

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200796Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

NDA: 200-796

Drug: Edarbi (Azilsartan Medoxomil) 40 & 80 mg Tablets

Class: ARB

Sponsor: Takeda Pharmaceuticals North America

Indication: Azilsartan medoxomil is an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Date of submission: April 22, 2010

PDUFA date: February 27, 2011

Approval date: February 25, 2011

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
 - Cross Discipline Team Leader (CDTL)
 - Shari Targum
 - Medical Reviewer
 - Maryann Gordon
 - Pharmacology & Toxicology
 - Philip Gatti & William Link
 - Regulatory Health Project Manager
 - Alexis Childers
- Office of New Drug Quality Assessment (ONDQA), Branch I
 - - Drug Product
 - Prafull Shiromani
 - - Drug Substance
 - Charles Jewell
 - – Biopharmaceutics
 - Tien Mien Chen
- Office of Clinical Pharmacology
 - Divya Menon-Andersen
- Office of Biostatistics, Division of Biometrics I
 - John Lawrence
- Office of Surveillance and Epidemiology
 - – DMEPA
 - Jibril Abdus-Samad
 - – DRISK
 - Barbara Fuller
 - - Risk Evaluation and Mitigation Strategy – REMS
 - Reema Jain

- Office of Medical Policy, Division of Drug Marketing, Advertising and Communications (DDMAC)
 - Emily Baker
 - Zarna Patel

❖ **BACKGROUND**

Azilsartain medoxomil (TAK-491) is a prodrug that converts rapidly to the active moiety, TAK-536, once metabolized and acts as an angiotensin II receptor blocker. With this NDA, the sponsor would like to obtain the standard antihypertensive indication [REDACTED] (b) (4). They have performed two studies each to demonstrate superiority to Valsartan and Olmesartan and performed co-administration studies with chlorthalidone (CLD) and amlodipine. This is the 8th drug in its class.

There have been three milestone meetings between the sponsor and the FDA: EOP2 April 2007, Type C May 2009, and pre-NDA December 2009. It was determined at the pre-NDA meeting in December 2009 that this NDA submission for TAK-491 would include all of the data for TAK -491, some data from TAK-536, and some supportive data for the co-administration with chlorthalidone. (The INDs associated with this NDA are IND 71,867 and [REDACTED] (b) (4).)

The Phase 3 program's main objectives were to compare the efficacy, safety and tolerability of TAK-491 with placebo and two other angiotensin II receptor blockers (ARB), olmesartan medoxomil and valsartan. Another objective was to characterize the antihypertensive effects of TAK-491 during long term administration, in subpopulations and when co-administered with other antihypertensive agents. There were 5 randomized, double-blind, controlled monotherapy studies of 6 weeks or 6 months duration, 2 randomized, controlled, 6 week studies where TAK-491 was co-administered with chlorthalidone 25 mg and with amlodipine 5 mg, and 2 open label studies up to 56 weeks in length. The Sponsor's proposed starting dose is 40 mg but may be increased to 80 mg alone or in combination with other antihypertensive agents.

There were no filing issues with this NDA submission. The review of the application proceeded fairly smoothly and in general met all of the 21st century review guidelines

User Fee

The user fee for this application was paid in full on 08 Apr 2010. User Fee ID 3010048.

Pediatric Review Committee (PeRC)

The PeRC meeting to discuss this application was held on 08 Dec 2011. The Sponsor submitted a waiver and a deferral request in Pediatrics. The committee agreed that the waiver for premature to <12 months was appropriate due to safety concerns. The committee also agreed with the deferral for 12 months to < 17 years on the basis that adult studies are completed and ready for approval. The committee felt the timelines for enrolling and completing the studies should be decreased or the sponsor should provide a good rationale for their timelines.

Advisory Committee

There was no Advisory Committee meeting for this NDA because this drug is not the first in its class and the safety profile is similar to other approved drugs in this class

Trade name

EDARBI was deemed conditionally acceptable for use on 19 Oct 2010 and fully acceptable on 18 Feb 2011. The final agreed upon carton & container labels appear as an appendix to the Approval Letter. The review Division did not have any concerns with the proposed name.

