CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022545Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA number	22-545
Submission type	Original, N-000
Submission date	10/29/2009
Applicant name	Novartis Pharmaceuticals Corporation
Proposed brand name	Tekamlo®
Generic name	Aliskiren/Amlodipine (Al/Am)
Dosage form	Film coated tablet
Dosage strengths (Al/Am in mg)	300/10, 300/5, 150/10, 150/5
Proposed indication	Hypertension (initial, add-on, replacement therapy)
OCP division	Division of Clinical Pharmacology 1
OND division	Cardiovascular and renal products
Reviewer	Divya Menon-Andersen, PhD
Team leader	Rajanikanth Madabushi, PhD

This is an addendum to the clinical pharmacology review dated 06/16/2010, addressing the question of possible pharmacokinetics drug interactions between aliskiren and amlodipine. The potential for a pharmacokinetic drug interaction between aliskiren and amlodipine was assessed in study SPP100A 2218 (An Open Label, Multiple Dose Study To Evaluate The Pharmacokinetic Drug-Drug Interaction Between Amlodipine And Aliskiren When Given Alone Or In Combination To Healthy Volunteers) submitted and reviewed under the original aliskiren NDA (NDA 21-985, review DARRTSed on 01/10/2007, pp 229-232). Information reflecting the conclusions of the study, that the pharmacokinetic drug interaction is not clinically relevant, are included in the current Tekturna label *(Tekturna label – section 7.1 Effects of Other Drugs on Aliskiren, lines 6 and 16*). Hence, no further review has been performed by this reviewer. Below is a brief description of the study and its results:

According to the reviewer "This was a single-center, open label, two-period, randomized, multiple-dose study. In period 1, subjects were administered 10 mg amlodipine for 14 days followed by 7 days of washout. In period 2, subjects were administered 300 mg aliskiren for 14 days followed by co-administered 300 mg aliskiren plus 10 mg amlodipine for 14 days. The subjects were admitted to the study center at least 12 hours prior to the initial dosing of amlodipine for baseline evaluation, and discharged the following morning after dosing. All subjects remained domiciled on PK sampling days 14, 35, and 49, until the last blood sample was drawn."

The results and conclusions, extracted from the review, are listed below.

"Table 2 Summary analysis results of Aliskiren PK parameters

Parameter	Ratio of geometric means (A+B:B)	90% CI for ratio
AUC_{τ}	1.29	(1.07, 1.55)
C_{max}^{ss}	1.18	(0.83, 1.69)

Treatment A = Amlodipine 10mg/day, Treatment B = Aliskiren 300mg/day

Table 3 Summary analysis results of Amlodipine PK parameters

Parameter	Ratio of geometric means (A+B:A)	90% CI for ratio
AUC_{τ}	0.98	(0.92, 1.05)
C_{max}^{ss}	0.98	(0.93, 1.05)

Treatment A = Amlodipine 10mg/day, Treatment B = Aliskiren 300mg/day

CONCLUSIONS: Aliskiren systemic exposure and peak plasma concentration were increased by 29% and 18%, respectively, by co-administration of amlodipine. However, inter-subject variability was high and it was not possible to obtain statistical significance. Amlodipine PK parameters were not affected by co-administration of aliskiren. The combination of amlodipine and aliskiren was considered to be well tolerated and safe."

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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
07/21/2010

RAJANIKANTH MADABUSHI
07/21/2010
concur

Office of Clinical Pharmacology Review

NDA number	22-545
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Applicant name	Novartis Pharmaceuticals Corporation
Proposed brand name	Tekamlo®
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Dosage form	Film coated tablet
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OCP division	Division of Clinical Pharmacology 1
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Reviewer	Divya Menon-Andersen, PhD
Team leader	Rajanikanth Madabushi, PhD

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1 EXECUTIVE SUMMARY

Novartis Pharmaceuticals Corporation is seeking approval via the 505(b) 2 pathway of Tekamlo, a fixed dose combination (FDC) tablet of aliskiren /amlodipine (**Al/Am**) for use in the treatment of hypertension. Tekamlo will be marketed in four strengths for once daily administration.

The application contains four clinical pharmacology studies and four clinical studies in support of the sponsor's claims of efficacy and safety. These include one relative bioavailability study (CSPA100A2101), two definitive bioequivalence (BE) studies (CSPA100A2102 and CSPA100A2103), one food effect study (CSPA100A2104), one pivotal placebo controlled multifactorial study (SPA100A2305), three supportive active controlled studies (SPA100A2303, SPA100A2304, and SPP100A2305), and three long term studies (SPA100A2301, SPP100A2323, and SPP100A2323E1).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) reviewed original NDA 22-545, 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 Tekamlo are approved for use in hypertension, and their pharmacokinetic (PK) and pharmacodynamic (PD) properties were reviewed under submissions NDA 19-787 (amlodipine) and NDA 21-985 (aliskiren).

The Clinical Pharmacology and Biopharmaceutics program for Tekamlo was designed primarily to enable association of the efficacy and safety data of the monotherapies to the FDC. Of the four clinical pharmacology studies submitted to the NDA, two definitive BE studies and one food effect study were reviewed.

The key clinical pharmacology and biopharmaceutics findings are listed below.

- Tekamlo is bioequivalent to the free combination of aliskiren and amlodipine.
- Systemic exposure to aliskiren was reduced by ~ 70% when Tekamlo 300/10 mg was administered with food. This observation is consistent with prior findings for aliskiren[1]. Sytemic exposure to amlodipine following administration of Tekamlo 300/10 mg was not affected by food.

The DSI audit report for study CSPA100A2102 will be submitted in July 2010. OCP recommendations will be documented as an amendment to the current OCP review.

Divya Menon-Andersen, PhD June 15, 2010
Reviewer, Division of Clinical Pharmacology 1
Rajanikanth Madabushi, PhD
Team leader, Division of Clinical Pharmacology 1

[1] *Tekturna, Package insert*

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

Tekamlo is a film coated, FDC tablet of aliskiren and amlodipine. Both components of Tekamlo have been previously approved for marketing in the US, for use in the treatment of hypertension[1,2].

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 aliskiren and amlodipine have been summarized under OCP reviews of NDA 21-985 (DARRTS 01/11/2007) and NDA 19-787 (DFS/DARRTS 10/1/1990), and in the respective package inserts.

