CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202331Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-331 (N-000)
Submission Dates:	02/21/11, 03/31/11, 08/30/11, and 10/19/11
Brand Name:	Edarbyclor
Generic Name:	Azilsartan medoxomil + Chlorthalidone
Formulation:	Immediate release (IR) oral tablet
Strength:	Fixed dose combination (FDC): [redacted] (b) (4) [redacted] (b) (4) 40/12.5, 40/25, [redacted] (b) (4)
Applicant:	Takeda
Type of submission:	Original (Standard 10-month review)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Background:
Takeda's Edarbi (azilsartan medoxomil) IR tablet was approved under NDA 200-796 on 02/25/11, with two strengths (40 and 80 mg). It is indicated for the monotherapy of hypertension. Chlorthalidone is an approved long-acting thiazide-type diuretic also indicated for the treatment of hypertension.

Submission:
On 02/21/11, Takeda submitted NDA 202-331 (N-000) for Edarbyclor IR tablets ([redacted] (b) (4) proposed, [redacted] (b) (4) 40/12.5, 40/25, [redacted] (b) (4)). The components of Edarbyclor are Edarbi (azilsartan medoxomil) and chlorthalidone (CLD: a thiazide-type diuretic). Edarbyclor is a [redacted] (b) (4) FDC tablet formulation that is being developed by Takeda for the treatment of hypertension. The applicant reported that with exception to colorant and printing ink, the clinical trial materials manufactured to support phase 3 studies have the same components and composition as those for the proposed commercial formulation. Both azilsartan medoxomil and chlorthalidone are reported as Biopharmaceutics Classification System (BCS) Class IV drug substances (low permeability and low solubility). Additional submissions were provided on 03/31/11, 08/30/11, and 10/19/11.

The Applicant [redacted] (b) (4) employed all 6 tablet strengths in the clinical studies. The *in vivo* bioavailability information for all these 6 strengths was estimated from a Phase 3 clinical trial using the population pharmacokinetics (POPPK) approach.

Biopharmaceutics Review:
The Biopharmaceutics review is being focused on the evaluation of the information/data supporting the proposed dissolution method and acceptance criteria for azilsartan medoxomil and chlorthalidone. Since there is bioavailability (BA) information for all [redacted] (b) (4) strengths, there are no BA waiver issues.

The Agency had the following communications with the Applicant during the review of this NDA submission.

- On 08/08/11, the Agency sent a letter indicating that the applicant's proposed dissolution method as shown below was acceptable.

  Apparatus: USP II (paddle) with 50 rpm
  Medium: 900 ml of pH 6.8 phosphate buffer containing 1.0% Tween 80, at 37°C
  Sample time: 10, 15, 20, 30, and 45 min

  However, it was recommended that the dissolution acceptance criteria be revised as follows;
  Acceptance Criteria: Change
  From: Q= (b) (4) at 30 min for both azilsartan medoxomil and chlorthalidone
  To: Q= (b) (4) at 30 min for azilsartan medoxomil and
  Q= (b) (4) at 15 min for chlorthalidone

- On 08/15/11, a teleconference was held between the applicant and the Agency to further discuss the dissolution testing using media without surfactants.
- On 08/30/11, the applicant submitted their response and the available dissolution data using media without surfactants for review. The applicant concluded that changes to their originally proposed dissolution method and specifications were no needed. The Agency evaluated the information and did not agree with the Applicant's conclusions.
- On 10/13/11, another teleconference was held between the Agency and the Applicant to further discuss the adequacy of the dissolution method and acceptance criteria. The following conclusions were reached during the teleconference:
  - The proposed dissolution method is acceptable and the following dissolution criteria are recommended on an interim basis.

    a. **Azilsartan medoxomil:**
    Q= (b) (4) at 30 min for (b) (4) 40/12.5, 40/25 mg strengths.
    (b) (4)

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

  - (b) (4)

  - The Applicant agreed to the Post Marketing Commitment (PMC) to provide additional dissolution data from the batches manufactured during the first year following post-approval date. FDA agreed that, if after the additional data gathered over the course of one year show that the Stage 2 (n=12) testing is observed to be (b) (4) then a justification can be presented to support re-evaluation of the dissolution acceptance criteria for both azilsartan medoxomil and chlorthalidone. If the Stage 2 testing is (b) (4) then the acceptance criteria will remain as final. The proposal for the final acceptance criteria and supportive

data will be submitted within 14 months of action date as a supplement to the NDA

- On 10/19/11, the Applicant officially submitted: **1)** The revised dissolution acceptance criteria for azilsartan medoxomil and chlorthalidone as recommended by the Agency, **2)** the updated specifications table for the drug product under Section M32P51, and **3)** The PMC as agreed upon in the 10/13/11 teleconference. The meeting minutes for the 10/13/11 Teleconference were also included.

RECOMMENDATION:
ONDQA-Biopharmaceutics had evaluated the overall information supporting the approval of this submission. From the Biopharmaceutics perspective, this NDA is recommended for approval with a PMC as agreed upon in the 10/13/11 teleconference with the Applicant. The following Post Marketing Commitment comment needs to be included in the Approval Letter or sent to the Applicant.

Post Marketing Commitment:
As agreed upon in the teleconference held on October 13, 2001, you commit to provide a Supplement to the NDA within 14 months of approval date. This supplement should include the dissolution data gathered for all strengths of azilsartan medoxomil and chlorthalidone from the batches manufactured during the first year following approval date. If the Stage 2 testing is observed to be (b) (4) then a justification will be presented to support re-evaluation of the dissolution acceptance criteria for all strengths of both azilsartan medoxomil and chlorthalidone. If the Stage 2 testing is (b) (4) then the current interim acceptance criteria will remain and will be set as the final regulatory criteria for your product.

_____ 10/24/11
Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ 10/24/11
Angelica Dorantes, Ph.D. Date
ONDQA Biopharmaceutics Team Leader

CC: NDA
Tien-Mien Chen, Don Henry

BIOPHARMACEUTICS QUALITY ASSESSMENT

BACKGROUND

Takeda's Edarbi (Azilsartan medoxomil) IR tablet has been approved under NDA 200-796 on 02/25/11 with two strengths (40 and 80 mg). It is indicated for the monotherapy of hypertension. Edarbi is the prodrug of the active moiety, azilsartan, which is an angiotensin II (AII) receptor blocker (ARB) with a potent and selective antagonist of AII subtype 1 (AT1) receptors. Chlorthalidone is an approved long-acting thiazide-type diuretic, indicated for the treatment of hypertension, and it shares a similar mechanism of action with the commonly used thiazide diuretic hydrochlorothiazide. There is a strong rationale for coadministration of an ARB with a diuretic. So, the Applicant developed this FDC tablet for the treatment of hypertension that is reportedly more effective than either component alone, in association with an acceptable tolerability and safety profile. Both azilsartan medoxomil and chlorthalidone are reported as BCS class IV drug substances (low permeability and low solubility).

CURRENT SUBMISSION

On 02/21/11, Takeda submitted NDA 202-331 (N-000) for Edarbyclor IR tablets (b) (4) 40/12.5, 40/25, (b) (4). The components of Edarbyclor are Edarbi (azilsartan medoxomil: an ARB) and chlorthalidone (CLD: a thiazide-type diuretic). Edarbyclor is a (b) (4) FDC tablet formulation that is being developed by Takeda for the treatment of hypertension.

