

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200796Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

**Date:** **October 26, 2010**

**To:** **Norman Stockbridge, M.D., Ph.D., Director**  
**Division of Cardiovascular and Renal Products (DCRP)**

**Through:** **Claudia Karwoski, Pharm.D., Director**  
**Division of Risk Management (DRISK)**

**From:** **(b) (4) DRISK Review Team**  
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**(OSE)**

**Subject:** **Review of Proposed Global Risk Management Plan submitted**  
**April 22, 2010**

**Drug Name(s):** **(b) (4) (azilsartan medoxomil)**

**Application** **NDA 200-796**  
**Type/Number:**

**Applicant/sponsor:** **Takeda Pharmaceuticals North America, Inc**

**OSE RCM #:** **2010-0980**

## 1 INTRODUCTION AND BACKGROUND

This review follows a request from the Division of Cardiovascular and Renal Products (DCRP) for the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) to review Takeda Pharmaceutical's April 22, 2010, submission for (b) (4) (azilsartan) (b) (4)

(b) (4) is an angiotensin II receptor blocker (ARB) with the proposed indication for the treatment of hypertension, alone or in combination with other antihypertensive agents. Azilsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. The recommended dose of (b) (4) is 40 mg orally once daily. The dose may be increased to a maximum of 80 mg once daily and/or combined with additional antihypertensive agents (including diuretics) when additional blood pressure reduction is required.

## 2 MATERIALS REVIEWED

The following documents were reviewed:

- (b) (4)
- Takeda Pharmaceuticals North America, Inc proposed Prescribing Information (PI) for (b) (4) (azilsartan medoxomil), April 2010.

## 3 RESULTS OF REVIEW

### 3.1 SPONSOR'S SUBMISSION

(b) (4) was examined in various Phase III, double-blind, randomized, placebo-controlled, and active comparator-controlled studies, ranging from 6 weeks to 6 months at 20 mg, 40 mg, and 80mg doses once daily, in patients with mild, moderate, and severe hypertension. Of these studies, 4814 patients received (b) (4), including 1688 patients who were treated for at least 6 months and 327 patients who were treated for at least 1 year. Among these studies, the most commonly reported adverse reactions reported in at least 1% of patients and occurring at a frequency greater than placebo included dizziness (2.1% (b) (4) vs. 0.9% placebo), blood creatine phosphokinase increased (1.1% (b) (4) vs. 0.7% placebo), and diarrhea (1.0% (b) (4) vs. 0% placebo).

The safety specification of the risk management plan includes elevated serum creatinine, hypotension-related events (i.e., hypotension, dizziness, and syncope) as identified risks associated with the use of (b) (4) and risk to an unborn child as a potential risk when used in pregnancy. Adverse events were mild to moderate in severity, with very few serious adverse events.

### 3.2 SPONSOR'S RISK MANAGEMENT PROPOSAL

The sponsor's risk management plan addresses the identified and potential risks above through routine pharmacovigilance, which includes monitoring and reporting of all spontaneous and serious adverse events, submitting Periodic Safety Update Reports as mandated, class labeling for use in pregnancy, hypotensive events, and serum creatinine elevations, assessment of the need for risk minimization measures, and communication with health authorities as appropriate.

## 4 DISCUSSION

Most adverse events in the clinical trials were mild to moderate in severity; the most commonly reported adverse reactions reported in at least 1% of patients and occurring at a frequency greater than placebo included dizziness (2.1% (b) (4) vs. 0.9% placebo), blood creatine phosphokinase increased (1.1% (b) (4) vs. 0.7% placebo), and diarrhea (1.0% (b) (4) vs. 0% placebo).

(b) (4) directly affects the renin-angiotensin system; therefore, (b) (4) can cause fetal and neonatal harm, including death, when administered to pregnant woman. (b) (4)

(b) (4). Cases of fetal injury and death have been reported in patients receiving angiotensin converting enzymes; therefore, physicians are recommended to discontinue use of ARBs in patients who become or are pregnant.

Elevations in serum creatinine have been reported with other ARBs and is not unique to (b) (4). (b) (4)

The change in renal function is a well recognized effect of the use of ARBs due to its inhibition of the renin-angiotensin system, resulting in decreases in the glomerular filtration rate. These increases in serum creatinine are generally transient and reversible upon discontinuation of the medication.

## 5 CONCLUSION

DRISK believes that the proposed routine approach by the Sponsor is adequate at this time. Additional strategies such as a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use do not appear to be warranted. The safety profile for (b) (4) is consistent with currently approved ARBs. There were no new or unique safety concerns associated with (b) (4) in the pivotal trials. Furthermore, none of the currently approved ARBs have REMS.

Should DCRP raise further concerns with the risks outlined above or identify additional risks associated with (b) (4) warranting more extensive risk mitigation or a formal risk evaluation and mitigation strategy (REMS), please send a consult to OSE DRISK.

This memo serves to close the existing consult request for (b) (4) under NDA 200-796, azilsartan medoxomil tablets. Please notify DRISK if you have any questions.

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

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/s/

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10/26/2010

CLAUDIA B KARWOSKI  
10/26/2010  
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