Tekamlo is a film coated (b) (4) tablet. In addition to the active ingredients Tekamlo contains the following inactive excipients: microcrystalline cellulose, crospovidone, povidone, colloidal silicon dioxide, and magnesium stearate. The (b) (4) contain hypromellose, titanium dioxide, polyethylene glycol (b) (4), talc, iron oxide red, and iron oxide yellow.

Tekamlo 300/10 mg and 150/5 mg are compositionally proportional while Tekmalo 300/10 mg and 300/5 mg are compositionally similar.

2.1.2 What are the proposed dosages and routes of administration?

Tekamlo will be formulated in four strengths of **Al/Am** for oral administration. These are 300/10 mg, 300/5 mg, 150/10 mg, and 150/5 mg.

The approved dosing range for aliskiren, and amlodipine for use in hypertension are 150 and 300 mg, and 5 and 10 mg, respectively.

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

Tekamlo is indicated for use as initial, replacement or add-on therapy in the treatment of hypertension. Aliskiren is a direct rennin inhibitor and amlodipine is a calcium channel blocker. Hence, Tekamlo 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 definitive bioequivalence studies and a food effect study were reviewed and the individual study reports are presented in **appendix 4.2**.

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[2] *Norvasc, Package Insert*

Table 1: Key design features of the clinical pharmacology and biopharmaceutics studies conducted with Tekamlo.

Study number	Design	Study population	Treatments
CSPA100A2101 Relative BA/BE 300/10 mg	Single center, open-label, five treatment, five period, crossover study	Healthy subjects (n=60)	Single dose of five variants of FDC formulation, and the free combination
CSPA100A2102 BE 300/10 mg	Single center, open-label, two period, crossover study	Healthy subjects (n=120)	Single dose of Tekamlo 300/10 mg, and the free combination of 300 + 2 x 5 mg
CSPA100A2103 BE 150/10 mg	Single center, open-label, two period, crossover study	Healthy subjects (n=120)	Single dose of Tekamlo 150/10 mg, and the free combination of 150 + 2 x 5 mg
CSPV100A2104 Food effect	Single center, open-label, two period, crossover study	Healthy subjects (n=35)	Single dose of Tekamlo 300/10 mg fed and fasted

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

Yes. Aliskiren and amlodipine are the only active moieties in Tekamlo. Please refer to section 2.6 for details of the bioanalytical method.

2.2.3 Exposure-Response

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

Yes. Tekamlo is a FDC of aliskiren, and amlodipine. The approved dosing range for aliskiren, and amlodipine, in hypertension are 150 and 300 mg, and 5 to 10 mg, respectively. Tekamlo will be formulated in four strengths of **Al/Am** that span the approved dosing range of the individual components for oral administration.

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

A greater decrease in mean seated diastolic blood pressure was observed with all dual combinations compared to that of the individual components (**Figure 1**). This increase was less pronounced for aliskiren (300 vs. 150 mg) when added to 10 mg amlodipine. A similar effect was observed with mean seated systolic blood pressure.

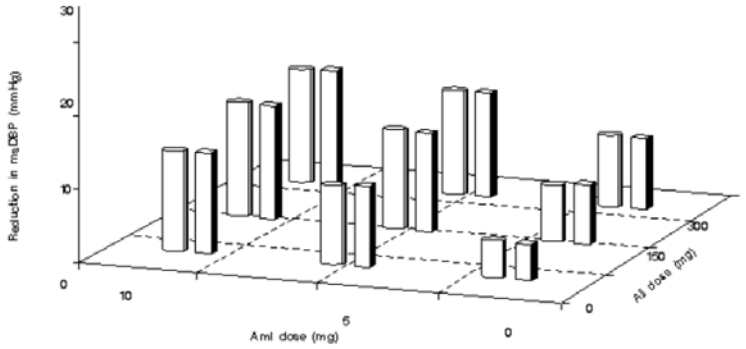

Figure 1 Observed mean reduction in seated diastolic blood pressure at study endpoint. Amlodipine and aliskiren doses are represented on the x and y axes, respectively. Reduction in mean seated diastolic blood pressure is represented on the z-axis.

(Ref: CSPA100A2305, Figure 11-5)

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 aliskiren and amlodipine have been reviewed and reported previously under NDAs 21-985 and 19-787. Following administration of a single dose of Tekamlo 300/10 peak plasma aliskiren and amlodipine concentrations were attained at about 2 h (range: 0.5 to 6 h) and 8h (range: 3 to 24 h), respectively. The mean (±SD) elimination half-life of aliskiren and amlodipine were 62.3 (± 12.9) h and 47.6 (± 10.5) h, respectively. Mean clearance for aliskiren was about 118 L/h and 113 L/h for the FDC and free combination, respectively. Mean clearance for amlodipine was around 27 L/h and 31 L/h for the FDC and free combination, respectively. Similar values were observed following administration of Tekamlo 150/10. These observations are consistent with previous findings for aliskiren and amlodipine.

2.3 General Biopharmaceutics

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

Yes. The pivotal clinical study and two of the supportive studies were conducted using the to-be-marketed fixed dose combination tablet. Bioequivalence studies with Tekamlo were conducted primarily to enable association of the efficacy and safety data of the monotherapies to the FDC.

Tekamlo 300/10 and Tekamlo 150/10 were shown to be bioequivalent to the respective free combination (**Table 2**). A biowaver is requested for the lower strengths of Tekamlo 300/5 and 150/5.

