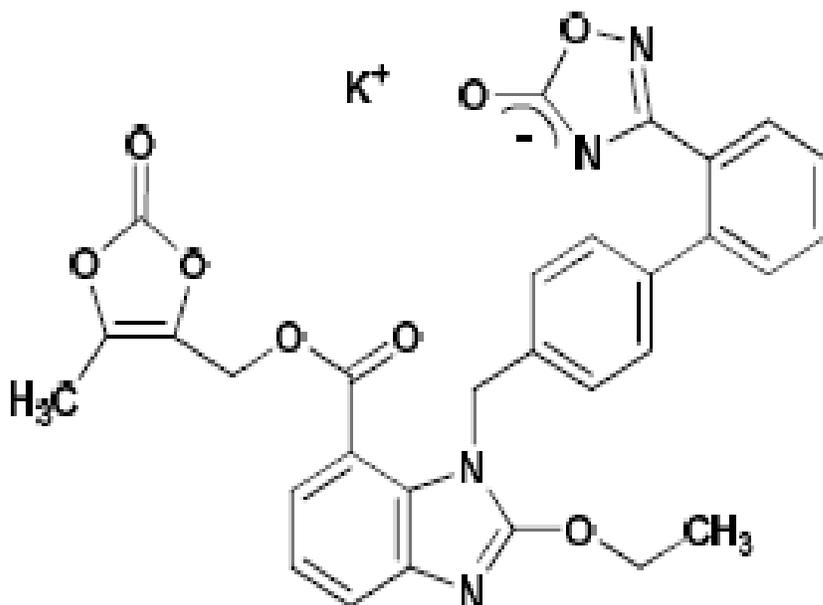
CHARLES F JEWELL  
12/21/2010

PRAFULL K SHIROMANI  
12/21/2010

RAMESH K SOOD  
12/21/2010

Initial Quality Assessment  
Branch I

**OND Division:** Division of Cardiovascular and Renal Products  
**NDA:** 200-796  
**Applicant:** Takeda Pharmaceuticals  
**Letter Date:** April 22, 2010  
**Stamp Date:** April 27, 2010  
**PDUFA Date:** Feb 27, 2011  
**Tradename:** Pending  
**Established Name:** Azilsartan medoxomil (Code name TAK 491)  
**Dosage Form:** Tablets, 40 and 80 mg  
**Route of Administration:** Oral  
**Indication:** Hypertension  
**Assessed by:** Kasturi Srinivasachar  
**ONDQA Fileability:** Yes



## Summary

This is an e-CTD NDA application for a NME, azilsartan medoxomil, which is a prodrug of an antagonist of the Angiotensin II subtype 1 receptor (i.e. an AII receptor blocker or ARB). Like other ARBs currently on the market, TAK 491 is indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents. After oral administration, TAK 491 is rapidly converted to the active moiety, TAK 536, by ester hydrolysis in the gut and/or during the process of absorption. (b) (4)

(b) (4) all information pertaining to this NDA was generated under IND 71,867. An (b) (4) for the fixed dose combination of TAK 491 and chlorthalidone was also submitted by Takeda on March 24, 2008 and is currently active.

Two CMC specific meetings have been held with the sponsor prior to submission of the NDA. The first was an EOP-2 meeting held on June 16, 2008 to discuss the designation of starting materials for the synthetic drug substance, drug substance and drug product specifications and stability protocols and dissolution testing methodology. (b) (4)

(b) (4) . The other major issue discussed was the dissolution methodology for the product. (b) (4)

(b) (4) The Sponsor agreed to provide additional details of dissolution method development in the NDA (b) (4)

The pre-NDA meeting scheduled for Nov 20, 2009 was cancelled based on the Agency's responses to the questions in the meeting package (b) (4)

## Drug Substance

The drug substance is the potassium salt of azilsartan medoxomil. It is a white (b) (4) powder which is practically insoluble in acidic and neutral aqueous solutions. The solubility increases slightly at pH > 9. (b) (4)

(b) (4)

There is a comprehensive discussion of actual and potential impurities in the drug substance. Many of these impurities were screened for genotoxic potential using DEREK software or the Ames test and based on the results from these, sensitive analytical methods with detection limits below the threshold of toxicological concern (TTC = 1.5 µg/day) were developed for the drug substance or intermediates. It is stated that all potential genotoxic impurities in TAK 491 are controlled below the TTC.

The specifications for the drug substance include limits for particle size in addition to the customary attributes of assay, impurities, identification tests (b) (4). Batch analysis data for numerous batches used in preclinical, clinical, stability and validation development have been provided. Drug substance stability has been conducted on 3 pilot scale batches and 12 months' data at long term and 6 months' data at accelerated conditions have been submitted. In addition, 6 months' data are also available on 4 full scale lots manufactured at the commercial site. A retest period of (b) (4) is proposed.