The Applicant (b) (4) employed all 6 tablet strengths in the clinical studies. The *in vivo* bioavailability information of all these 6 strengths was estimated from a Phase 3 clinical trial (No. TAK-491CLD_302) using the POPPK approach. Therefore, there is no biowaiver issue.

The Applicant submitted the dissolution development report, comparative dissolution data for the (b) (4) strengths, and proposed dissolution specifications for azilsartan medoxomil and chlorthalidone. They are reviewed here.

On 08/08/11, the Agency sent an information request to the Applicant and on 08/15/11, a teleconference was held between the Applicant and the Agency for further discussions on the dissolution media without surfactants. On 08/30/11, the Applicant submitted their response and the available data for review. The Applicant's 08/30/11 response is further reviewed and discussed internally. On 10/13/11, another teleconference was held between the Agency and the Applicant for further discussions on these issues. The Applicant submitted response on 10/19/11. These responses are reviewed here. Please see Applicant's responses for details.

FORMULATION COMPARISONS

The composition/formulation of all 6 tablet strengths is shown below. (b) (4) (b) (4) 40/12.5, 40/25, (b) (4), are proposed for marketing. They are compositionally the same, but not exactly dose-proportional among the (b) (4) strengths. The Applicant reported that 1). The (b) (4) formulation was selected to

proceed to phase 3 clinical studies and 2). With exception of colorant and printing ink, the clinical trial materials manufactured to support phase 3 studies have the same components and composition as those for the proposed commercial formulation.

Table 1. Composition/Formulation of Edarbyclor FDC Oral IR Tablets

Component	Quantity per Tablet (mg)			
	(b) (4)	40 mg +12.5mg	(b) (4)	(b) (4)	40 mg +25mg	(b) (4)
			(b) (4)			
TAK-491 (As the free acid)	(b) (4)	42.68 (40)	(b) (4)	(b) (4)	42.68 (40)	(b) (4)
Mannitol						(b) (4)
Microcrystalline cellulose (b) (4)						
Fumaric Acid						
Sodium Hydroxide						
Hydroxypropyl cellulose						
						(b) (4)
Chlorthalidone (b) (4)						(b) (4)
						(b) (4)
Crospovidone (b) (4)						(b) (4)
Magnesium stearate						
						(b) (4)
Hypromellose 2910						(b) (4)
Talc						
Titanium dioxide						
Ferric oxide, red						
Polyethylene glycol 8000 (b) (4) (b) (4)						
Tablet weight	(b) (4)	370	(b) (4)	(b) (4)	370	(b) (4)

(1) The amounts of polyethylene glycol 8000 are not included in the total tablet weight.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERIA

Both azilsartan medoxomil and chlorthalidone are reported as BCS Class IV drug substances (low permeability and low solubility). The Applicant submitted the dissolution development report and proposed the dissolution method as shown below. Several surfactants and concentrations as well as dissolution media and the paddle speeds were explored. The Applicant also provided justification/conclusion on the final dissolution method chosen. Please see Appendix 1 for details.

Apparatus: USP II (paddle) with 50 rpm
Medium: 900 ml of pH 6.8 Phosphate buffer containing 1.0% Tween 80, at 37°C
Sample time: 10, 15, 20, 30, and 45 min

The proposed dissolution acceptance criterion is as follows:

Q= (b) (4) **at 30 min** for both Azilsartan medoxomil and Chlorthalidone

The mean dissolution profiles for the (b) (4) strengths (3 batches/strength) are shown below. They are primary stability batches and the typical batch sizes of manufacture are (b) (4) tablets for (b) (4) 40/12.5, and 40/25 mg strengths, (b) (4)

I. For Azilsartan Medoxomil:

Figure 1. Mean Dissolution Profile of Azilsartan Medoxomil, Edarbyclor (b) (4) Tablet (n=6 tablets/lot)

(b) (4)

Figure 2. Mean Dissolution Profile of Azilsartan Medoxomil, Edarbyclor 40/12.5 mg Tablet (n=6 tablets/lot)

(b) (4)

Figure 3. Mean Dissolution Profile of Azilsartan Medoxomil, Edarbyclor 40/25 mg Tablet (n=6 tablets/lot)

(b) (4)

Figure 4. Mean Dissolution Profile of Azilsartan Medoxomil, Edarbyclor (b) (4) Tablet (n=6 tablets/lot)

(b) (4)

II. For Chorthalidone

Figure 5. Mean Dissolution Profile of Chlorthalidone, Edarbyclor (b) (4) Tablet (n=6 tablets/lot)

(b) (4)

Figure 6. Mean Dissolution Profile of Chlorthalidone, Edarbyclor 40/12.5 mg Tablet (n=6 tablets/lot)

(b) (4)

Figure 7. Mean Dissolution Profile of Chlorthalidone, Edarbyclor 40/25 mg Tablet (n=6 tablets/lot)

(b) (4)

Figure 8. Mean Dissolution Profile of Chlorthalidone, Edarbyclor 40/12.5 mg Tablet (n=6 tablets/lot)

(b) (4)

Please see the mean dissolution data in Appendix 2 and the individual dissolution data of these stability batches in M32P83 Stability Report for details.

Reviewer's Comments:
The proposed dissolution method was initially found acceptable and the recommendation was sent to the sponsor on 08/08/11 that the proposed dissolution method is acceptable. However, it was recommended that the proposed dissolution specifications for both azilsartan medoxomil and chlorthalidone be tightened as follows.

From: Q= (b) (4) at 30 min for both azilsartan medoxomil and chlorthalidone
To: Q= (b) (4) at 30 min for azilsartan medoxomil and
Q= (b) (4) at 15 min for chlorthalidone

On 08/15/11, a teleconference was held between the Applicant and the Agency for further discussions on the use of dissolution media without surfactants. On 08/30/11, the Applicant submitted the available data and concluded that no changes to their originally proposed dissolution method and specifications were needed (see 08/30/11 responses for details), i.e.;

Apparatus:	**USP II (paddle) with 50 rpm**
Medium:	**900 ml of pH 6.8 Phosphate buffer containing 1.0% Tween 80, at 37ºC**
Sample time:	**10, 15, 20, 30, and 45 min**
Specifications:	**Q= (b) (4) at 30 min** for both Azilsartan medoxomil and Chlorthalidone

The Applicant's 08/30/11 response was reviewed and further discussed internally within the Biopharmaceutics team. The Agency, however, did not agree with the Applicant's conclusions. On 10/13/11, another teleconference was held between the Agency and the Applicant for further discussions on these issues. In this teleconference, the Applicant and the Agency agreed upon on the following:

- *Dissolution acceptance criteria on an interim basis*:
  1. Azilsartan medoxomil:
     Q= (b) (4) at 30 min for (b) (4) 40/12.5, 40/25 mg strengths. (b) (4)

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

- *Update the specifications for the drug product under Module 32P51:*
  Per request, the Applicant will update the proposed specifications (b) (4) strengths of azilsartan medoxomil and chlorthalidone and submit the revised specifications to Module 32P51 of this NDA.

- *Post marketing commitment (PMC):*
  The Applicant agreed to provide new dissolution data post approval and within one year, submit more dissolution data for the setting of the final dissolution acceptance criteria for both azilsartan medoxomil and chlorthalidone.