Table 2 Summary of the results of the BE studies for Tekamlo (Ref: CSPA100A2102, CSPA100A2103, Table 14.2-1.2)

	BE metric	**Aliskiren**			**Amlodipine**		
		Geometric mean (%CV)		Test/Ref (90% CI)	Geometric mean (%CV)		Test/Ref (90% CI)
		Test (FDC)	Ref (FrC)		Test (FDC)	Ref (FrC)	
Tekamlo 300/10	$AUC_{0-\infty}$ (ng/mL*h)	2127 (51.6)	2352 (53.0)	0.96 (0.9,1.03)	298.6 (33.0)	309.2 (31.6)	0.97 (0.94, 0.99)
	AUC_{0-t} (ng/mL*h)	2261 (51.4)	2352 (53.0)	0.96 (0.89, 1.03)	271.8 (29.7)	279.6 (28.2)	0.97 (0.95, (0.99)
	C_{max} (ng/mL)	293.6 (73.1)	305.3 (71.2)	0.95 (0.85,1.07)	4.7 (24.4)	4.9 (20.7)	0.97 (0.95, 1.00)
Tekamlo 150/10	$AUC_{0-\infty}$ (ng/mL*h)	1305 (51.1)	1325 (58.7)	0.98 (0.91, 1.05)	346.8 (27.5)	353.5 (27.0)	0.99 (0.96,1.02)
	AUC_{0-t} (ng/mL*h)	1189 (52.7)	1231 (60.2)	0.97 (0.9, 1.04)	302.5 (26.0)	307.3 (27.0)	0.99 (0.96, 1.01)
	C_{max} (ng/mL)	169.9 (68.6)	172.4 (80.1)	0.99 (0.88, 1.12)	5.7 (21.0)	5.43 (22.0)	0.98 (0.96, 1.01)

FDC – Fixed dose combination; FrC – Free combination

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

Systemic exposure to aliskiren was reduced by > 70% when Tekamlo was administered along with a standard FDA recommended high fat meal (**Table 3**). This observation is consistent with previous findings, and is not clinically significant. Consequently, dose adjustments are not recommended.

Table 3 Summary of the results of the food effect studies for Tekamlo (Ref: CSPA100A2104, Table 14.2-1.2)

	BE metric	**Aliskiren**			**Amlodipine**		
		Geometric mean (%CV)		Test/Ref (90% CI)	Geometric mean (%CV)		Test/Ref (90% CI)
		Test (Fed)	Ref (Fasted)		Test (Fed)	Ref (Fasted)	
Tekamlo 300/10	$AUC_{0-\infty}$ (ng/mL*h)	454.8 (35.5)	2152 (45.6)	0.21 (0.19, 0.24)	327.9 (23.5)	318.1 (31.2)	1.03 (0.97, 1.09)
	AUC_{0-t} (ng/mL*h)	411.8 (35.3)	2044 (45.9)	0.2 (0.18, 0.23)	292.5 (22.0)	284.5 (26.2)	1.03 (0.97, 1.08)
	C_{max} (ng/mL)	24.54 (42.5)	258.0 (67.2)	0.1 (0.08, 0.12)	4.9 (18.5)	4.8 (21.0)	1.02 (0.97, 1.07)

There was no change in systemic exposure to amlodipine when Tekamlo was administered along with a standard FDA recommended high fat meal (**Table 3**).

2.4 Analytical Section

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

Plasma concentrations of aliskiren, and amlodipine were simultaneously determined using a validated HPLC/MS/MS method. Briefly, (b) (4)

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

Total concentrations of aliskiren, and amlodipine were measured.

2.4.3 What bioanalytical methods are used to assess concentrations?

Please refer to section 2.6.1. **Table 4** provides the details of the bioanalytical method used to support the BA/BE studies. 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 4: Assay validation results for aliskiren, and amlodipine (Ref: DMPK-r0700893)

	Aliskiren	**Amlodipine**
Standard curve range	0.5 to 100 ng/mL (weighted $1/x^2$, $r \geq 0.98$)	0.025 to 10 ng/mL (weighted $1/x^2$, $r \geq 0.98$)
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: 0.6 to 5.4% At LLOQ: 6.6 to 12.5% Inter-day: 1.9 to 3.9% At LLOQ: 9.4%
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: -0.9 to 5.9% At LLOQ: 0.4 to 6.4% Inter-day: 0 to 4.9% At LLOQ: 3.6%
Internal standard	D6 – aliskiren Lot number: WFQ0177 Purity: 99.8%	D4 – amlodipine Lot number: 12-MJC-118-1 Purity: 98%
Reference standard	Aliskiren Lot number: 0544031 Purity: 98.1%	Amlodipine Lot number: F0D167 Purity: 99.6%
Specificity	No interference	No interference
Recovery	Aliskiren: 68.5% D6 – aliskiren: 73.5 %	Amlodipine: 72.9% D4 – amlodipine: 73.5%
Matrix	Human plasma	Human plasma

Stability (in human plasma)	Benchtop: 26 hours At 8°C (autosampler): 96 h Long term stability: 139 days at 2-8°C	Benchtop: 28 hours At 8°C (autosampler): 96 h Long term stability: 139 days at 2-8°C

Reviewer's comment: No data were reported for freeze-thaw stability. However, such data have been submitted, reviewed and judged acceptable for aliskiren under NDAs 21-985 and 22-217, and for amlodipine under NDA 22-314.

3 DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for NDA 22-545 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.

12.3 Pharmacokinetics
Absorption and Distribution
Tradename
Following oral administration of the aliskiren/amlodipine combination tablets, the median peak plasma concentration time are within 3.0 hour for aliskiren and 8.0 hours for amlodipine. *The rate and extent of absorption of aliskiren and amlodipine from Tekamlo are the same as when administered as individual tablets.* When taken with food, mean AUC and Cmax of aliskiren are decreased by 79% and 90%, respectively, while there is no impact of food on the AUC and Cmax of amlodipine. (b) (4)

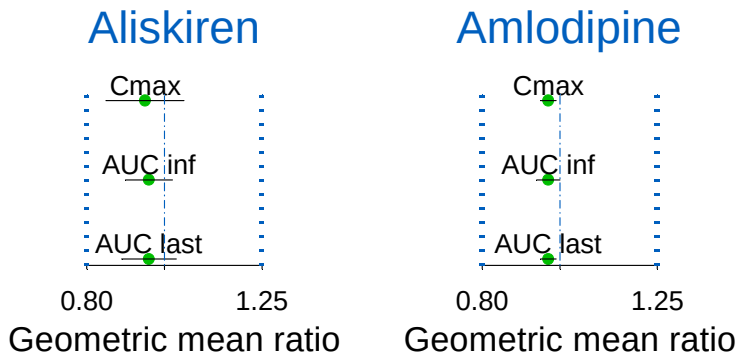
Drug Interactions

Aliskiren exposure is increased slightly (up to 29%) when co-administered with amlodipine, but amlodipine exposure remains unchanged when co- administered with aliskiren. The slight exposure change of aliskiren in the presence of amlodipine is not clinically relevant.