Facilities Inspection

EES Report: The Office of Compliance provided an overall recommendation of acceptability on 09 Jun 2010 for the manufacturing sites.

Division of Scientific Investigations: It was agreed by the medical officer and Division Director, at the NDA filing meeting, that no clinical site inspections were needed.

❖ REGULATORY TIMELINE

- IND Filed: 19 Apr 2005 (IND 71,867)
- End of Phase 2 Meeting (EoP2): 26 Apr 2007 (minutes dated 06 Jun 2007)
- CMC End of Phase 2 Meeting (EoP2): 13 Jun 2008 (minutes dated 10 Jul 2008)
- Request for a Special Carcinogenicity Protocol Assessment:
 - 10 Nov 2006 (CAC minutes dated 20 Dec 2006)
 - 03 Apr 2007 (CAC minutes dated 02 May 2007)
 - 23 May 2007 (CAC minutes dated 13 Jun 2007)
 - 31 May 2007 (CAC minutes dated 11 Jul 2007)
 - 20 Nov 2007 (CAC minutes dated 03 Jan 2008)
- Type C Guidance Meeting: 19 May 2009 (minutes dated 22 Jun 2009)
- Pre-NDA Meeting: 27 Oct 2009 (minutes dated 10 Dec 2009)
- Pre-NDA CMC : preliminary comments dated 17 Nov 2009
- NDA Received Date: 27 Apr 2010
- Filing Meeting: 08 Jun 2010
- Filing/74 Day Letter: 07 Jul 2010
- Executive Carcinogenicity Assessment Committee (CAC) Meeting: 14 Sep 2010
- Mid-cycle Meeting: 27 Sep 2010
- Advisory Committee: N/A
- Type C Dosing Discussion Meeting: 21 Jan 2011 (minutes dated 1 Feb 2011)
- PDUFA Date: 27 Feb 2011
- Approval Date: 25 Feb 2011

❖ REVIEWS

Below are the conclusions reached by the EDARBI team members, organized by role or discipline.

Office Memorandum (dated 25 Feb 2011)

Dr. Temple's memo conveys the decision to issue an approval letter. The recommended dose is 80 mg and the option for 40 mg in patients who are volume-depleted. (b) (4)

other standard ARBs, valsartan and olmesartan.

Divisional Memorandum (dated 8 Feb 2011)

Dr. Stockbridge's memo recommends issuing an approval letter. He discusses the issue of which dose to approve. He concurs with the reviewers that only one dose should be approved since the blood pressure difference between the two doses is small. With such a small effect difference between the two doses, it could delay someone needing additional blood pressure effect from receiving additional therapy. Dr. Stockbridge feels either dose could be approved depending on how the creatinine data with the 80 mg dose is interpreted.

Subsequently this view was discussed with the sponsor. The sponsor provided a memo justifying the use of 80 mg.

Cross-Discipline Team Leader (CDTL) Review (dated 21 Jan 2011)

Dr. Targum provided an integrated review, summarizing each disciplines review. She concurs with the discipline reviews and recommends approval pending resolution of dose selection and labeling. Dr. Targum recommends approving the 40 mg dose due to creatinine elevations at 80 mg. She provided rationale in her review. She also recommends periodic serum creatinine monitoring when azilsartan is co-administered with diuretics and lower doses of diuretics should be prescribed or alternative therapy should be considered if there is an increase in creatinine. Dr. Targum also recommends routine monitoring for renal-related adverse events.