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/s/

TIEN MIEN CHEN
10/24/2011

ANGELICA DORANTES
10/24/2011

Office of Clinical Pharmacology Review

NDA number	202-331
Submission type	Original, N_000
Submission date	02/24/2011
Applicant name	Takeda Pharmaceuticals North America
Proposed brand name	Edarbyclor®
Generic name	Azilsartan/chlorthalidone (Azm/Cld)
Dosage form	Non scored film coated tablet
Dosage strengths (Azm/Cld in mg)	(b) (4) 40/12.5, (b) (4) 40/25
Proposed indication	Hypertension (initial, add-on, replacement therapy)
OCP division	Division of Clinical Pharmacology 1
OND division	Cardiovascular and renal products
Reviewers	Tzu-Yun McDowell, PhD Divya Menon-Andersen, PhD
Team leader	Rajanikanth Madabushi, PhD

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1 EXECUTIVE SUMMARY

Edarbyclor is a fixed dose combination (FDC) tablet of azilsartan medoxomil and chlorthalidone (Azm/Cld) for use in treatment of hypertension. The sponsor proposes to market (b) (4) Edarbyclor for once daily administration.

The application contains four clinical pharmacology studies and eight clinical studies in support of the sponsor's claims of efficacy and safety. These include three relative bioavailability studies, one food effect study, one pivotal factorial design study, four supportive active controlled studies, and three long term studies.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) reviewed original NDA 202-331, and recommends approval from a clinical pharmacology perspective.

1.2 Phase 4 Requirements / Commitments

There are no Phase 4 requirements or commitments.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The components of Edarbyclor are approved for use in hypertension, and their pharmacokinetic (PK) and pharmacodynamic (PD) properties were reviewed under submissions NDA 200-796 (azilsartan medoxomil) and NDAs 12-283 and 19-574 (chlorthalidone).

The Clinical Pharmacology and Biopharmaceutics program for Edarbyclor was designed to enable association of the efficacy and safety data of the mono therapies to the FDC, and to provide a context for interpreting the results of the pivotal factorial trial. Of the four clinical pharmacology studies submitted to the NDA, two relative BA studies and one food effect study were reviewed.

The key clinical pharmacology and biopharmaceutics findings are listed below.

- Systemic exposure (C_{max} and AUC) to azilsartan following administration of Edarbyclor was equivalent to that following administration of azilsartan medoxomil tablets.
- Total systemic exposure (AUC) to chlorthalidone following administration of Edarbyclor was equivalent to that following administration of chlorthalidone tablets, while peak systemic exposure (C_{max}) was on average 47% higher. However, this is not clinically significant.
- The effect of food on systemic exposure to azilsartan and chlorthalidone, following administration of Edarbyclor, is not clinically significant.
- Blood pressure reduction effect of Edarbyclor appears to result from an additive effect of its components.

2 QUESTION BASED REVIEW

This is an abridged version of the question based review.

2.1 General Attributes of the individual components and the FDC

Edarbyclor is a film coated, FDC tablet of azilsartan medoxomil and chlorthalidone.

Both components of Edarbyclor have been previously approved for marketing in the US, for use in the treatment of hypertension[1].

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The physical and chemical properties of azilsartan and chlorthalidone have been summarized under OCP reviews of NDA 200-796 (DARRTS 01/11/2011) and NDA 12-283 (Hygroton, approved 1960) and 19-574 (Thalitone, approved 1988), and in the respective package inserts.

Edarbyclor is a film coated (b) (4) tablet. In addition to the active ingredients Edrabyclor contains the following inactive excipients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, sodium hydroxide, crospovidone, and magnesium stearate. (b) (4) hypromellose, titanium dioxide, polyethylene glycol 8000, talc, (b) (4) oxide red, and (b) (4)

The final formulation was used in the Phase 3 pivotal factorial design study.

2.1.2 What are the proposed dosages and routes of administration?

Edarbyclor will be marketed (b) (4) Azm/Cld for oral administration. These are (b) (4) 40/12.5 mg, (b) (4) and 40/25 mg.

2.1.3 What are the proposed mechanisms of action and therapeutic indications?

Edarbyclor is indicated for use as initial, replacement or add-on therapy in the treatment of hypertension. Azilsartan is an angiotensin receptor blocker and chlorthalidone is a diuretic. Hence, Edarbyclor is expected to exert its effect by a combination of the two mechanisms of action.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

A summary of the clinical pharmacology studies submitted to the NDA are presented in **Table 1**. Two relative bioavailability studies, and the food effect study were reviewed and the individual study reports are presented in **Appendix 4.1**.

[1] *Edarbi(NDA 200-796), Thalitone (NDA 19-574), Hygroton (NDA 12-283), Chlorthalidone (ANDA 86-831, Mylan)*

Table 1 Key design features of the relevant clinical studies conducted with Edarbyclor.

Study number	Design	Study population	Treatments
491CLD_103 Relative BA 80/25 mg	Single center, open-label, two period, crossover study	Healthy subjects (n=48)	Single dose of Edarbyclor, and the free combination
491CLD_105 Relative BA 80/25 mg	Single center, open-label, two period, parallel group, crossover study	Healthy subjects (n=48)	Single dose of a fixed dose combination of Azm+P, and Azm alone. Single dose of a fixed dose combination of Cld+P, and Cld alone.
491CLD_104 Food effect 80/25 mg	Single center, open-label, two period, parallel group, crossover study	Healthy subjects (n=48)	Single dose of Edarbyclor 80/25 mg fed and fasted Single dose of a free combination of Azm and Cld
491CLD_302 Exposure-response	Multicenter, 8 week, active controlled, double blind, factorial design study	Moderate to severe hypertensive subjects (n=1714)	Edrabyclor - 80/25, 80/12.5, 40/25, 40/12.5, 20/25, 20/12.5 Monotherapy – P/12.5, P/25, 80/P, 40/P, 20/P

2.2.2 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Azilsartan and chlorthalidone are the only active moieties in Edarbyclor. Please refer to section 2.4 for details of the bioanalytical method.

2.2.3 Exposure-Response

2.2.3.1 What are the characteristics of the exposure-response relationship for efficacy?

A concentration dependent decrease in blood pressure was observed (**Figure 1**) for the combination in the dose range tested in the phase 3 factorial design study (491CLD_302). The doses tested in this study are presented in **Table 1**.

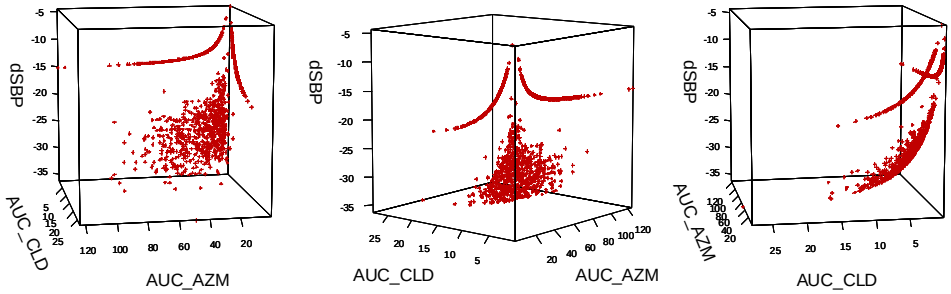

Figure 1 Exposure-response relationship for Edarbyclor indicates an additive effect of the two components. Predicted change from baseline SBP (dSBP, mm Hg) at week 8 is presented on the z-axis, and azilsartan (AUC_AZM, µg/mL*h) and chlorthalidone total systemic exposure (AUC_CLD, µg/mL*h) are presented on the x and y axis, respectively. The plot is rotated around the z-axis to present three different perspectives.