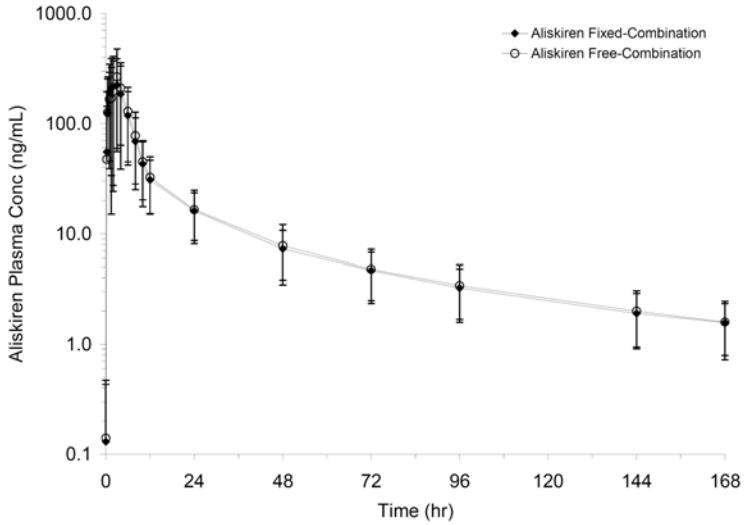
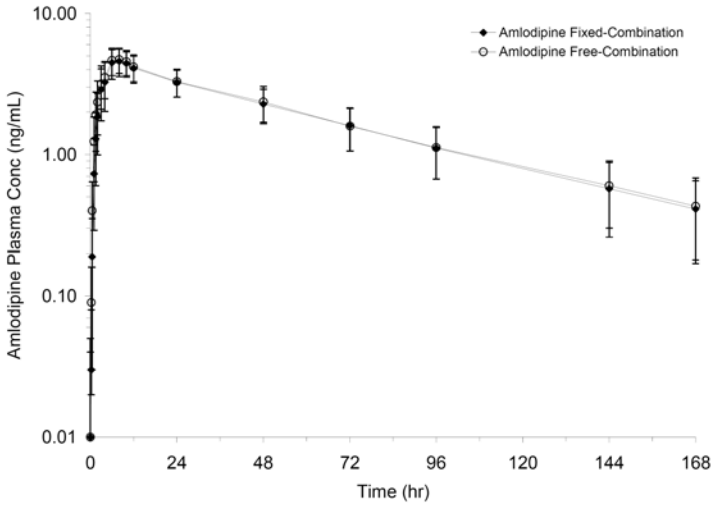
4 APPENDIX

4.1 Individual Study Reports

4.1.1 Study CSPA100A2102 (Bioequivalence)

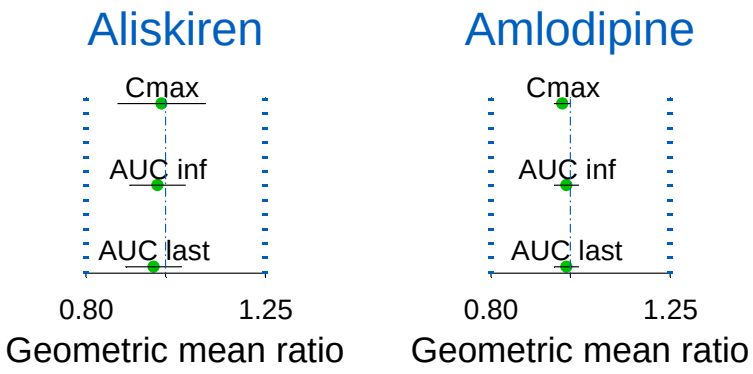
Study Report # CSPA100A2102		**Protocol #** SPA100A2102	
Title	An open-label, randomized, two treatment, two-period, single-dose, crossover study to determine the bioequivalence of fixed combination of SPA100 (aliskiren/amlodipine 300/10 mg oral tablet) and the free combination of aliskiren 300 mg market tablet and amlodipine 10 mg (2x5 mg tablets) in healthy adult subjects.		
Objectives	Bioequivalence ☒ Bioavailability ☐		
Study Design	Parallel ☐ Crossover ☒ The two periods were separated by a minimum of 14 days.		
Formulation		**Test**	**Reference**
	Dosage Form	Fixed combination tablet (Aliskiren/Amlodipine)	Free combination tablets (Aliskiren/Amlodipine)
	Dosage Strength	300/10 mg	300 mg / 2 x 5 mg
	Batch #.	AEUS/ 2008-0173	X301LA / 610025930 D
PK Sampling	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 12, 24, 48, 72, 96, 120, 144, and 168 hours post-dose.		
Statistical Method	A mixed-effect ANOVA model on log transformed parameters. Two-sided 90% CI for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.		
Population	Total randomized 120 Completed 112		
Results	 **Figure 1** Results of the statistical analysis. The geometric mean ratios are depicted on the x-axis. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the		

