CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-410

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number:	21-410	**Brand Name:**	AVANDAMET
OCPB Division (I, II, III):	DPE-II (HFD-870)	**Generic Name:**	Rosiglitazone / metformin
Clinical Division:	DMEDP (HFD-510)	**Drug Class:**	Combination
CPB Reviewer:	Steven B. Johnson, Pharm.D.	**Indication(s):**	Type 2 DM
CPB Team Leader:	Hae-Young Ahn, Ph.D.	**Dosage Form:**	Tablet
Submission Date:	29-NOV-2001	**Dosing Regimen:**	1, 2, & 4 mg + 500 mg
CPB Review Due Date:	30-AUG-2002	**Route of Administration:**	PO (oral)
Division Due Date:	02-SEP-2002	**Sponsor:**	SmithKline Beecham
PDUFA Date:	02-OCT-2002	**Priority Classification:**	Standard

Clinical Pharmacology and Biopharmaceutics Information

Information Type	"X" if included at filing	# of Studies Submitted	# of Studies Reviewed	Critical Comments (if any)
Table of Contents	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bio- & Analytical Methods	X			
I. Clinical Pharmacology				
Mass Balance:				
Isozyme Characterization:				
Blood/Plasma Ratio:				
Plasma Protein Binding:				
Pharmacokinetics (PK) –				
– Healthy Volunteers –				
Single-Dose:				
Multiple-Dose:				
– Patients –				
Single-Dose:				
Multiple-Dose:				
Dose Proportionality –				
Single-Dose:	X	1	1	1 mg/500 mg and 4 mg/500 mg
Multiple-Dose:				
Drug-Drug Interaction Studies –				
In-vivo Effects ON Primary Drug:				
In-vivo Effects OF Primary Drug:				
In-vitro Studies:				
Subpopulation Studies –				
Ethnicity:				
Sex:				
Pediatrics:				
Geriatrics:				
Renal Impairment:				
Hepatic Impairment:				
Pharmacodynamics (PD) –				
Phase 2:				
Phase 3:				
PK / PD –				
Phase 1:				
Phase 2:				
Phase 3:				
Population Analyses –				
Rich Data Set:				
Sparse Data Set:				
II. Biopharmaceutics				
Absolute Bioavailability:				
Relative Bioavailability –				
Solution as Reference				
Other Formulation as Reference:				
Bioequivalence Studies –				
– Traditional Design –				
Single-Dose:	X	1	1	AVANDAMET vs. Individual Components
Multiple-Dose:				

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– Replicate Design –				
Single-Dose:				
Multiple-Dose:				
Food-Drug Interaction Studies:	X	1	1	
Dissolution:	X	1	1	
In-vitro/In-vivo Correlation:				
BCS Based Biowaiver Request:				
BCS Classification Information:				
III. Other CPB Studies				
Genotype / Phenotype Studies:				
Chronopharmacokinetics:				
Pediatric Development Plan:				
Literature References:	X	16		
TOTAL # OF STUDIES		3 + (16)		

Primary Reviewer Signature:	Steven B. Johnson	Date:	
Secondary Reviewer Signature:	Xiao-Xiong "Jim" Wei for Hae-Young Ahn	Date:	

– Line Listing of Studies Included in this Application –

Study #	Study Title
270	A Bioequivalence Study With a Combination Tablet Formulation of Rosiglitazone and Metformin (4 mg/500 mg) Compared to Concomitant Dosing of Rosiglitazone 4 mg and Metformin 500 mg Commercial Tablets and a Dose Proportionality Study Comparing the 4 mg/500 mg & 1 mg/500 mg Combination Formulations.
271	A Study to Assess the Effect of Food on the Pharmacokinetics of a Rosiglitazone 4 mg and Metformin 500 mg Combination Tablet Formulation and a Study Comparing the Pharmacokinetics of Rosiglitazone 4 mg and Metformin 500 mg Combination Tablet to Concomitant Dosing of Rosiglitazone 4 mg and Metformin 500 mg Commercial Tablets in the Fed State in Healthy Volunteers.

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NDA #:	21-410	**RELEVANT IND #:**	———
BRAND NAME:	AVANDAMET	**GENERIC NAME:**	Rosiglitazone/Metformin HCl
STRENGTH(S):	1/500 mg, 2/500 mg, 4/500 mg	**DOSAGE FORM:**	Combination Tablets
APPLICANT:	GlaxoSmithKline, Research Triangle Park, NC 27709		
LETTER DATE:	29-NOV-2001	**PDUFA DATE:**	29-SEP-2002
OCPB DIVISION:	DPE-2	**OND DIVISION:**	DMEDP
CPB REVIEWER:	Steven B. Johnson, Pharm.D.	**CPB TEAM LEADER:**	Hae-Young Ahn, Ph.D.