Change from baseline in systolic blood pressure (SBP) at week 8 as assessed by ABPM was the primary endpoint. Pharmacokinetic samples were also collected using a sparse sampling strategy at weeks 4 and 6 in the study. As seen in **Figure 1** and **Table 2**, blood pressure reduction with the combination of Azm/Cld was higher than that with the azilsartan or chlorthalidone alone (mono therapies).

Table 2 Observed and predicted response based on AUC model (ref: 491CLD_302 PPK/PD report)

	Observed [Predicted] (95%CI)							
	TAK-491 Placebo		**TAK-491 20 mg**		**TAK-491 40 mg**		**TAK-491 80 mg**	
CLD Placebo	NA	[0] (NA)	-12.1	[-11.8] (-14.9, -8.8)	-12.8	[-13.4] (-16.0, -10.8)	-15.1	[-14.4] (-16.8, -12.0)
CLD 12.5 mg	-12.7	[-12.4] (-17.3, -7.5)	-22.9	[-24.2] (-29.9, -18.5)	-24.4	[-25.8] (-31.3, -20.3)	-26.3	[-26.8] (-32.2, -21.4)
CLD 25 mg	-15.9	[-16.4] (-21.6, -11.2)	-26.3	[-28.2] (-34.2, -22.2)	-29.8	[-29.8] (-35.6, -24.0)	-28.0	[-30.8] (-36.5, -25.1)

Exposure-response analysis also indicated that the blood pressure reduction effect caused by Edarbyclor appears to result from the additive effects of its two components, azilsartan and chlorthalidone.

2.2.3.2 What are the characteristics for exposure-response relationships for safety?

No serious adverse events or tolerability issues were observed with Edarbyclor. Hence, exposure-response relationships for safety were not evaluated.

2.2.3.3 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

The sponsor is seeking approval of Edarbyclor (b) (4) 40/12.5, (b) (4) and 40/25 to be administered once daily. The proposed dosing frequency is consistent with that of the components of Edarbyclor and also with the duration effect of Edarbyclor over the interdosing interval.

Edarbyclor was effective in reducing blood pressure at all strengths when compared to the approved doses of azilsartan and chlorthalidone. (b) (4)

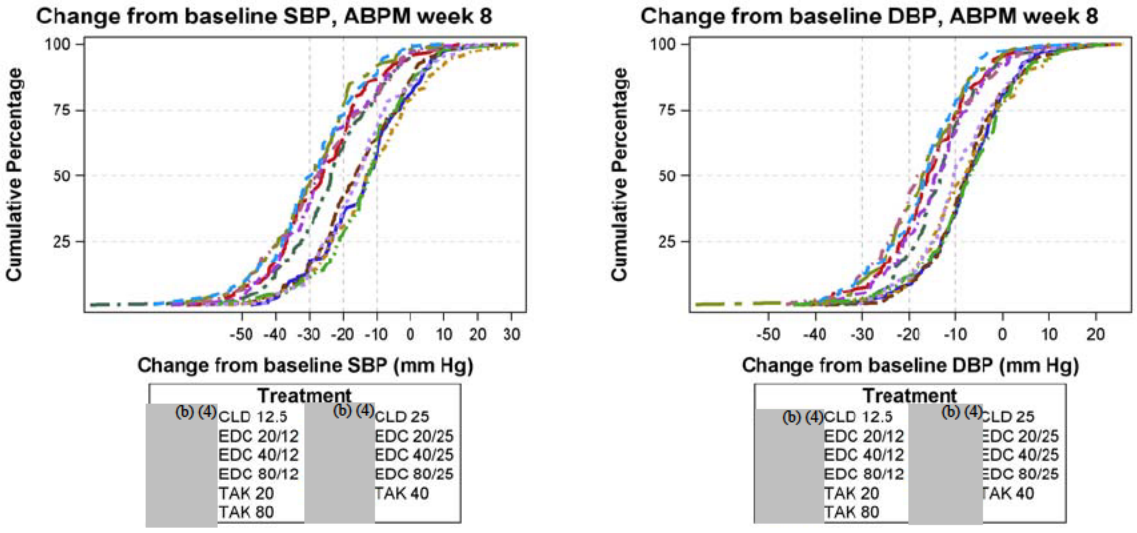

Figure 2 The range of blood reduction is similar for all strengths of Edarbyclor (491CLD_302).

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters?

The pharmacokinetic properties of azilsartan and chlorthalidone have been reviewed and reported previously under NDAs 200-796 and 12-283/19-574.

Following administration of a single dose of Edarbyclor 80/25 peak plasma azilsartan and chlorthalidone concentrations were attained at about 3 h (range: 1.0 to 6 h) and 1 h (range: 0.5 to 3 h), respectively. The mean (±SD) elimination half-life of azilsartan and

chlorthalidone were [redacted] (b) (4), respectively. These observations are consistent with previous findings for azilsartan and chlorthalidone.

2.3 General Biopharmaceutics

2.3.1 Was an adequate link established between the clinical service formulation and the to-be-marketed formulations?

The final to be marketed formulation was used in the pivotal phase 3 factorial design study, obviating the need to establish BE between the clinical service formulation and the to be marketed formulation.

The relative bioavailability of azilsartan and chlorthalidone following administration of a single dose of Edarbyclor was evaluated in TAK_CLD-103 (**Figure 3**). Peak systemic exposure (C_{max}) to chlorthalidone following administration of Edarbyclor was ~ 47% higher when compared to the free combination.

In addition, to maintain blind in the pivotal trial, a fixed dose combination tablet of azilsartan+placebo and chlorthalidone+placebo was used. Systemic exposure (AUC, Cmax) to azilsartan following administration of the FDC of azilsartan+placebo was equivalent to that of azilsartan given alone. While total systemic exposure (AUC) to chlorthalidone was equivalent to that of chlorthalidone alone, peak systemic exposure (Cmax) was 36% higher (**Figure 3**, TAK_CLD-105).