<table>
<tr><td></td><td>horizontal line represents the 90%CI associated with the mean.</td></tr>
<tr><td>Site Inspection</td><td>Performed: Yes ☒ No ☐ Note: DSI audit report expected in July 2010.</td></tr>
<tr><td>Assay Method</td><td>The performance of the assay method during study sample analysis is summarized in the table below.
<table>
<tr><th></th><th>Aliskiren</th><th>Amlodipine</th></tr>
<tr><td>Method</td><td colspan="2">HPLC/MS/MS – simultaneous detection of both analytes.</td></tr>
<tr><td>LOQ (ng/mL)</td><td>0.5</td><td>0.025</td></tr>
<tr><td>Range (ng/mL)</td><td>0.5 to 200</td><td>0.025 to 10</td></tr>
<tr><td>QCs (ng/mL)</td><td>1.5, 10, 60, 160</td><td>0.075, 0.5, 3, 8</td></tr>
<tr><td>Accuracy/Bias</td><td>-3.8 to 2.0 %</td><td>-8.5 to 0.7 %</td></tr>
<tr><td>Precision</td><td>6.4 to 59.9 % *</td><td>5.4 to 60.9 % *</td></tr>
</table>
*QCs that failed to qualify were included in the calculation. Precision of the qualifying QCs were < 15%.</td></tr>
<tr><td>Safety</td><td>Death/SAE: None</td></tr>
<tr><td>Conclusion</td><td>The fixed combination is bioequivalent to the free combination.</td></tr>
<tr><td>Detailed Results</td><td>Table 1 Summary of pharmacokinetic variables for aliskiren.
<table>
<tr><th></th><th></th><th colspan="3">Geometric Mean (%CV)</th></tr>
<tr><th>Parameter</th><th>N</th><th>Test</th><th>N</th><th>Reference</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>116</td><td>293.6 (73.1)</td><td>115</td><td>305.3 (71.2)</td></tr>
<tr><td>t_{max} (h)*</td><td>116</td><td>2.0 (0.5 – 6.0)</td><td>115</td><td>3.0 (0.25 – 8.0)</td></tr>
<tr><td>$AUC_{0\text{-last}}$ (ng/mL*h)</td><td>115</td><td>2127 (51.6)</td><td>115</td><td>2214 (53.0)</td></tr>
<tr><td>$AUC_{0\text{-}\infty}$ (ng/mL*h)</td><td>115</td><td>2261 (51.4)</td><td>115</td><td>2352 (53.0)</td></tr>
<tr><td>$t_{1/2}$ (h)**</td><td>115</td><td>62.3 ± 12.9</td><td>115</td><td>63.0 ± 14.5</td></tr>
</table>
Table 2 Summary of pharmacokinetic variables for amlodipine.
<table>
<tr><th></th><th></th><th colspan="3">Geometric Mean (%CV)</th></tr>
<tr><th>Parameter</th><th>N</th><th>Test</th><th>N</th><th>Reference</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>116</td><td>4.7 (24.4)</td><td>115</td><td>4.9(20.7)</td></tr>
<tr><td>t_{max} (h)*</td><td>116</td><td>8.0 (3.0-24.0)</td><td>115</td><td>8.0 (2.0 – 12.0)</td></tr>
<tr><td>$AUC_{0\text{-last}}$ (ng/mL*h)</td><td>115</td><td>271.8 (29.7)</td><td>115</td><td>279.6 (28.2)</td></tr>
<tr><td>$AUC_{0\text{-}\infty}$ (ng/mL*h)</td><td>115</td><td>298.6 (33.0)</td><td>115</td><td>309.2 (31.6)</td></tr>
<tr><td>$t_{1/2}$ (h)**</td><td>115</td><td>47.6 ± 10.5</td><td>115</td><td>48.5 ± 12.3</td></tr>
</table></td></tr>
</table>

	**Median (range) ** Mean ± SD*
Concentration time-course	 **Figure 2:** Plasma aliskiren concentration versus time profile following administration of the free combination (Reference, open circles) or fixed combination tablet (Test, closed circles).  **Figure 3:** Plasma amlodipine concentration versus time profile following administration of the free combination tablet (Reference, open circles) or fixed combination tablet (Test, closed circles).

4.1.2 Study CSPA100A2102 (Bioequivalence)

Study Report # CSPA100A2103	**Protocol #** SPA100A2103

Title	An open-label, randomized, two treatment, two-period, single-dose, crossover study to determine the bioequivalence of fixed combination of SPA100 (aliskiren/amlodipine 150/10 mg oral tablet) and the free combination of aliskiren 150 mg market tablet and amlodipine 10 mg (2x5 mg tablets) in healthy adult subjects.
Objectives	Bioequivalence ☒ Bioavailability ☐
Study Design	Parallel ☐ Crossover ☒ The two periods were separated by a minimum of 14 days.
Formulation	**Test** / **Reference** Dosage Form: Fixed combination tablet (Aliskiren/Amlodipine) / Free combination tablets (Aliskiren/Amlodipine) Dosage Strength: 150/10 mg / 150 mg / 2 x 5 mg Batch #.: AEUS/ 2008-0183 / S0118 / 610025930 D
PK Sampling	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 12, 24, 48, 72, 96, 120, 144, and 168 hours post-dose.
Statistical Method	A mixed-effect ANOVA model on log transformed parameters. Two-sided 90% CI for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of AUC $_{0\text{-}t}$, AUC$_{0\text{-}\infty}$ and C$_{max}$.
Population	Total randomized 120 Completed 109
Results:	 **Figure 1** Results of the statistical analysis. The geometric mean ratios are depicted on the x-axis. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric means 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 summarized in the table below.

	Aliskiren	**Amlodipine**
Method	HPLC/MS/MS – simultaneous detection of both analytes.	
LOQ (ng/mL)	0.5	0.025
Range (ng/mL)	0.5 to 200	0.025 to 10
QCs (ng/mL)	1.5, 10, 60, 160	0.075, 0.5, 3, 8
Accuracy/Bias	-8.1 to -4.3 %	-5.8 to -5.3 %
Precision	3.0 to 5.1 %	3.0 to 5.4 %

Safety

Death/SAE: **None**

Conclusion

The fixed combination is bioequivalent to the free combination.

Detailed Results

Table 1 Summary of pharmacokinetic variables for aliskiren.

		Geometric Mean (%CV)		
PK variable	**N**	**Test**	**N**	**Reference**
C_{max} (ng/mL)	115	169.9 (68.6)	116	172.4 (80.1)
t_{max} (h)*	115	3.0 (0.5-6.05)	116	3.0 (0.5-6.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	113	1189 (52.7)	116	1231 (60.2)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	111	1305 (51.1)	116	1325 (58.7)
$t_{1/2}$ (h)**	111	64.02 ± 21.1	116	60.0 ± 17.2

Table 2 Summary of pharmacokinetic variables for amlodipine.