EXECUTIVE SUMMARY

An indication for the combined use of rosiglitazone (AVANDIA) and metformin hydrochloride (GLUCOPHAGE) was approved by the Agency on May 25, 1999 for NDA 21-071. The intent of this submission, then, is to provide evidence in support of a fixed-dose combination product containing these two drug substances. As such, the recommendation for approval will be based on the results of the Clinical Pharmacology and Biopharmaceutics, and Chemistry reviews, respectively, as no additional clinical studies were submitted.

To aid in the approval of this application the sponsor put forward two new pharmacokinetic studies: 1) a bioequivalence/dose-proportionality study (# 270); and 2) a food-effect study (# 271). There was also inclusion of an *in vitro* dissolution method, with appropriate data, and a biowaiver request for the 2 mg/500 mg AVANDAMET tablet strength that was not studied *in vivo*.

The bioequivalence portion of study 270 examined the relative rate and extent of exposure of a single dose of 4 mg/500 mg AVANDAMET tablets to a single dose of 4 mg AVANDIA (rosiglitazone) plus 500 mg metformin in 25 normal healthy male and female subjects under fasting conditions. Results of this study showed that both $AUC_{0\text{-}inf}$ and C_{max} were comparable between the formulations. However, T_{max} was slightly prolonged when subjects were administered AVANDAMET, for both rosiglitazone and metformin components (0.95 vs. 0.57 hrs, and 2.97 vs. 2.50 hrs), respectively.

The dosage-form proportionality portion of study 270 compared single doses of 1 mg/500 mg and 4 mg/500 mg strength tablets of AVANDAMET in 24 healthy male and female subjects under fasting conditions. Results showed that a relative proportionality was achieved, with a ratio of 1:4.13. However, the time to reach maximum concentration (T_{max}) of both components was delayed by approximately 30 minutes for the 4 mg/500 mg strength.

In the second study, 4 mg/500 mg AVANDAMET was compared under fed and fasted conditions, and with an equivalent dose of the individual components administered concomitantly under fed conditions. Study results indicate that under fed conditions, both AVANDAMET and its single components administered concomitantly exhibit a small food-effect (i.e., C_{max} was reduced by approximately 22% and 15% for rosiglitazone and metformin, respectively). There was also a 1.5 hour delay in the fed AVANDAMET T_{max}. However, there was no difference in the extent of absorption of either component, as measured by AUC, regardless of meal state. These findings are consistent with current AVANDIA and GLUCOPHAGE labeling.

Multipoint dissolution data from a single lot of each of the to-be-marketed strengths was included for evaluation. Results indicated that the method was appropriate for AVANDAMET, although a bit fast, but that a new tolerance specification of ' ——— ' 15 minutes should be used for this product.

Since the individual strength formulations were shown to be proportional, dosage-form equivalence was demonstrated between strengths representing the extremes of the strength range, and dissolution was comparable between strengths, then a biowaiver for the 2 mg/500 mg strength not studied *in vivo* should be granted.

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Since there were no clinical studies submitted in this application, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) requested that the Division of Scientific Investigation (DSI) conduct a clinical site audit. The DSI audit revealed several infractions that resulted in a Form 483 issuance (see APPENDIX). Specifically, there were unanswered questions regarding assay selectivity for rosiglitazone, bench-top metformin stability, and [redacted] The most grievous of these issues, that could affect the approvability of this application, were quickly clarified by the sponsor and the response was deemed acceptable to the Agency. The sponsor is currently addressing the remaining issue, [redacted]

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed Section 6 of NDA 21-410 for AVANDAMET and finds the results acceptable pending sponsor acceptance of labeling (see Labeling Recommendations) and dissolution tolerance specification changes. The appropriate dissolution method and tolerance specification for AVANDAMET is listed here:

Apparatus Type	2 (paddles)
Media	0.01 N HCl
Volume	900 mL
Speed of Rotation	75 RPM
Tolerance Specifications	[redacted] **15 minutes**

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SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

- Each of the 3 tablet strengths of AVANDAMET was found to be proportionally similar in formulation;
- AVANDAMET 4 mg/500 mg is bioequivalent to 4 mg AVANDIA plus 500 mg metformin administered concomitantly under fasting conditions;
- Dose-proportionality was established between the 1 mg/500 mg and 4 mg/500 mg strengths;
- The food effects seen in the AVANDAMET study are similar to those observed in the AVANDIA and GLUCOPHAGE labels;
- Dissolution was similar between all three of the proposed AVANDAMET tablet strengths; and
- Sufficient data was provided to support a biowaiver for the intermediate strength that was not studied *in vivo*.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