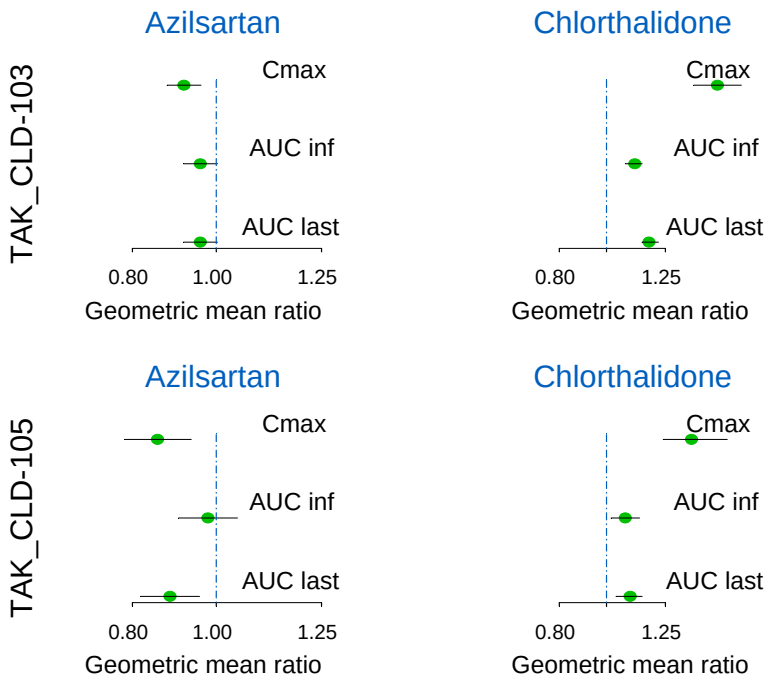

Figure 3 Edarbyclor is equivalent to the free combination of azilsartan and chlorthalidone (Studies TAK491CLD-103 and TAK491CLD-105). The geometric mean ratios are depicted on the x-axis. The closed circles represent the geometric mean of the ratio (drug in combination/individual) and the horizontal line represents the 90%CI associated with the mean.

Chlorthalidone is a long acting diuretic, suggesting that its effect is not related to Cmax. Therefore, the observed increase in C_{max} is not clinically relevant and do not require dose adjustments.

2.3.2 What is the effect of food on the bioavailability of the drug from the dosage form?

Systemic exposure (AUC and C_{max}) to azilsartan was reduced to about 80% when Edarbychlor was administered along with a standard FDA recommended high fat meal when compared to that given fasted. Peak plasma concentrations of chlorthalidone was also reduced to about 80% when administered with a standard FDA recommended high fat meal (**Figure 4**) when compared to that given fasted. In contrast, food did not affect systemic exposure (AUC and C_{max}) to azilsartan or chlorthalidone when given as a free combination.

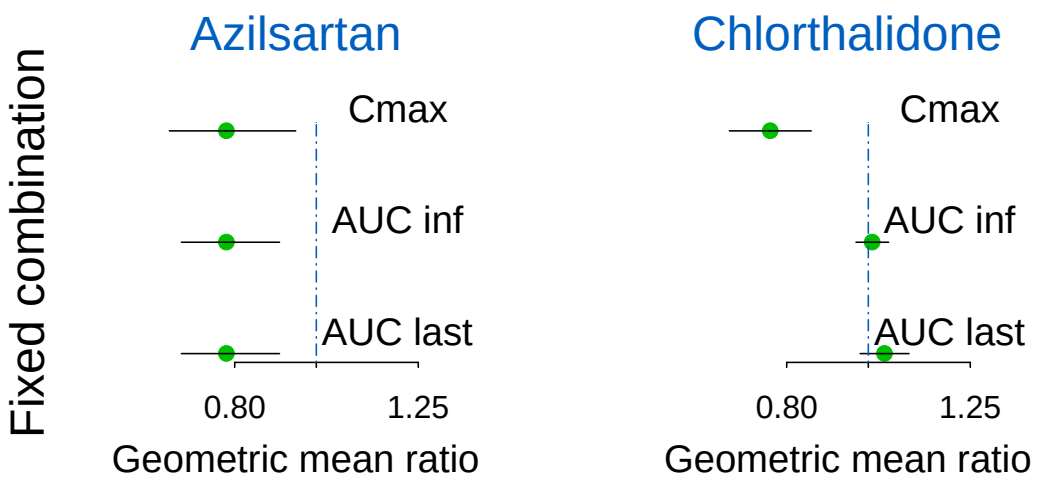

Figure 4 The effect of food on systemic exposure to azilsartan and chlorthalidone is not clinically significant. The geometric mean ratios (Fed/Fasted) are depicted on the x-axis. The closed circles represent the geometric mean of the ratio and the horizontal line represents the 90%CI associated with the mean.

These observations are not clinically significant for the following reasons and do not require dose adjustments.

- The exposure-response relationship for azilsartan is flat at doses above 10 mg. Also, the observed fluctuation in PK does not translate into a PD effect as inferred from the ABPM data.
- Chlorthalidone is a long acting diuretic, indicating that peak levels are not critical to its effect.

2.4 Analytical Section

2.4.1 How are the active moieties identified and measured in the plasma?

Plasma concentrations of azilsartan and chlorthalidone were determined using validated HPLC/MS/MS methods.

2.4.2 For all moieties measured, is free, bound, or total measured?

Total concentrations of azilsartan and chlorthalidone were measured.

2.4.3 What bioanalytical methods are used to assess concentrations?

The details of the bioanalytical method used to support studies in this NDA are presented in **Table 3**. The method satisfied all criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and was therefore acceptable.

Table 3 Assay validation results for azilsartan, and chlorthalidone (Ref: Method validation reports LCMS 389.2, 7128-364)

	Azilsartan	**Chlorthalidone**
Standard curve range	10 to 5000 ng/mL (weighted 1/x2, r ≥ 0.98)	2.0 to 1000 ng/mL (weighted 1/x2, r ≥ 0.99)
Precision (%CV)	Intra-day: 1.1 to 4.1% At LLOQ: 2.3 to 6.7% Inter-day: 2.6 to 3.4% At LLOQ: 4.7%	Intra-day: 1.2 to 7.6% At LLOQ: 3.6 to 7.6% Inter-day: 2.1 to 7.3% At LLOQ: 3.7%
Accuracy (Bias)	Intra-day: -1.0 to 7.0% At LLOQ: 1.8 to 6.4% Inter-day: 2.3 to 5.0% At LLOQ: 4.6%	Intra-day: -5.0 to 9.8% At LLOQ: -2.8 to 9.8% Inter-day: -2.6 to 3.7% At LLOQ: 3.7%
Internal standard	T-61265 Lot number: B17886-070-28	D4 – chlorthalidone Lot number: A5120168
Reference standard	Azilsartan Lot number: B17413-003-27	Chlorthalidone Lot number: I0C255
Specificity	No interference	No interference
Recovery	Azilsartan: 105% T-61265: 103 %	Chlorthalidone: 82.8% D4 – chlorthalidone: 78.6%
Matrix	Human plasma	Human plasma
Stability (in human plasma)	Benchtop: 24 hours At 8°C (autosampler): 65 h Long term stability: 155 days at 2-8°C Freeze-thaw: 5 cycles	Benchtop: 24 hours Post-prep extract at RT: 53 h Long term stability: 217 days at 2-8°C Freeze-thaw: 3 cycles

3 DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for NDA 202-331 and finds it acceptable pending the following revisions. ~~Strikethrough text~~ is recommended to be deleted and underlined text is recommended to be added. Labeling discussions are currently ongoing.