		Geometric Mean (%CV)		
PK variable	**N**	**Test**	**N**	**Reference**
C_{max} (ng/mL)	115	5.7 (21.0)	116	5.43 (22.0)
t_{max} (h)*	115	6.0 (2.0-12.0)	116	5.5 (2.0-24.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	113	302.5 (26.0)	116	307.3 (27.0)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	111	346.8 (27.5)	113	353.5 (27.0)
$t_{1/2}$ (h)**	111	53.13 ± 11.5	113	51.82 ± 10.6

**Median (range) ** Mean ± SD*

4.1.3 Study CSPA100A2104 (Food effect)

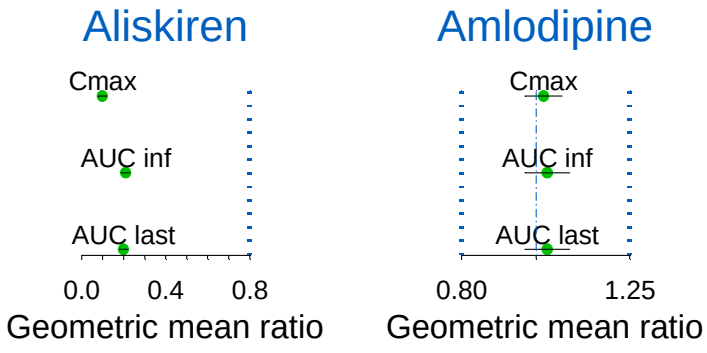
<table>
<tr><td colspan="2">Study Report # CSPA100A2104</td><td colspan="2">Protocol # CSPA100A2104</td></tr>
<tr><td>Title</td><td colspan="3">A single center, open-label, randomized, two-period, crossover, single-dose study to determine the effect of food on the bioavailability of fixed combination SPA100 (aliskiren/amlodipine 300/10 mg oral tablets) in healthy subjects.</td></tr>
<tr><td>Objectives</td><td colspan="3">Bioequivalence ☐ Bioavailability ☒</td></tr>
<tr><td>Study Design</td><td colspan="3">Parallel ☐ Crossover ☒
The two periods were separated by a minimum of 14 days. 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.</td></tr>
<tr><td>Formulation</td><td colspan="3"><table><tr><th></th><th>Test</th><th>Reference</th></tr><tr><td>Dosage Form</td><td>Fixed combination fed (Aliskiren/Amlodipine)</td><td>Fixed combination fasted (Aliskiren/Amlodipine)</td></tr><tr><td>Dosage Strength</td><td>300/10 mg</td><td>300 mg / 10 mg</td></tr><tr><td>Batch #.</td><td>AEUS/ 2008-0173</td><td>AEUS/ 2008-0173</td></tr></table></td></tr>
<tr><td>PK Sampling</td><td colspan="3">Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 12, 24, 48, 72, 96, 120, 144, and 168 hours post-dose.</td></tr>
<tr><td>Statistical Method</td><td colspan="3">A mixed-effect ANOVA model on log transformed parameters. Two-sided 90% CI for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of AUC $_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max}.</td></tr>
<tr><td>Population</td><td colspan="3"><table><tr><td>Total randomized</td><td>36</td><td>Completed</td><td>35</td></tr></table></td></tr>
<tr><td>Results</td><td colspan="3"> 

Figure 1 Results of the statistical analysis. The geometric mean ratios are depicted on the x-axis. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric means of the BE metrics and the horizontal line represents the 90%CI associated with the mean.</td></tr>
</table>

<table>
<tr><td>Site Inspection</td><td>Performed: Yes ☐ No ☒</td></tr>
<tr><td>Assay Method</td><td>The performance of the assay method during study sample analysis is summarized in the table below.
<table>
<tr><td></td><td>Aliskiren</td><td>Amlodipine</td></tr>
<tr><td>Method</td><td colspan="2">HPLC/MS/MS – simultaneous detection of both analytes.</td></tr>
<tr><td>LOQ (ng/mL)</td><td>0.5</td><td>0.025</td></tr>
<tr><td>Range (ng/mL)</td><td>0.5 to 200</td><td>0.025 to 10</td></tr>
<tr><td>QCs (ng/mL)</td><td>1.5, 10, 60, 160</td><td>0.075, 0.5, 3, 8</td></tr>
<tr><td>Accuracy/Bias</td><td>-5.3 to -2.9 %</td><td>-7.7 to -4.3 %</td></tr>
<tr><td>Precision</td><td>5.2 to 9.7 %</td><td>~ 5 %</td></tr>
</table></td></tr>
<tr><td>Safety</td><td>Death/SAE: None</td></tr>
<tr><td>Conclusion</td><td>Following administration of a single dose of Tekamlo with food, systemic exposure to aliskiren was reduced by > 70% while that to amlodipine was not affected. The observed decrease in exposure to aliskiren is consistent with previous findings, and was previously judged not to be clinically significant.</td></tr>
</table>

Detailed Results

Table 1 Summary of pharmacokinetic variables for aliskiren.

		Geometric Mean (%CV)		
PK variable	**N**	**Test (Fed)**	**N**	**Reference (Fasted)**
C_{max} (ng/mL)	35	24.54 (42.5)	36	258.0 (67.2)
t_{max} (h)*	35	3.0 (1-10)	36	1.5 (1-6)
$AUC_{0\text{-last}}$ (ng/mL*h)	35	411.8 (35.3)	36	2044 (45.9)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	35	454.8 (35.5)	36	2152 (45.6)
$t_{1/2}$ (h)**	35	49 ± 28.6	36	58 ± 9.6

Table 2 Summary of pharmacokinetic variables for amlodipine.

		Geometric Mean (%CV)		
PK variable	**N**	**Test (Fed)**	**N**	**Reference (Fasted)**
C_{max} (ng/mL)	35	4.9 (18.5)	36	4.8 (21.0)
t_{max} (h)*	35	8.0 (4.0-12.0)	36	8.0 (3.0-10.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	35	292.5 (22.0)	36	284.5 (26.2)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	35	327.9 (23.5)	36	318.1 (31.2)
$t_{1/2}$ (h)**	35	49.6 ± 11.0	36	50.1 ± 16