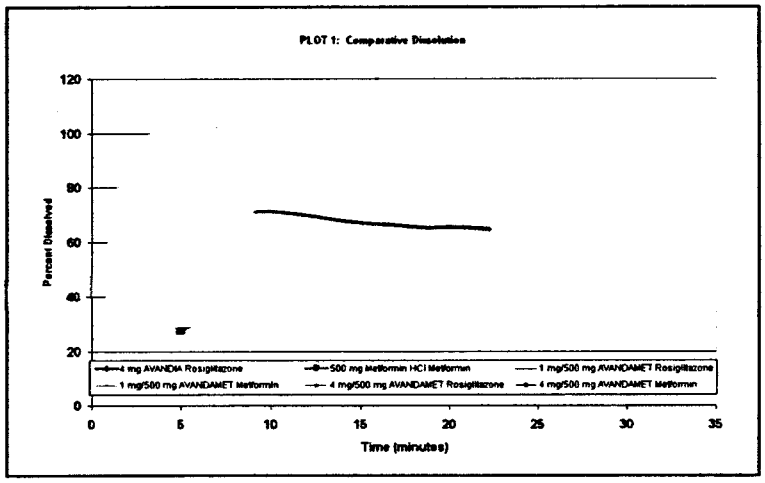
1 page

Dissolution

Is the dissolution method and tolerance specification appropriate for AVANDAMET tablets?

To answer this question, a multipoint dissolution study was conducted that compared AVANDAMET 1 mg/500 mg tablets and 4 mg/500 mg tablets, 4 mg AVANDIA (rosiglitazone), and 500 mg metformin HCl. The dissolution method used to perform this study is described in TABLE 2. The products used in this study were of the same batch as those used in the *in vivo* studies.

TABLE 2: AVANDAMET – Rosiglitazone and Metformin Component Method	
Apparatus Type	USP # 2 (paddles)
Media	0.01 N HCl
Volume	900 mL @ 37° C
Speed of Rotation	75 RPM
Sampling Times	5, 10, 15, and 30 minutes
Tolerance Specifications	——— 30 minutes



Results of this study show two things quite clearly. One, the dissolution method is product specific – as evidenced by the rosiglitazone and metformin commercial product profiles (in bold), and two, the 1 mg/500 mg and 4 mg/500 mg AVANDAMET tablet profiles are very similar. The degree of their similarity is discussed in the section entitled "Biowaiver." In addition, the tolerance specification that was proposed by the sponsor is too lenient. The dissolution plateau occurs at approximately ——— and does not change with additional time. Therefore, after consultation with Dr. Xavier Ysern, FDA chemist, a recommendation of ——— 15 minutes will be made to the sponsor for all AVANDAMET strength tablets.

General Biopharmaceutics

Bioequivalence and Dose Proportionality

Is there a correlation between the combination formulation of rosiglitazone 4 mg plus metformin 500 mg (4 mg/500 mg) and the respective individual marketed counterparts; and is the 1 mg/500 mg AVANDAMET tablet proportional to the 4 mg/500 mg AVANDAMET tablet with regard to the rosiglitazone component?

Study CPMS–270 serves to answer both of the above questions in which 27 (25 completers) were enrolled in an open-label, randomized, three period, period-balanced, fasting, single-dose crossover study. Each subject was administered one of the following treatments per study period: Tx A – 1 x 4 mg/500 mg combination rosiglitazone/metformin tablet with 240 mL water; Tx B – 1 x 4 mg rosiglitazone plus 1 x 500 mg metformin with 240 mL water; or Tx C – 1 x 1 mg/500 mg combination rosiglitazone/metformin tablet with 240 mL water. Treatments were separated by a one-week washout period.

Results of the bioequivalence portion of study CPMS-270 clearly showed that bioequivalence was achieved between the 4 mg/500 mg AVANDAMET tablets and the respective components, for both AUC and C_{max} parameters. Data summaries for the respective components are presented in TABLES 3 and 4.