(b) (4)

4 APPENDIX

4.1 Individual Study Reports

4.1.1 Study TAK-491CLD_103 (Relative bioavailability)

Report # TAK491CLD 103	Study Period: 30 August 2008 to 13 October 2008	EDR Link[2]
Title	A Randomized, Open-Label, 2-Period Crossover Study to Determine the Relative Bioavailability of the TAK-491 CLD High-Dose Formulation of Fixed-Dose Combination Tablets Compared to Coadministration of Individual TAK-491 (azilsartan medoxomil) and Chlorthalidone Tablets in Healthy Adult Subjects	

Study Design

☐ Bioequivalence ☑ Bioavailability

Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers

Screening: ≤ 27 days	Washout: 14 days, outpatient
Period 1/2	6 days, Inpatient stay ☑Y ☐ N:

Treatments: (Active Ingredient: Azilsartan (TAK-536) + Chlorthalidone)

	Test TAK-491 CLD	Reference TAK-491 + Chlorthalidone
Dosage Form	(b) (4) Tablet	Tablet
Dosage Strength	80 mg + 25 mg	TAK-491: 80 mg + Chlorthalidone: 25 mg
Batch #.	Z657N012	Z624D072, 1S0503
Administration	Oral	Oral

Sampling Times:
PK sampling scheme was the same in both test and reference drugs as shown below:
TAK-536 & TAK-536 M-II: pre-dose and post-dose at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours
Chlorthalidone: pre-dose and post-dose at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours

Analytical Method:
The performance of the analytical method is acceptable and is summarized in the table below (ref: TAK-491CLD_103 Bioanalytical Report-2009-01-20 and TAL-491CLD_103 Bioanalytical Report 2009-01-22)

Analyte	TAK-536	Chlorthalidone
Method	HPLC/MS/MS	
LOQ (ng/ml)	10	2

[2] *\\cdsesub1\evsprod\NDA202331\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tak-491cld-103\csr-tak-491cld-103.pdf*

Range (ng/ml)	10 to 5000	2 to 1000
QCs (ng/ml)	30, 500, 4000, 20000	2, 5, 12, 45, 150, 760
Accuracy	86.5 to 120.0%	102.8 to 104.6%
Precision	3.3 to 154.4% §	3.3 to5.9%
§ QCs that failed to qualify were included in the calculation.		

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	48/44/1
Age [Median (range)]	36.1 [36.5 (20-54)]
Male/Female	32/16
Race (Caucasian/Black/Asian/other)	37/11/0/0

Results

	N	Test	Reference	Mean Ratio	90% CI
TAK-536 AUC (ng h/mL mg) C max (ng/ml)	47	40,206.9 4,357.0	41,804.7 4,722.0	96.18 92.27	(92.69, 99.80) (88.35,96.36)
Chlorthalidone AUC (ng h/mL mg) C max (ng/ml)	47	3734.6 231.7	3254.6 157.1	114.75 147.46	(111.37, 118.24) (137.99, 157.59)

Site Inspected

Requested: Yes☐ No ☑	Performed: Yes☐ No ☑ N/A ☐

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

The 90% CI for TAK-536 AUC and Cmax were within the bioequivalence standard of 80% to 125% for the comparison between the TAK-491 CLD and the coadministered tablets.
The 90% CI for chlorthalidone AUC was within the bioequivalence standard of 80% to 125% between the TAK0491 CLD and the coadministrated tablets; however Cmax exceeded the upper 90% CI by 12-25%.
A total of 34 treatment-emergent AE were reported by 14 of 48 subjects (29.2%). All AE were mild in intensity and non were considered definitely related to study drug.

Comments

Chlorthalidone is a long acting diuretic, suggesting that its effect is not related to Cmax. Therefore, the observed increase in Cmax is not clinically relevant and do not require dose adjustments.

4.1.2 Study TAK-491CLD_105 (Relative bioavailability)

Study Report # CSR TAK-491CLD_105	Protocol # TAK-491CLD_105 [3]

Title An open-label randomized 2-cohort 2-period crossover study to evaluate the relative bioavailability of two TAK-491 fixed dose combination tablets compared to individual TAK-491 and chlorthalidone tablets in healthy subjects.

Objectives Bioequivalence ☐ Bioavailability ☒ Food effect ☐

Study Design Parallel ☒ Crossover ☒

		Period 1		Period 2	
Group	**Treatment Sequence**	**Day 1**	**Days 2 to 14**	**Day 1**	**Days 2 to 5**
1	I (N=12)	A	Washout	B	Washout
	II (N=12)	B	Washout	A	Washout
2	III (N=12)	C	Washout	D	Washout
	IV (N=12)	D	Washout	C	Washout

Group 1 → Azilsartan medoxomil
A: Fixed dose combination of azilsartan medoxomil (TAK 491) 80 mg and placebo.
B: Azilsartan medoxomil (TAK 491) 80 mg tablet.
Group 2→ Chlorthalidone
A: Fixed dose combination of chlorthalidone 25 mg and placebo.
B: Chlorthalidone 25 mg tablet.

Study medication

	Test	Reference
Dosage Form	Tablet	Tablet
Dosage Strength		
TAK-491	80 mg	80 mg
CLD	25 mg	25 mg
Batch #		
TAK-491/P	Z657L012	Z624D072
CLD/P	Z657K012	1S0503
Administration	Oral	

PK Sampling

Group 1: Blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 36, 48, and 72 hours post-dose.

Group 2: Blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 36, 48, 72, 96 and 120 hours post-dose.

Statistical Method

[3] *\\cdsesub1\evsprod\NDA202331\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\tak-491cld-104\csr-tak-491cld-104.pdf*

ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

Study population

Randomized/Completed/ Discontinued because of AE	Group 1 - 24/22/1 Group 2 - 24/21/2
Age [Median (range)] in years	Group 1 – 34.7 [33.5 (18,51)] Group 2 - 34.9 [32.0 (18,55)]
Male/Female	Group 1 - 12/12 Group 2 - 16/8
Race (Caucasian/Black/Asian/other)	Group 1 - 19/5/0/0 Group 2 - 15/9/0/0

Results

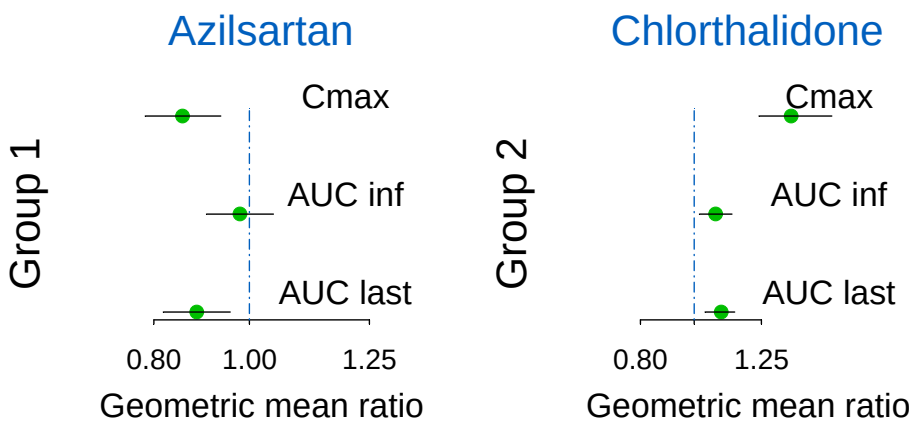

Figure 1 Results of the statistical analysis for azilsartan (TAK-536) and chlorthalidone. The geometric mean ratios are depicted on the x-axis. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean.

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below (ref: TAK-491cld_105 bioanalytical report – 2009-02-06 and 2009-01-22-NIT).

Analyte	TAK 536	Chlorthalidone
Method	HPLC/MS/MS	
LOQ (ng/mL)	10	0.025
Range (ng/mL)	10 to 5000	2.0 to 1000
QCs (ng/mL)	30, 500,4000	5, 12, 45, 150, 760
Accuracy/Bias	90.0 to 116%	93 to 100 %
Precision	3.5 to 96.7 % §	3.7 to 6.79 %

[§]QCs that failed to qualify were included in the calculation.