### Drug Product

Conventional excipients (mannitol, fumaric acid, sodium hydroxide, hydroxypropyl cellulose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate) are used in the manufacture of the immediate release tablets. Data are provided for 3 strengths, 20, 40, and 80 mg of azilsartan medoxomil tablets. The 3 different strengths are differentiated by size and debossing codes (b) (4). The drug substance belongs to BCS Class 4, i.e. low solubility and low permeability and is unstable in aqueous solution of pH 1 and pH 7 and relatively stable from pH 3 to pH 5. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Some process parameters had impact on product quality (b) (4). No significant effects from the process parameters were observed for other tablet qualities. Optimization studies were conducted on individual unit operations at commercial scale to develop appropriate manufacturing conditions. Based on the results of all the studies described in 3.2.P.2.3, the execution of two large studies designed using DOE, and the verification of performance at commercial scale, no critical process parameters were identified in the manufacture of TAK-491 tablets. All manufacturing processes were shown to be controllable within the acceptable process ranges. No design space seems to have been proposed.

Since the product is sensitive to moisture, the container closure system has been chosen to minimize exposure to humidity. The aluminum blisters are integrated with desiccant and the HDPE bottles have a desiccant sachet in addition to a desiccant canister mounted on the closure. The product specification is what is expected for a solid oral dosage form; (b) (4).

The dissolution test is performed with USP apparatus 2 at 50 rpm in phosphate buffer at pH 7.8. Development of the dissolution method is described in the pharmaceutical development section.

Primary stability studies have been carried out with 3 pilot scale batches of each strength packaged in the proposed commercial configurations. 12 and 6 months' data have been submitted for storage at 25°C/60% RH and 40°C/75% RH respectively and an initial expiration dating period of 24 months is proposed for all packaging configurations.

## Critical Review Issues

### Drug Substance

- Has the Applicant carried out comprehensive (b) (4) ?
- Has the Applicant satisfactorily addressed the Agency's concerns regarding the designation of (b) (4) ?
- Are the specifications for (b) (4) acceptable? Is the downstream fate of the numerous impurities listed in the (b) (4) specification adequately documented?
- None of the impurities considered by the Applicant to be potentially genotoxic is listed in the drug substance specification. Is the upstream control strategy in place for these impurities sufficient to exclude them from the drug substance specification?

(b) (4)

- In the drug substance specification:
  - is the limit of (b) (4) qualified?
  - Is the particle size acceptance criteria adequately justified? Is this a CQA for this BCS class 4 substance?
  - Is the identification test by IR specific for the potassium salt?

(b) (4)

### Drug Product

- Have the compatibility studies between the drug substances and the excipients been adequately performed?
- There is a detailed formulation development section in 3.2.P. which should be evaluated in-depth, especially, (b) (4). Likewise, there is a comprehensive report in 3.2.P. on manufacturing process development and experimental investigation to define the statistical significance of (b) (4) process parameters. This should also be reviewed to verify the Applicant's contention that no critical process parameters can be identified in the manufacture of TAK-491 tablets.
- Is the proposed strategy of controlling key operating parameters in combination with in-process material controls for the (b) (4) operations sufficient for routine manufacture of TAK-491 tablets at commercial scale?
- 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. and the BCS 4 classification of azilsartan medoxomil.
- Two analytical methods, HPLC or UPLC, are listed in the product specification for assay, content uniformity and related substances. Is one of these an alternate method? Which one will be used for routine batch release? The regulatory and alternate methods need to be clearly denoted in the specification sheet.
- Are the limits for related substances, particularly (b) (4), reasonable?
- Has adequate justification been provided for not including the microbial limits test in the release specification of TAK-491 tablets?
- The post approval testing plan for the first 3 commercial batches is somewhat different from the registration batch stability studies in that the former does not include LOD, tablet hardness or friability testing. Is this acceptable?

(b) (4)

### **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 should be noted that all labeling submitted carries the proprietary name, [REDACTED]<sup>(b) (4)</sup>, which has been rejected by DMEPA. Another name, [REDACTED]<sup>(b) (4)</sup>, has 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 pharmaceutical development section with cause and effect (fishbone) diagrams, Pareto analysis of factors affecting various quality attributes etc. and a team review is recommended with one CMC reviewer for the drug substance and one reviewer with QbD experience for the drug product.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead

May 28, 2010  
Date

Ramesh Sood, Ph.D.  
Branch Chief

May 28, 2010  
Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

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/s/

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KASTURI SRINIVASACHAR  
06/01/2010

RAMESH K SOOD  
06/07/2010