TABLE 3: Bioequivalence Summary and Analysis – Rosiglitazone Component						
Parameter	Unit	Tx A	Tx B	Point Estimate (%)	90% Confidence Intervals	
					Low	High
$AUC_{0\text{-}inf}$	ng*hr/dL	1442 ± 324	1398 ± 340	1.03	0.99	1.08
C_{max}	ng/dL	242 ± 70	254 ± 69	0.95	0.88	1.02
T_{max}	h	0.95 (0.48-2.47)	0.57 (0.43-2.58)	--	--	--
$T_{1/2}$	h	4.26 ± 1.18	3.95 ± 0.81	--	--	--
Tx A = 4 mg/500 mg Avandamet; Tx B = 4 mg rosiglitazone plus 500 mg metformin Mean ± SD						

TABLE 4: Bioequivalence Summary and Analysis – Metformin Component						
Parameter	Unit	Tx A	Tx B	Point Estimate (%)	90% Confidence Intervals	
					Low	High
$AUC_{0\text{-}inf}$	ng*hr/dL	7116 ± 2096	7413 ± 2096	0.95	0.88	1.02
C_{max}	ng/dL	1106 ± 329	1135 ± 253	0.95	0.87	1.03
T_{max}	h	2.97 (1.02-4.02)	2.50 (1.03-3.98)	--	--	--
$T_{1/2}$	h	3.46 ± 0.96	3.36 ± 0.54	--	--	--
Tx A = 4 mg/500 mg Avandamet; Tx B = 4 mg rosiglitazone plus 500 mg metformin Mean ± SD						

The second portion of study CPMS-270 addressed the issue of dose-proportionality. In order to determine whether the 1 mg/500 mg AVANDAMET tablet was proportional to the 4 mg/500 mg AVANDAMET tablet, the rosiglitazone component was dose-normalized prior to analysis. Results of this analysis are presented in TABLE 5, and shows that dose-proportionality has been achieved. The comparative ratio for the rosiglitazone component is 1:4.13.

TABLE 5: Dose-Proportionality Summary and Analysis – Dose-Normalized Analysis of Rosiglitazone						
Parameter	Unit	Tx A	Tx C	Point Estimate (%)	90% Confidence Intervals	
					Low	High
$AUC_{0\text{-}inf}$	ng*hr/dL	1442 ± 324	349 ± 91	1.05	1.01	1.10
C_{max}	ng/dL	242 ± 70	63.0 ± 15.0	0.94	0.87	1.00
T_{max}	h	0.95 (0.48-2.47)	0.57 (0.47-1.45)	--	--	--
$T_{1/2}$	h	4.26 ± 1.18	3.87 ± 0.88	--	--	--
Tx A = 4 mg/500 mg Avandamet; Tx B = 4 mg rosiglitazone plus 500 mg metformin Mean ± SD						

Food Effect

Does food alter the bioavailability of AVANDAMET?

To determine the effect of food on AVANDAMET tablets, and to determine if there is a food-effect difference between AVANDAMET and its individual marketed counterparts, an open-label, three-period, period-balanced, randomized crossover study was conducted in 18 healthy male and female subjects. Treatments were as follows: Tx A – 1 x 4 mg/500 mg AVANDAMET tablet administered fasting; Tx B - 1 x 4 mg/500 mg AVANDAMET tablet administered after a standard FDA high fat breakfast; or Tx C – 1 x 4 mg rosiglitazone plus 1 x 500 mg metformin administered after a standard FDA high fat breakfast. Each of the treatment periods was separated by a one-week washout period.

The summaries of findings from the food-effect study are presented in TABLES 6, 7, 8, and 9. These results show that when AVANDAMET is compared under fed and fasted conditions, a small food-effect is present for both the rosiglitazone and metformin components. The C_{max} point estimate for the fed:fasted comparison was 0.78 and 0.85, with corresponding 90% confidence intervals of 0.73, 0.83 and 0.79, 0.92, respectively, for the rosiglitazone and metformin components. The rosiglitazone T_{max} was also delayed by approximately 1.5 hours when AVANDAMET was administered under fed conditions. There was no effect on extent of absorption, as measured by AUC. These findings are consistent with the information found in the current AVANDIA (rosiglitazone) and GLUCOPHAGE (metformin) labels.

In addition, there was no food-effect difference between AVANDAMET, and rosiglitazone plus metformin administered concomitantly, under high-fat fed conditions. However, there was a one-hour delay in AVANDAMET T_{max} for both components.

TABLE 6: Food Effect Summary – Rosiglitazone Component				
Parameter	**Unit**	**Tx A AVANDAMET – FASTING**	**Tx B AVANDAMET – FED**	**Tx C CONCOMITANT ADMIN.**
$AUC_{0\text{-}inf}$	ng*hr/dL	1405 ± 321	1335 ± 302	1328 ± 339
C_{max}	ng/dL	270 ± 58	209 ± 37	212 ± 47
T_{max}	h	0.98 (0.48-4.02)	2.56 (1.48-4.02)	1.53 (0.50-3.98)
$T_{1/2}$	h	3.53 ± 0.75	3.50 ± 0.65	3.51 ± 0.78
Mean ± SD				