Safety Death/SAE: None

Conclusions

Systemic exposure to TAK 536 and chlorthalidone following administration of the FDC/P combinations were similar to that following administration of TAK 536 and chlorthalidone tablets alone.

Detailed Results

Group 1 -TAK 536

	Geometric mean (%CV)			
	N	Tablets, TAK/P	N	Tablets, TAK
Cmax (ng/mL)	24	4586.3 (27.8)	22	5369.7 (27.5)
tmax (h) ⸸	24	3 (1.5, 5.0)	22	2.0 (1.5, 5.0)
AUC0-last (ng/mL*h)	24	41371.7 (35.0)	22	46902.5 (25.0)
AUC0-∞ (ng/mL*h)	24	41994.8 (36.0)	22	47493.7 (25.6)
t1/2 (h)	24	13.4 (21.1)	22	13.4 (16.2)

Group 2 - CLD

	Geometric mean (%CV)			
	N	Tablets, CLD/P	N	Tablets, CLD
Cmax (ng/mL)	23	270.3 (33.3)	22	198.1 (36.3)
tmax (h)⸸	23	1.0 (0.5, 3.0)	22	1.8 (1.0, 4.0)
AUC0-last (ng/mL*h)	23	4158.9 (21.2)	22	3748.2 (25.5)
AUC0-∞ (ng/mL*h)	20	4810.8 (21.6)	19	4385.5 (25.2)
t1/2 (h)	23	46.1 (22.2)	22	48.7 (26.9)

⸸ Median (range)

4.1.3 Study TAK-491CLD_104 (Food effect)

Study Report # CSR TAK-491CLD_104	Protocol # TAK-491CLD_104 [4]

Title A randomized, open-label, 2-period, crossover parallel group study to determine the effect of food on the pharmacokinetics of scaled-up fixed dose combination formulation of TAK-491 and chlorthalidone in healthy subjects.

Objectives Bioequivalence ☐ Bioavailability ☐ Food effect ☒

Study Design Parallel ☒ Crossover ☒

		Period 1		Period 2	
Group	**Treatment Sequence**	**Day 1**	**Days 2 to 14**	**Day 1**	**Days 2 to 5**
1	I (N=12)	A	Washout	B	Washout
	II (N=12)	B	Washout	A	Washout
2	III (N=12)	C	Washout	D	Washout
	IV (N=12)	D	Washout	C	Washout

Group 1 → Azilsartan medoxomil (TAK 491) 80 mg and chlorthalidone 25 mg administered as separate dosage forms, concomitantly (A – fasted, B – fed).

Group 2→ Azilsartan medoxomil (TAK 491) 80 mg + chlorthalidone 25 mg administered as fixed combination dosage forms (C – fasted, D – fed).

The composition and calorie content of the high fat meal used in the study is as per "Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies" and is therefore acceptable.

Study medication

	Test	Reference
Dosage Form	Tablet	Tablet
Dosage Strength		
TAK-491	80 mg	80 mg
CLD	25 mg	25 mg
Batch #		
TAK-491/CLD	Z657N012	Z657N012
TAK-491	Z624D072	Z624D072
CLD	1S0503	1S0503
Administration	Oral	

PK Sampling Blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, 36, 48, 72, 96 and 120 hours post-dose.

Statistical Method

[4] *\\cdsesub1\evsprod\NDA202331\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\tak-491cld-104\csr-tak-491cld-104.pdf*

ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

Study population

Randomized/Completed/ Discontinued because of AE	Group 1 - 24/21/1 Group 2 - 24/23/0
Age [Median (range)] in years	Group 1 - 32.7 [29.0 (19,55)] Group 2 - 33.0 [30.5 (18,54)]
Male/Female	Group 1 - 14/10 Group 2 - 11/13
Race (Caucasian/Black/Asian/other)	Group 1 - 18/6/0/0 Group 2 - 17/5/2/0

Results

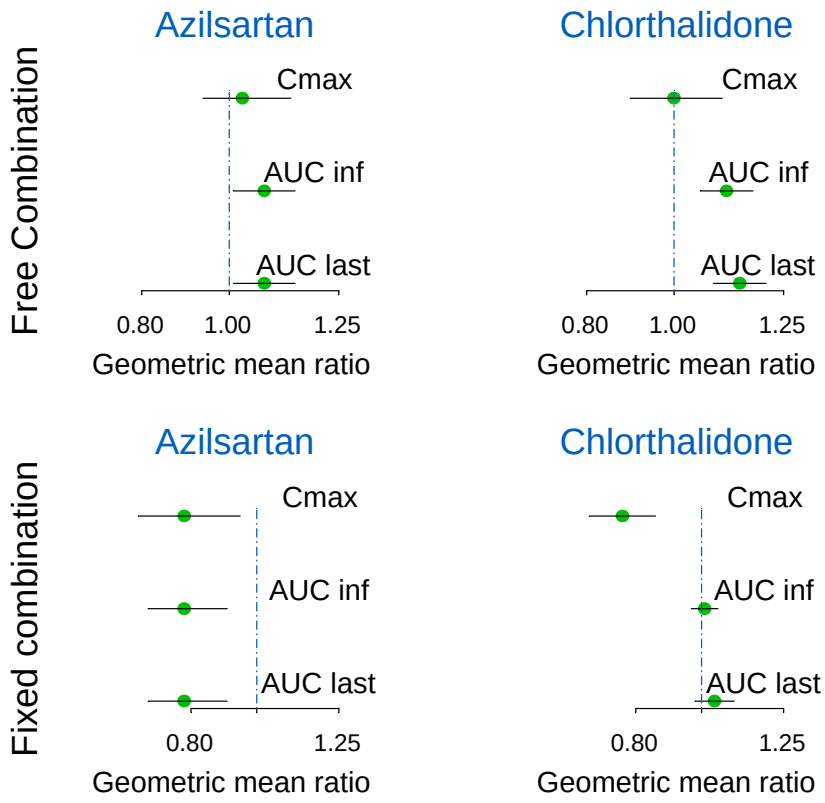

Figure 1 Results of the statistical analysis for azilsartan (TAK-536) and chlorthalidone. The geometric mean ratios are depicted on the x-axis. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean.

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is

summarized in the table below (ref: TAK-491cld_104 bioanalytical report – 2008-12-08 and 2008-12-16).

Analyte	TAK 536	Chlorthalidone
Method	HPLC/MS/MS	
LOQ (ng/mL)	10	0.025
Range (ng/mL)	10 to 5000	2.0 to 1000
QCs (ng/mL)	30, 500,4000	5, 12, 45, 1510, 760
Accuracy/Bias	95.5 to 110%	98 to 100 %
Precision	5.7 to 9.5 %	4.0 to 6.79 %

Safety Death/SAE: None

Conclusions

- Food dose not significantly affect the bioavailability of TAK 536 or chlorthalidone following administration of fixed dose combination of TAK 491 and chlorthalidone tablet.
- Peak and total systemic exposure (Cmax and AUC) to TAK 536 was decreased by about 20% following administration of the FDC with food. But because of the shallow D-R relationship of TAK536, this decrease in exposure is not expected to be significant.
- Peak plasma concentration (Cmax) of chlorthalidone was decreased by about 25% following administration of the FDC with food. The long duration of effect of chlorthalidone (corresponding to a long half-life) suggests that AUC rather than Cmax is the relevant PK metric. Therefore, decrease in Cmax is not expected to be significant.