Medical and Biostatistics Review (dated 16 Dec 2010 review, 3 Jan 2011 appendix, 31 Jan 2011 financial disclosure, 2 Feb 2011 safety update)

Drs. Gordon and Lawrence provided a combined clinical-statistical review. The reviewers concluded that:

- The safety profile is similar to other ARBs
- The results of the studies have shown that azilsartan medoxomil has the ability to lower blood pressure.
- Increases with serum creatinine levels are seen in subjects receiving, a diuretic such as chlorthalidone, have impaired renal function at baseline, or are over 75 years of age.
- There was little difference in effect between doses of 10-80 mg.
- It is not consistently superior in lowering blood pressure compared to other ARBs, specifically olemsartan medoxomil and valsartan.
- The recommended starting dose should be 5 mg or 10 mg once per day in subjects who are volume depleted. Doses may be increased up to 80 mg once per day.

The reviewers recommend approval.

Subsequent to the signed review the Division met on 10 Jan 2011 to discuss the appropriate dose and

(b) (4) . (b) (4) The Division believed there was (b) (4) . The Division agreed that a dose should be chosen between 10-80 mg since dose responses were flat. Since 40 mg is developed the suggested dose is 40 mg.

Clinical Pharmacology Review (dated 11 Jan 2011, 26 Jan 2011)

Dr. Menon-Andersen's review indicates that the dose response relationship is flat between doses of 10-80 mg. Since the 80 mg dose did not show a consistent benefit over the 40 mg, Dr. Menon-Andersen recommends approval at 40 mg.

Pharmacology & Toxicology Review (dated 21 Dec 2010)

Drs. Gatti and Link noted the following in their review: The Genetic toxicology tests ultimately were concluded to be negative, although the in vitro chromosomal aberration assay was highly clastogenic in the absence of metabolic activation. All of the other in vitro and in vivo genetic toxicology assays were negative. The carcinogenicity studies were also negative and the doses tested were considered adequate by the Executive CAC. Toxicology findings are consistent with effects seen in other ARBs. Minor variations in fetal development and adverse effects were seen on pup viability in the reproductive toxicology studies.

The reviewers concluded that azilsartan medoxomil is comparable to other FDA approved ARBs and is approvable with recommended label changes that can be found in their review.

Carcinogenicity Statistical Review (dated 24 Nov 2010)

Dr. Jackson performed the statistical review of the carcinogenicity studies. Two types of tumors appeared to be statistically significant in studies using the prodrug; hemolymphoreticular histiocytic sarcoma in female rats and adrenal cortical cell adenomas. The metabolite TAK 536-MII was also studied for carcinogenicity. The metabolite study had a significant result in the incidence of hemangiosarcomas in the nasal cavity. The reviewer noted that it is difficult to determine if the tumors are rare or common. Since there was no relevant historical control data, concurrent control data from both the prodrug and metabolite studies were used to determine if the tumors were rare or common. Upon reviewing the analysis, the Exec CAC concluded that no neoplasms were statistically significant and all studies were acceptable.

Office of New Drug Quality Assessment (ONDQA), Branch I, Review (dated 16 Dec 2010, 21 Dec 2010, 14 Jan 2011, & 19 Jan 2011)

Drs. Jewell and Shiromani wrote a combined review. There is one item to note regarding the drug substance (b) (4). This step can produce potentially genotoxic impurities. The sponsor developed high resolution assays to detect the impurities at levels below the calculated threshold of toxicological concern. They have also demonstrated that these materials are not (b) (4). The ONDQA team sent several information requests to the sponsor in which the sponsor agreed to make the Agency requested changes or to supply the requested information. All of the sponsor's submissions were deemed acceptable. The review indicates that the NDA is approvable from an ONDQA perspective.

This submission qualifies for categorical exclusion.

Dr. Chen from the ONDQA Biopharmaceutics team reviewed the dissolution methodology for the 20, 40 and 80 mg strengths. Dr. Chen found the methodology to be acceptable but the specifications needed to be revised. The sponsor complied with the request. In a subsequent memo, Dr. Chen indicated that the proposed dissolution methodology and specifications are acceptable.

❖ **CONSULTS**

Office of Surveillance and Epidemiology Reviews (dated 26 Oct 2010, 27 Jan 2011, 4 Feb 2011)

Reema Jain from DRISK evaluated the sponsor's risk management plan based on the (b) (4) format. Since the safety profile is consistent with other ARBs, She concluded that the proposed plan is acceptable.