TABLE 7: Food Effect Summary – Metformin Component				
Parameter	**Unit**	**Tx A AVANDAMET – FASTING**	**Tx B AVANDAMET – FED**	**Tx C CONCOMITANT ADMIN.**
$AUC_{0\text{-}inf}$	ng*hr/dL	6098 ± 1653	5745 ± 1150	5684 ± 1221
C_{max}	ng/dL	909 ± 247	762 ± 150	756 ± 150
T_{max}	h	3.00 (1.48-4.03)	3.96 (1.97-5.98)	3.03 (1.02-4.03)
$T_{1/2}$	h	3.52 ± 0.63	3.31 ± 0.42	3.37 ± 0.61
Mean ± SD				

TABLE 8: Food Effect Analysis – Rosiglitazone Component				
Parameter	**Comparison**	**Point Estimate**	**90% Confidence Intervals**	
			Low	**High**
$AUC_{0\text{-}inf}$	B:A	0.95	0.91	0.99
	B:C	1.01	0.97	1.05
C_{max}	**B:A**	**0.78**	**0.73**	**0.83**
	B:C	0.99	0.93	1.06

TABLE 9: Food Effect Analysis – Metformin Component				
Parameter	**Comparison**	**Point Estimate**	**90% Confidence Intervals**	
			Low	**High**
$AUC_{0\text{-}inf}$	B:A	0.95	0.90	1.01
	B:C	1.01	0.95	1.08
C_{max}	**B:A**	**0.85**	**0.79**	**0.92**
	B:C	1.01	0.94	1.09

Biowaiver

Can the biowaiver request be granted for the 2 mg/500 mg AVANDAMET tablet strength?

In order to grant a biowaiver for an intermediate strength product, several criteria must be considered. These criteria include proportional formulations, *in-vivo* dose-proportionality between 2 of the 3 strengths, and similar dissolution profiles – as determined by f_2 comparisons. The first two requirements have been met (see Formulation and Bioequivalence and Dose-proportionality sections). To determine if the 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 AVANDAMET tablets were similar, a multidose dissolution study was conducted using the dissolution method described in TABLE 2. Results of this study, including the calculated f_2 values, are presented in TABLE 10.

Since this product meets all three of the criteria listed above, a biowaiver should be considered for the 2 mg/500 mg strength AVANDAMET tablet that was not studied *in vivo*.

TABLE 10: Multipoint Dissolution Comparison of AVANDAMET						
	Rosiglitazone Component			**Metformin Component**		
TIME	**1 mg/500 mg**	**2 mg/500 mg**	**4 mg/500 mg**	**1 mg/500 mg**	**2 mg/500 mg**	**4 mg/500 mg**
5						
10						
15						
30						
45						
f_2	1 mg/500 mg vs. 2 mg/500 mg =			1 mg/500 mg vs. 2 mg/500 mg =		
	2 mg/500 mg vs. 4 mg/500 mg =			2 mg/500 mg vs. 4 mg/500 mg =		
	1 mg/500 mg vs. 4 mg/500 mg =			1 mg/500 mg vs. 4 mg/500 mg =		

Analytical

Have the analytical methods been sufficiently validated?

Human plasma samples were analyzed for rosiglitazone and metformin using ——— ——— The respective methods, BRL-049653/RSD-100WK8/1 and BRL-049653/RSD-101J0H/1, were developed by GlaxoSmithKline, The Frythe, UK. Analytical methods were found to be acceptable by the Agency. Results of the quality control analysis are presented in the TABLES 11 and 12. Both accuracy and precision are within acceptable values.

TABLE 11	CPMS-270					
	Rosiglitazone			Metformin		
LLOQ (ng/mL)						
Calibration (ng/mL)	2.5 – 1000			20 – 10000		
Quality Control	5	500	800	80	1000	8000
Mean	5.0	503.7	804.9	83.97	1058.45	7753.86
SD	0.3	18.8	23.6	4.46	21.46	177.82
% CV (precision)	6.0	5.3	2.9	5.31	2.03	2.29
Accuracy (%)	100.0	100.0	100.6	104.96	105.85	96.92
Average Bias	-0.6	0.7	0.6	4.96	5.84	-3.08
N	42	42	41	42	42	42
Avg intra-run precision	4.5	1.8	1.8	3.37	1.42	1.66
Between run precision	5.2	2.2	1.9	4.62	1.61	2.03

TABLE 12	CPMS-270					
	Rosiglitazone			Metformin		
LLOQ (ng/mL)						
Calibration (ng/mL)	2.5 – 1000			15.6 – 7800		
Quality Control	5	500	800	62.4	780	6240
Mean	5.1	503.9	816.9	60.6	794.3	6047.0
SD	0.3	11.5	14.7	3.1	39.2	244.4
% CV (precision)	5.9	2.3	1.8	5.0	4.9	4.0
Accuracy	102.0	100.8	102.1	97.1	101.8	96.9
Average Bias	1.5	0.8	2.1	-2.9	1.8	-3.1
N	53	54	54	30	30	30
Avg intra-run precision	4.8	1.9	1.1	2.6	2.8	3.8
Between run precision	5.5	2.1	1.3	2.9	3.8	4.6