Detailed Results – Group 1

TAK 536

	Geometric mean (%CV)			
	N	Tablets, fasted	N	Tablets, fed
Cmax (ng/mL)	23	5251.3 (20.8)	23	5632.5 (29.44)
tmax (h) ⋆	23	3 (1.5, 4.0)	23	3.0 (1.1, 6.0)
AUC0-last (ng/mL*h)	23	45234.9 (21.0)	23	38454.6 (24.92)
AUC0-∞ (ng/mL*h)	23	45678.2 (21.0)	23	39216.0 (24.87)
t1/2 (h)	23	12.0 (12.6)	23	9.5 (1.4)

CLD

	Geometric mean (%CV)			
	N	Tablets, fasted	N	Tablets, fed
Cmax (ng/mL)	23	181.2 (49.0))	23	186.0 (26.9)
tmax (h)⋆	23	2.0 (1.0, 4.0)	23	4.0 (2.0, 5.1)
AUC0-last (ng/mL*h)	23	3615.1 (28.0)	23	4326.7 (23.3)
AUC0-∞ (ng/mL*h)	19	4318.3 (24.6)	20	4920.8 (21.0)
t1/2 (h)	23	40.2 (22.3)	23	37.7 (21.0)

Group 2

TAK 536

	Geometric mean (%CV)			
	N	Tablets, fasted	N	Tablets, fed
Cmax (ng/mL)	23	4198.4 (38.4)	23	3330.7 (59.6)
tmax (h) ⅄	23	2.0 (1.5, 5.0)	23	2.0 (1.5, 6.0)
AUC0-last (ng/mL*h)	23	37574.3 (34.1)	23	29639.3 (42.5)
AUC0-∞ (ng/mL*h)	23	38034.3 (34.0)	23	30102.5 (42.4)
t1/2 (h)	23	12.8 (14.6)	23	12.4 (16.7)

CLD

	Geometric mean (%CV)			
	N	Tablets, fasted	N	Tablets, fed
Cmax (ng/mL)	23	239.7 (45.4))	24	181.8 (30.0)
tmax (h)⅄	23	1.0 (0.6, 4.0)	24	2.0 (1.0, 5.0)
AUC0-last (ng/mL*h)	23	3758.5 (26.0)	24	3877.3 (18.9)
AUC0-∞ (ng/mL*h)	20	4448.3 (21.1)	22	4461.2 (16.0)
t1/2 (h)	23	41.7 (19.7)	23	40.3 (20.3)

⅄ Median (range)

Concentration time-course

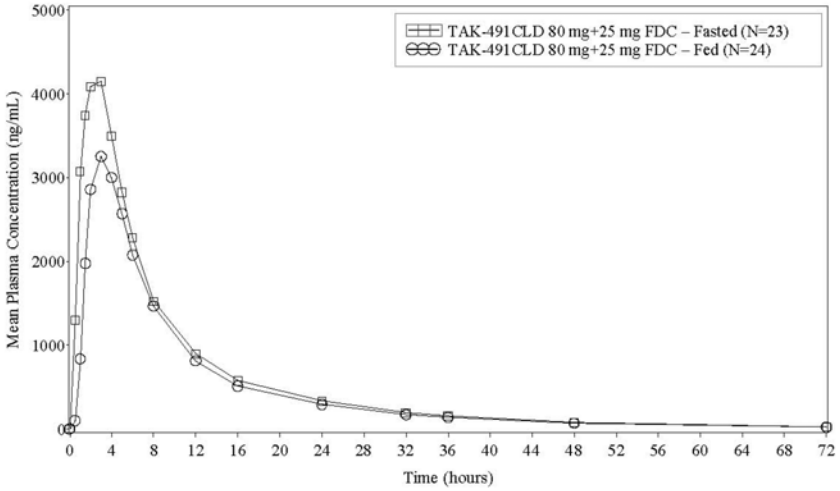

Figure 2 Plasma TAK 536 concentration versus time profile following administration of fixed dose combination of TAK 491 80 mg and chlorthalidone 25 mg, fasted (□) or fed (○). (ref. CSR TAK491cld-104, Figure 11d)

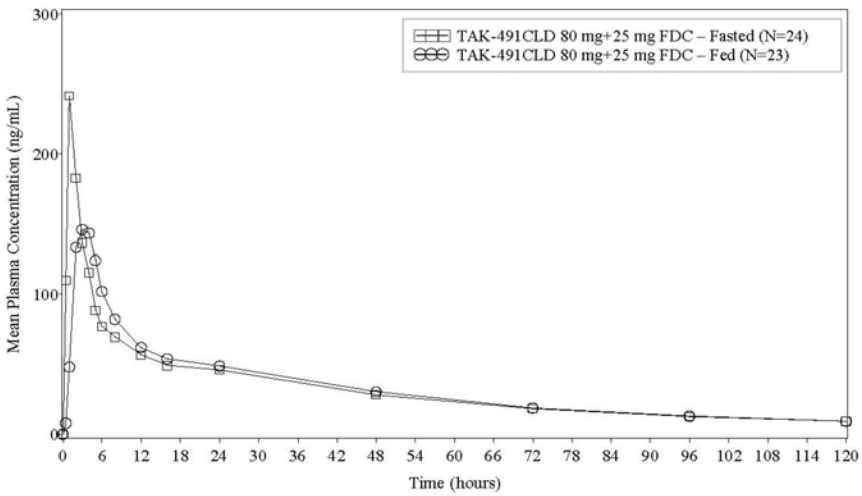

Figure 3 Plasma chlorthalidone concentration versus time profile following administration of fixed dose combination of TAK 491 80 mg and chlorthalidone 25 mg, fasted (□) or fed (○). (ref. CSR TAK491cld-104, Figure 11f)

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/s/

DIVYA MENON ANDERSEN
08/22/2011

TZU-YUN C MCDOWELL
08/22/2011

RAJANIKANTH MADABUSHI
08/22/2011
Concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202-331	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	I	**Generic Name**	Azilsartan/chlorthalidone
Medical Division	DCRP	**Drug Class**	ARB/Diuretic
OCP Reviewer	Divya Menon-Andersen	**Indication(s)**	Antihypertensive
OCP Team Leader	Raj Madabushi	**Dosage Form**	Tablet
Pharmacometrics Reviewer	-	**Dosing Regimen**	Once daily
Date of Submission	02/24/2011	**Route of Administration**	Oral
Estimated Due Date of OCP Review	08/28/2011	**Sponsor**	TGRD
Medical Division Due Date	11/11/2011	**Priority Classification**	Standard
PDUFA Due Date	12/24/2011		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2	2	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:		1	1	Exposure-response analysis
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	X	3	2	
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1	1	
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**7**	**6**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The final formulation was used in the pivotal factorial trial. Therefore, BE studies were not conducted.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Divya Menon-Andersen 04/04/2011
Reviewing Clinical Pharmacologist Date

Raj Madabushi 04/04/2011
Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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

/s/

DIVYA MENON ANDERSEN
04/04/2011

RAJANIKANTH MADABUSHI
04/04/2011