Barbara Fuller from DRISK evaluated patient labeling (PPI). The PPI is considered acceptable pending recommended changes. The changes can be found in the review.

Jibril Abdus-Samad reviewed that carton and container labels using a Failure Mode and Effects Analysis. The following deficiencies were noted: color differentiation between the strengths, moving or deleting information to avoid over crowding, correcting storage statement and revising sample product strength. Full detail on recommendations can be found in the review.

Division of Drug Marketing, Advertising and Communications (DDMAC) (dated 28 Jan 2011)
Emily Baker and Zarna Patel reviewed the proposed product label and provided comments throughout the label for the sponsor to update. All comments can be found in the review. DDMAC reviewed the proposed trade name, EDARBI, on 27 Aug 2010, and had no concerns regarding the proposed name from a promotional perspective.

CONCLUSION

All of the reviewers agreed on approving the application. There were questions on appropriate dose to approve (b)(4). There were two teleconferences with the sponsor, (4, and 11 Feb 2011) where the sponsor provided justification for doses (b)(4). Ultimately the 80 mg dose is approved with the 40 mg as an option for patients on high dose diuretics. (b)(4).

An Approval Letter was issued for this application and signed by Robert Temple, M.D., on 25 Feb 2011.

The Approval Letter was appended with the agreed upon labeling. The letter also detailed the below post marketing requirements (PMRs) that were sent by the sponsor in their email communication/submission dated 04 Feb 2011 and officially submitted on 09 Feb 2011:

- | | |
|--------|---|
| 1733-1 | A Comparative Single-Dose Pharmacokinetic and Safety Study of TAK-491 Between Infants, Children and Adolescents with Hypertension and Healthy Adults (PK) |
| | Final Protocol Submission: November 2009 |
| | Study/Trial Completion: May 2012 |
| | Final Report Submission: December 2012 |
| 1733-2 | An efficacy and safety, dose-finding study in children 6 years to less than 18 years with hypertension |
| | Final Protocol Submission: March 2012 |
| | Study/Trial Completion: June 2015 |
| | Final Report Submission: January 2016 |
| 1733-3 | An efficacy and safety, dose-finding study in children 12 months and older, weighing less than 25 kg, with secondary hypertension |
| | Final Protocol Submission: April 2016 |
| | Study/Trial Completion: September 2020 |
| | Final Report Submission: April 2021 |

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ALEXIS T CHILDERS
02/28/2011

**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: February 4, 2011

Application Type/Number: NDA 200796

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products (DCRP)

Through: Todd Bridges, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Edarbi (Azilsartan Medoxomil) Tablets
40 mg and 80 mg

Applicant: Takeda Pharmaceuticals North America

OSE RCM #: 2010-1026

1 INTRODUCTION

This review evaluates the proposed Edarbi labels and labeling submitted by the Applicant on October 20, 2010, for their vulnerability to contribute to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) and lessons learned from postmarketing experience to evaluate the labels and labeling submitted by the Applicant on October 20, 2010 (see Appendices A through F, no image of insert labeling).

Our review noted the following deficiencies:

- The color differentiation between strengths requires improvement to minimize the risk of selection errors.
- Information on the labels requires relocation and deletion to avoid crowding and provide room for more important information.
- The storage statement requires revisions so that it is consistent with the product labeling.
- The sample product strength requires revision to provide clarity of milligram content per capsule.

3 RECOMMENDATIONS

Our evaluation identified areas of needed improvement in order to minimize the potential for medication errors for this product. We provide recommendations for the container labels and carton labeling in Section 4.1, *Comments to the Applicant*. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Nina Ton, OSE project manager, at 301-796-1648.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3.1 COMMENTS TO THE APPLICANT

A. General Comments

Improve the color differentiation between the two strengths by avoiding the use of the same colors (orange and gray) in the trade dress strength differentiation scheme. Incorrect product selection errors are more likely to occur because both strengths utilize the same colors (orange and gray) on the labels and labeling. The use of different colors will improve the strength differentiation and decrease the likelihood of wrong strength selection errors.