Labeling Recommendations

(~~Strikeout text~~ should be removed from labeling; Underlined text should be added to labeling; ☛ indicates an explanation only and is not intended to be included in the labeling)

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Package Insert labeling for AVANDAMET and finds it acceptable pending the following revision:

In ——— –animal models, rosiglitazone's antidiabetic activity was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle and adipose tissue. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

☛ The ~~strikethrough~~ of drug interaction text under the heading "Drug Interactions – Rosiglitazone" is justified, since two of the three drugs removed from this section result in no significant drug-drug interaction (the third is Metformin HCl), and they are listed as possibly significant interactions under the heading "Drug Interactions – Metformin).

☛ **This product does not have the necessary safety and efficacy documentation to allow its use as a first-line agent for the treatment of type 2 diabetes mellitus. The reviewing Medical Officer will address this issue with one or two sentences in the Dosage and Administration section of the label, or as appropriate.**

Confidential

SmithKline Beecham

SB-712753

Rosiglitazone Maleate and Metformin Hydrochloride

Item 2.A Proposed Labeling for AVANDAMET™

SB Document Number: SB-712753/RSD-101N2J/1.

Number of Pages Redacted 19

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Draft Labeling
(not releasable

Report Synopsis

Title

A Bioequivalence Study With a Combination Tablet Formulation of Rosiglitazone and Metformin (4 mg/500 mg) Compared to Concomitant Dosing of Rosiglitazone 4 mg and Metformin 500 mg Commercial Tablets and a Dose Proportionality Study Comparing the 4 mg/500 mg & 1 mg/500 mg Combination Formulations

Investigator(s) and Center(s)

Hubert Chou, MD, PhD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center of Philadelphia, University of Pennsylvania Health System, 51 North 39th Street, Philadelphia, Pennsylvania, 19104, USA

Publication

None as of September 2001.

Study Dates

13 February 2001 to 19 April 2001

Objective(s)

Avandia® (rosiglitazone) has been approved by the US Food & Drug Administration for combination therapy with Glucophage® (metformin) for the treatment of type 2 diabetes mellitus. In order to increase compliance among patients who are prescribed a combination therapy with both these drugs, three combination formulations of rosiglitazone maleate (1 mg, 2 mg & 4 mg, respectively) mixed with metformin hydrochloride 500 mg have been developed.

1. To demonstrate the bioequivalence of the combination formulation of rosiglitazone 4 mg plus metformin 500 mg (4 mg/500 mg) relative to concomitant dosing of rosiglitazone 4 mg and metformin 500 mg commercial tablets
2. To assess the dose proportionality of the rosiglitazone in the combination formulations 1 mg plus metformin 500 mg (1 mg/500 mg) and the rosiglitazone 4 mg plus metformin 500 mg (4 mg/500 mg)
3. To assess the tolerability of dosing with combination formulations of rosiglitazone 1 mg plus metformin 500 mg (1 mg/500 mg) and rosiglitazone 4 mg plus metformin 500 mg (4 mg/500 mg)

Study Design

This was an open-label, randomized, three-period, period-balanced crossover study. Each subject received one of the following three treatments in each session in a fasted state:

Regimen A: a single tablet combination formulation of rosiglitazone 4 mg plus metformin 500 mg (denoted 4 mg/500 mg)

Regimen B: concomitant dosing of rosiglitazone 4 mg tablet AND metformin 500 mg tablet (denoted 4 mg+500 mg)

Regimen C: a single tablet combination formulation of rosiglitazone 1 mg plus metformin 500 mg (denoted 1 mg/500 mg)

Subjects were randomized according to a schedule prepared in advance of the study. There was a washout period of at least one week between each of the 3 treatment sessions. Blood samples for pharmacokinetic analysis were collected at predose and for approximately 24 hours during each session. Study duration was 7-8 weeks from screening to end of study.

Study Population

Healthy male/female subjects between the ages of 18 and 65 years, weighing at least 50 kg (and within 35% of ideal weight based on height and body frame) were eligible for the study. A sufficient number of subjects were enrolled so that a total of 24 subjects completed the study.

Treatment and Administration

Study medication consisted of oral tablets, rosiglitazone 1 mg plus metformin 500 mg (Lot number ND1025), or rosiglitazone 4 mg plus metformin 500 mg (Lot number ND1032), or commercially available rosiglitazone (Avandia®) and metformin (Glucophage®). Study medication was administered with 240 mL tepid water under fasting conditions.