**Median (range) ** Mean ± SD*

Concentration time-course

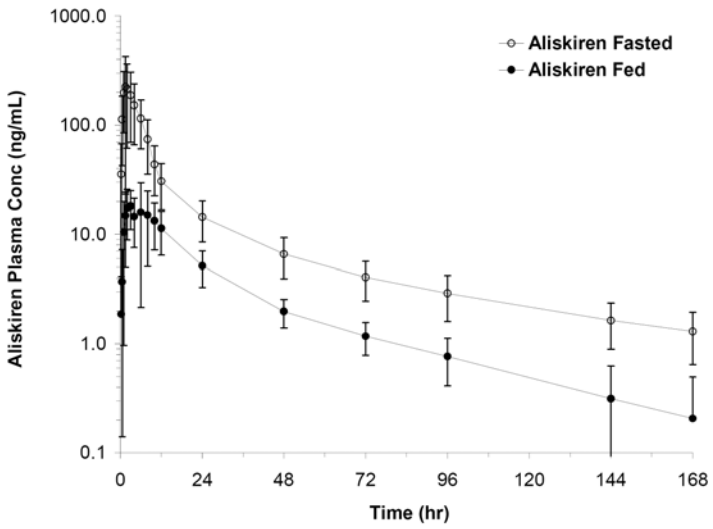


Figure 2: Plasma aliskiren concentration versus time profile following administration of the fixed combination fasted (Reference, open circles) or fixed combination fed (Test, closed circles).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

DIVYA MENON ANDERSEN
06/16/2010

RAJANIKANTH MADABUSHI
06/16/2010
I concur with the finding, interpretation and recommendations of the review

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-545 (N-000)
Submission Date:	10/29/09, 03/12/10, and 04/26/10
Brand Name:	Tekamlo
Generic Name:	Aliskiren/Amlodipine
Formulation:	Fixed Dose Combination (FDC) Immediate Release (IR) Tablets
Strength:	300/10mg, 300/5mg, 150/10mg, and 150/5 mg
Sponsor:	Novartis
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

On 10/29/09, Novartis submitted NDA 22-545 (N-000) for Tekamlo (b) (4) film-coated IR tablets. The above NDA is submitted under 505(b)(2) referencing the approved individual NDAs, Takturna (aliskiren) tablets, 300 and 150 mg (NDA 21-985) and Norvasc (amlodipine), 5 and 10 mg tablets (NDA 19-787).

Tekamlo (aliskiren/amlodipine) IR tablets are proposed in four strengths, 300/10 mg, 300/5 mg, 150/10 mg and 150/5 mg. The four strengths are considered compositionally the same and dose proportional among the strengths. Tekamlo is indicated for the treatment of hypertension.

The to-be-marketed (TBM) formulations of 300/10 mg and 150/10 mg Tekamlo IR tablets have been used in two bioequivalence (BE) studies compared to their individual components. The above BE studies are currently under review by the Office of Clinical Pharmacology.

Novartis also submitted for review, 1). The proposed dissolution methodology and specifications with the dissolution development report using 4 media and 2). A biowaiver request and the comparative dissolution data for the two lower strengths, 300/5 mg and 150/5 mg vs. the highest strength, 300/10 mg.

From the 4 tested media, the sponsor selected the following dissolution methodology:

Apparatus: **1 (Basket)**
Speed: **100 rpm**
Medium: **0.01N HCL (pH 2.0), 500 mL at 37°C.**

The selected methodology is consistent with the currently FDA approved dissolution methodology for aliskiren and amlodipine drug products. After reviewing the dissolution data, the Agency requested tightening the dissolution specifications for both aliskiren and amlodipine. As agreed upon between the Agency and the sponsor, the proposed dissolution specifications to be amended are shown below.

Specifications:
From: Q= (b) (4) **at 30 min for both aliskiren and amlodipine**
To: Q= (b) (4) **at 30 min for both aliskiren and amlodipine**

RECOMMENDATION

From the Biopharmaceutics perspective, 1). The biowaiver request for the two lower strengths, 300/5 mg and 150/5 mg is granted and 2). The newly revised dissolution method and specifications that were submitted on 04/26/10 were reviewed and found acceptable. Therefore, the following comment should be conveyed to the sponsor.

COMMENT: (Needs to be sent to the sponsor)

The following revised dissolution method and specifications should be implemented:

Apparatus: **1 (Basket)**
Speed: 100 rpm
Medium: 0.01N HCL (pH 2.0), 500 mL at 37°C
Specifications: Q= (b) (4) **at 30 min for both aliskiren and amlodipine**

BACKGROUND

Both Takturna (aliskiren) tablets, 300 and 150 mg (NDA 21-985) and Norvasc (amlodipine), 5 and 10 mg tablets (NDA 19-787) are approved single-entity products in the US. Aliskiren is a direct renin inhibitor and amlodipine is a dihydropyridine calcium channel blocker. Novartis has developed FDC IR tablet formulation containing both aliskiren and amlodipine.

CURRENT SUBMISSION

On 10/29/09, Novartis submitted NDA 22-545 (N-000) for Tekamlo (b) (4) film-coated IR tablets. It is submitted under 505(b)(2) referencing the individual approved NDAs. Tekamlo (aliskiren/amlodipine) IR tablets are proposed in four strengths, 300/10 mg, 300/5 mg, 150/10 mg and 150/5 mg. The four strengths are considered compositionally the same and dose proportional among the strengths. Tekamlo is indicated for the treatment of hypertension.

The to-be-marketed (TBM) formulations of 300/10 mg and 150/10 mg tablets have been used in two BE studies compared to their individual components. The above BE studies are currently under review by the Office of Clinical Pharmacology.

Under this NDA, Novartis also submitted for review, 1). The proposed dissolution methodology and specifications plus the dissolution development report and 2). A biowaiver request with comparative dissolution data for the 300/5 mg and 150/5 mg strengths vs. the highest strength, 300/10 mg.

FORMULATION COMPARISONS

The TBM formulations of four strengths are shown below in **Table 1**.