B. Trade Blister Container Labels, 40 mg and 80 mg (10 count)

1. Revise the presentation of the established name to read *tablet* rather than *tablets* since each blister contains only one tablet.
2. Revise the presentation of the established name by including parenthesis before and after the established name to read:

(azilsartan medoxomil) tablet

3. Remove the storage information as this label is too small and it crowds the label. Moreover, the storage information is inconsistent with the insert labeling. Removing this information will improve readability of the label.
4. Remove the statement, *See insert*. Typically, the statement, *See package insert for dosing information*, is used if the adequate directions for use cannot be listed on the label. However, this statement will occupy too much space on the small blister label and does not provide any meaningful information.

C. Trade Carton Labeling, 40 mg and 80 mg (30 count unit dose)

1. Revise the presentation of the established name by including a parenthesis before and after the established name to read:

(azilsartan medoxomil) tablets

2. Increase the font size of the dosage form, tablets, to match the font size and weight of the established name.
3. Include the strength after the appearance of proprietary and established names on the side panels.

D. Physician Sample Blister Container Labels and Carton Labeling, 40 mg and 80 mg (7 count)

Include a statement on the principal display panel that indicates each tablet contains x mg of Edarbi. As currently presented, a patient may mistakenly ingest all seven tablets for a 40 mg or 80 mg dose, resulting in a total dose of 280 mg or 560 mg of Edarbi, respectively.

E. Physician Sample Blister Container Labels, 40 mg and 80 mg (7 count)

1. Revise the statement, *See insert*, to read:

See package insert for dosing information.

2. Remove the storage information statement, *Store at 25°C (77°F)*. It is incomplete and inconsistent with the insert labeling, which provides a range of temperatures for storage. Additionally, the blister labels appear crowded. The storage information is not required on small labels and therefore, removal of this abbreviated storage information will improve readability of the label.

F. Physician Sample Carton Labeling, 40 mg and 80 mg (5 cartons of 7 count)

Include the strength after the appearance of proprietary and established names on the upper panel.

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/s/

JIBRIL ABDUS-SAMAD
02/04/2011

CAROL A HOLQUIST
02/04/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: January 28, 2011

To: Alexis Childers – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Zarna Patel – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 200796 Edarbi (azilsartan medoxomil) Tablets

DDMAC has reviewed the proposed product labeling (PI) for Edarbi (azilsartan medoxomil) tablets (Edarbi), submitted for consult on May 24, 2010.

The following comments are provided in response to the updated proposed PI sent via email on January 14, 2011 by Alexis Childers. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

EMILY K BAKER
01/28/2011

ZARNA PATEL
01/28/2011

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

PATIENT LABELING REVIEW

Date: January 27, 2011

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products (DCRP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management (DRISK)

From: Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): Edarbi (azilsartan medoxomil)

Dosage Form and Route: Tablets

Application Type/Number: NDA 200796

Applicant: Takeda Pharmaceuticals North America

OSE RCM #: 2010-980

1 INTRODUCTION

This review is written in response to a request by the Division of Cardiovascular and Renal Products (DCRP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Edarbi (azilsartan medoxomil) Tablets.

On April 22, 2010 Takeda Pharmaceuticals North America submitted a New Drug Application (NDA) 200796 for Edarbi (azilsartan medoxomil) Tablets with a proposed indication of treatment of hypertension. If blood pressure is not controlled with Edarbi alone, Edarbi may be coadministered with other antihypertensive agents, including diuretics.

On October 26, 2010 DRISK performed a separate review of Takeda Pharmaceutical's April 22, 2010, submission for Edarbi (azilsartan medoxomil) containing a proposed pharmacovigilance plan based on European Union (EU) format and believes that the proposed routine pharmacovigilance is adequate.