Evaluation Criteria

Safety Parameters

Clinical monitoring, adverse events, safety laboratory tests, and vital signs were evaluated.

Pharmacokinetic Parameters

Blood samples (approximately 5 mL) were collected from an arm vein into tubes containing EDTA at pre-dose and up to 24 hours post-dose in all three treatment sessions. Plasma samples were assayed for rosiglitazone (BRL-49653) and metformin using a method based on [redacted] analysis. The lower limit of quantification for the rosiglitazone and metformin assays were [redacted] using a 50 uL aliquot of plasma, respectively. [redacted] analysis was used to calculate the following pharmacokinetic parameters: AUC(0-inf), Cmax, T1/2, and Tmax for rosiglitazone and metformin. Descriptive statistics by regimen were presented for these pharmacokinetic parameters.

Statistical Methods

Bioequivalence: Following $\log_e$-transformation, AUC(0-inf) and Cmax of rosiglitazone and metformin were analyzed separately by analysis of variance (ANOVA) using a model appropriate to the study design, fitting terms for sequence, subject-within-sequence, period and regimen. Point estimates and associated 90% confidence intervals for the ratio "4/500 mg rosiglitazone/metformin: 4+500 mg rosiglitazone/metformin" (A:B) for both rosiglitazone and metformin were constructed using the residual variances. Equivalence was demonstrated when the 90% confidence intervals for AUC(0-inf) and Cmax were contained within the range (0.80, 1.25).
Dose proportionality: Dose-normalized AUC(0-inf) and Cmax of rosiglitazone were separately analyzed by analysis of variance (ANOVA) with a model appropriate to the study design, fitting terms for sequence, subject-within-sequence, period and regimen. Dose normalized AUC(0-inf) and Cmax were $\log_e$-transformed prior to analysis. Point estimates and 90% confidence intervals for the ratio "4/500 mg rosiglitazone/metformin : 1/500 mg rosiglitazone/metformin" for rosiglitazone were constructed using the residual variances. Dose proportionality was demonstrated when the 90% confidence intervals for dose-normalized AUC(0-inf) and Cmax were contained within the range (0.70, 1.43). Tmax was analyzed non-parametrically and point estimates and 90% confidence intervals were derived for the comparisons of interest.

Subject Disposition and Key Demographic Data

A total of 27 healthy male and female subjects were enrolled and dosed in this study. Twenty-four subjects completed the study and provided complete data. Demographic data for all enrolled subjects are summarized in the following table:

Parameter	Age (years)	Height (m)	Weight (kg)
n	27	27	27
Mean	40	1.74	80.2
SD	10.9	0.10	13.9
Range	22-59	1.55-1.94	52.8-112.8

41% female, 59% male
56% Black; 33% White; 11% Other

Safety Results

There were no deaths, or serious adverse events. Three subjects withdrew, 2 subjects due to adverse events (AEs) and 1 subject after multiple attempts to insert an IV line were unsuccessful in Session 3. Summary details for the non-serious, treatment-emergent AEs reported during this study are listed by regimen in the table below. Diarrhea and abdominal pain were the only events considered by the investigator to be possibly related to study drug.

	Regimen A	Regimen B	Regimen C	Total
Total Number of AEs	19	10	12	41
Most frequent AE = Diarrhea	2	2	3	7
Number of Subjects with AEs	9	8	9	18
Number of Subjects Exposed	26	26	25	27

There were no clinically significant changes in vital signs or safety laboratory values of potential clinical concern during this study.

Pharmacokinetics

Mean (SD) pharmacokinetic data for rosiglitazone and metformin are presented in the following table:

		Pharmacokinetic parameter			
Regimen	N	AUC(0-inf) (ng.h/mL)	Cmax (ng/mL)	Tmax* (h)	T1/2 (h)
Rosiglitazone					
A	25	1442 (324)	242 (70)	0.95 (0.48-2.47)	4.26 (1.18)
B	25	1398 (340)	254 (69)	0.57 (0.43-2.58)	3.95 (0.81)
C	24	349 (91)	63.0 (15.0)	0.57 (0.47-1.45)	3.87 (0.88)
Metformin					
A	25	7116 (2096)	1106 (329)	2.97 (1.02-4.02)	3.46 (0.96)
B	25	7413 (1838)	1135 (253)	2.50 (1.03-3.98)	3.36 (0.54)
C	24	6945 (2045)	1080 (327)	2.97 (1.00-5.98)	3.35 (0.59)