Ingredient	Amount of SPA100 150/5 mg/tablet	Amount of SPA100 150/10 mg/tablet	Amount of SPA100 300/5 mg/tablet	Amount of SPA100 300/10 mg/tablet	Function	Reference to standards
Amlodipine	6.94[a]	13.87[b]	6.94[a]	13.87[b]	active ingredient	Novartis monograph
Aliskiren	165.75[c]	165.75[c]	331.50[d]	331.50[d]	active ingredient	USP/Ph. Eur.
Microcrystalline cellulose	(b) (4)				(b) (4)	NF/Ph. Eur.
Povidone						USP/Ph. Eur.
Crospovidone						NF/Ph. Eur.
(b) (4)						NF/Ph. Eur.
Magnesium stearate						NF/Ph. Eur.
Core weight						
(b) (4)						Novartis monograph
						Novartis monograph
						Novartis specifications
Final weight	509.50	509.50	1013.00	1013.00		

[a] corresponds to 5 mg of Amlodipine free base;
[b] corresponds to 10 mg of Amlodipine free base
[c] corresponds to 150mg of Aliskerin free base, d corresponds to 300mg of Aliskerin free base

- The qualitative composition of the 300/5 mg and 300/10 mg tablets are identical and their quantitative composition is similar. The amount of amlodipine besylate and microcrystalline cellulose is (b) (4) (b) (4). Microcrystalline cellulose is a (b) (4) and the sponsor reported that a small change in quantity should not change the performance of the drug product.

- The qualitative composition of the 150/5 mg and 150/10 mg tablets are identical and their quantitative composition is similar. The amount of amlodipine besylate and microcrystalline cellulose is (b) (4)

DISSOLUTION COMPARISONS

The sponsor submitted comparative dissolution data of the above two lower strengths with the highest strength (300/10 mg) in 4 different dissolution media to support the biowaiver request and the selection of the proposed dissolution methodology. The dissolution data on the 150/10 mg strength, however, was not submitted. Upon request (an IR sent on 02/26/10), the sponsor submitted the needed information on 03/12/10.

(b) (4)

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(b) (4)

Reviewer's Comments:
It is concluded that

1). The sponsor's proposed new dissolution specifications as shown below are acceptable to the Agency:

Specifications: Q (b) (4) at 30 min for both aliskiren and amlodipine.

2). The biowaiver request for the two strengths (300/5 mg and 150/5 mg) are acceptable since the f2 values are >50 indicating similarity when compared to the highest strength of 300/10 mg.

_____ 06/11/10

Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ 06/11/10

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

NDA 22-545 for Tekamlo
(Aliskiren and Amlodipine) FDC IR Tablets
(300/10 mg, 300/5 mg, 150/10 mg, and 150/5 mg)

Appendix 1

Mean Comparative Dissolution Profiles in the Rest of the Three Media Tested (300/5 mg and 150/5 mg vs. 300/10 mg Tablets)

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NDA 22-545 for Tekamlo
(Aliskiren and Amlodipine) FDC IR Tablets
(300/10 mg, 300/5 mg, 150/10 mg, and 150/5 mg)

Appendix 2

Additional Analysis on Dissolution Data
(submitted on 04/26/10 and reviewed by Dr. Angelica Dorantes)

Office of New Drugs Quality Assessment ***BIOPHARMACEUTICS REVIEW***			
Application No.:	NDA 22-545/Amendment Serial-016	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	April 26, 2010	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	Cardiovascular & Renal Products	**Date Assigned:**	May 14, 2010
Sponsor:	Norvartis Pharmaceuticals Corporation	**Date of Review:**	May 17, 2010
Trade Name:	Tekamlo™ Film-Coated Tablets	**Type of Submission:** Amendment to NDA - Response to FDA request	
Generic Name:	Aliskiren/Amlodipine (SPA100A)		
Indication:	Hypertension		
Formulation/strengths	Film Coated Tablets/ aliskiren/amlodipine 150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg		
Route of Administration	Oral		
Type of Review:	***NDA Amendment – Dissolution Specifications***		

SUBMISSION:

On April 26, 2010, Norvartis submitted an Amendment to their pending NDA 22-545 for Tekamlo™ Film Coated Tablets, including their responses to the FDA's Information Request Letter dated April 8, 2010. This Review specifically addresses the sponsor's response to Biopharmaceutics Question No. 9.

BIOPHARMACEUTICS:

Question 9 and the sponsor's response are summarized next:

Biopharmaceutics Question No. 9

Based on the results of the comparative dissolution testing, we recommend the following revision to the product dissolution specifications.

- *The Q-value for Amlodipine should be* (b) (4) *release in 20 minutes*
- *The Q-value for Aliskiren should be* (b) (4) *release in 20 minutes*

Sponsor's Response

The evaluation of the registration stability dissolution data for Amlodipine and Aliskiren 150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg strengths tablets at the 20 minutes time point shows wide variability of the individual points for both components. This variability is illustrated in the box plots presented below. Alternatively, the data at 30 minutes show less variability.

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(b) (4)

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed the dissolution information included in the April 26, 2010, Amendment Serial 016 to NDA 22-545 for Tekamlo™ (aliskiren/amlodipine) Film-Coated Tablets and considers that Norvartis' proposed dissolution acceptance criterion of a Q-value of (b) (4) in 30 minutes for both components (amlodipine and aliskiren) is acceptable.

The above recommendation should be conveyed to the sponsor as appropriate.

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 22-545, Don Henry, Tien-Mien Chen

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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

/s/

TIEN MIEN CHEN
06/11/2010

PATRICK J MARROUM
06/11/2010

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	**22-545**	**Brand Name**	**TEKAMLO**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Aliskiren/amlodipine**
Medical Division	**DCRP**	**Drug Class**	**Direct rennin inhibitor/CCB**
OCP Reviewer	**Divya Menon-Andersen**	**Indication(s)**	**Hypertension**
OCP Team Leader	**Raj Madabushi**	**Dosage Form**	**Tablet**
Pharmacometrics Reviewer	**-**	**Dosing Regimen**	**Once daily**
Date of Submission	**10/29/2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**07/29/2009**	**Sponsor**	**Novartis**
Medical Division Due Date	**08/29/2009**	**Priority Classification**	**Standard**
PDUFA Due Date	**08/29/2009**		

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**	5	5	2 validation reports, 3 in study reports
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:	**X**	**2**	**0**	**Previously reviewed under NDA 21-985 (Aliskiren)**
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**	**1**	**1**	PRA and PRC, dose-response data from SPA 2305 (pivotal trial)
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**X**	**3**	**2**	**2 pivotal BE 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			**8**	

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			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Fixed dose combination of previously approved agents
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	X			

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

	appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	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?				
	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 12/08/09
Reviewing Clinical Pharmacologist Date

Raj Madabushi 12/08/09
Team Leader/Supervisor Date

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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
01/04/2010

RAJANIKANTH MADABUSHI
01/04/2010