2 MATERIAL REVIEWED

- Draft Edarbi (azilsartan medoxomil) Tablets Patient Package Insert (PPI), received on April 22, 2010, and revised by the review division throughout the review cycle, and sent to DRISK on January 14, 2011.
- Draft Edarbi (azilsartan medoxomil) Tablets Prescribing Information (PI) received April 22, 2010, revised by the Review Division throughout the current review cycle, and received by DRISK on January 14, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

BARBARA A FULLER
01/27/2011

LASHAWN M GRIFFITHS
01/28/2011

Executive CAC

Date of Meeting: September 14, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Barbara Hill, Ph.D., DDDP, Alternate Member
Muriel Saulnier, D.V.M, Ph.D., D.A.B.T., DCaRP Team Leader
Philip Gatti, Ph.D., DCaRP Presenting Reviewer

Author of Draft: Philip Gatti, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 200-796

Drug Name: azilsartan

Sponsor: Takeda

Four carcinogenicity studies were reviewed. Two (rat and Tg.rasH2 mouse) for the pro drug, TAK 491, and two (rat and Tg.rasH2 mouse) for the metabolite, TAK 563-MII.

Pro Drug TAK 491:

Rat Carcinogenicity Study

Strain: F344/Jcl rats

Dose (oral): 60, 200 and 600 mg/kg/day

Vehicle: 0.5w/v% methylcellulose in 0.005w/v% citric acid

Duration: 24 months

The incidence of hemolymphoreticular histiocytic sarcomas in rats was numerically increased at the high dose in the females as shown in the following table.

	Control (Combined)	60 mg/kg	200 mg/kg	600 mg/kg
Incidence	1/100	1/50	1/50	4/50
Poly-3 adjusted incidence rate	1.1%	2.2%	2.1%	8.2%
p-value of pairwise and trend tests	.0168 (trend)	.5604	.5730	.0483

The two control groups received the same vehicle treatment. Relevant historical data were not available. Therefore the concurrent control data from this study and the study with the metabolite (discussed below) were used to determine whether this tumor was

common. In addition to the tumor diagnosed in the one female control, these tumors were also diagnosed in 2/100 males in vehicle control groups and in 1/50 females in a vehicle control group in the study of the metabolite. In the absence of historical control data, the concurrent control data suggest that these tumors should be assessed using common tumor criteria of $\alpha=0.005$ for trend and $\alpha=0.01$ for pairwise comparisons. Consequently, the trend and pairwise analyses do not reach statistical significance. In addition to the statistical analysis, the mode of action of the compound, i.e. competitive reversible antagonist at AT-1 receptors, does not suggest that these tumors are pharmacologically related.

Tg.rasH2 Mouse Carcinogenicity Study

Doses (oral): 50, 150 and 450 mg/kg/day

Vehicle: 0.5w/v% methylcellulose in 0.005w/v% citric acid

Duration: 26 weeks

No neoplasm was statistically significant by the CDER criteria.

Metabolite TAK 536-MII:

Rat Carcinogenicity Study

Strain: F344/Jcl rats

Dose (oral): 100 (males), 300 (both sexes), 1000 (both sexes) and 3000 (females)

Vehicle: Corn oil

Duration 24 months

No neoplasm was statistically significant by the CDER criteria.

Tg.rasH2 Mouse Carcinogenicity Study

Concentration in diet: 1.25, 3.5 and 5%

Controls: Normal diet

Duration: 26 weeks

No neoplasm was statistically significant by the CDER criteria.

Executive CAC Recommendations and Conclusions:

Pro Drug TAK-491

Rat:

- The Committee agreed that the study was acceptable, noting prior FDA concurrence with the protocol.
- The Committee concurred that there no drug-related neoplasms.

Tg.rasH2 Mouse:

- The Committee agreed that the study was acceptable, noting prior FDA concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms

Metabolite TAK-536 MII:

Rat:

- The Committee agreed that the study was acceptable, noting prior FDA concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Tg.rasH2 Mouse:

- The Committee agreed that the study was acceptable, noting prior FDA concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DCRP
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ADELE S SEIFRIED
09/23/2010

DAVID JACOBSON KRAM
09/23/2010