* = Median and range presented for Tmax

Regimen Key: Regimen A = 4/500 mg rosiglitazone/metformin
Regimen B = 4 + 500 mg rosiglitazone + metformin
Regimen C = 1/500 mg rosiglitazone/metformin

Point estimates and 90% confidence intervals for the ratios A:B (4/500:4 + 500) and A:C (4/500:1/500) of geometric least squares mean are presented in the following table:

Parameter	Comparison	Point Estimate (90% CI)
Rosiglitazone – BE		
AUC(0-inf)	A : B	1.03 (0.99, 1.08)a
Cmax	A : B	0.95 (0.88, 1.02)a
Tmax	A – B	0.02 h (-0.02 h, 0.18 h)b
Metformin – BE		
AUC(0-inf)	A : B	0.95 (0.88, 1.02)[a]
Cmax	A : B	0.95 (0.87, 1.03)[a]
Tmax	A – B	0.04 h (-0.05 h, 0.48 h)[b]
Rosiglitazone – Dose Prop		
DN - AUC(0-inf)	A : C	1.05 (1.01, 1.10)a
DN – Cmax	A : C	0.94 (0.87, 1.00)a
Tmax	A – C	0.15 h (-0.06 h, 0.15 h)b

a = ratio of adjusted geometric means between regimens
b = estimated median difference between regimens
DN-AUC = Dose-normalized AUC; DN-Cmax = Dose-normalized Cmax

Regimen Key: Regimen A = 4/500 mg rosiglitazone/metformin
Regimen B = 4 + 500 mg rosiglitazone + metformin
Regimen C = 1/500 mg rosiglitazone/metformin

Bioequivalence of the combination formulation of rosiglitazone 4 mg plus metformin 500 mg

relative to concomitant dosing of rosiglitazone 4 mg and metformin 500 mg commercial tablets was demonstrated as the 90% confidence interval for both AUC(0-inf) and Cmax of rosiglitazone and metformin were contained within the range (0.80, 1.25). Dose proportionality of rosiglitazone in the combination formulations 1 mg plus metformin 500 mg (1 mg/500 mg) and rosiglitazone 4 mg plus metformin 500 mg (4 mg/500 mg) was also demonstrated as the 90% confidence interval for AUC(0-inf) and Cmax were contained within the range (0.70, 1.43). Additionally, metformin AUC(0-inf) and Cmax values for the combination formulation 1 mg rosiglitazone plus 500 mg metformin were similar to those for metformin (500 mg) when administered concomitantly with rosiglitazone (4 mg). Rosiglitazone and metformin Tmax and T1/2 appeared to be similar for all three regimens.

Conclusion

Bioequivalence of the combination formulation of rosiglitazone 4 mg plus metformin 500 mg relative to concomitant dosing of rosiglitazone 4 mg and metformin 500 mg commercial tablets was demonstrated.

Dose proportionality of rosiglitazone in the combination formulations 1 mg plus metformin 500 mg and the rosiglitazone 4 mg plus metformin 500 mg was also demonstrated.

Dosing with combination formulations of rosiglitazone 1 mg plus metformin 500 mg and rosiglitazone 4 mg plus metformin 500 mg was safe and well tolerated.

Report Synopsis

Title

A Study to Assess the Effect of Food on the Pharmacokinetics of a Rosiglitazone 4 mg and Metformin 500 mg Combination Tablet Formulation and a Study Comparing the Pharmacokinetics of Rosiglitazone 4 mg and Metformin 500 mg Combination Tablet to Concomitant Dosing of Rosiglitazone 4 mg and Metformin 500 mg Commercial Tablets in the Fed State in Healthy Volunteers

Investigator(s) and Center(s)

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Publication

None as of October 2001.

Study Dates

30 May 2001 to 10 July 2001

Objective(s)

It is desirable to develop a rosiglitazone/metformin combination tablet to increase compliance among patients who are prescribed a combination therapy using these drugs. Since the combination tablet may likely be administered with food, it is desirable that any food effect on the single dose pharmacokinetics of rosiglitazone and metformin, respectively, in the combination tablet be similar to the effect of food after concomitant dosing of rosiglitazone and metformin commercial tablets. The objectives of this trial were:

1. To estimate the effect of food on the single dose pharmacokinetics of rosiglitazone and metformin, respectively, in a rosiglitazone/metformin (4/500 mg) combination tablet.
2. To compare the pharmacokinetics of rosiglitazone and metformin in the combination tablet (4/500 mg) to those after concomitant dosing of rosiglitazone 4 mg and metformin 500 mg tablets in the fed state.
3. To assess the tolerability of dosing with the rosiglitazone/metformin (4/500 mg) combination tablet and concomitant dosing of rosiglitazone 4 mg and metformin 500 mg commercial tablets.

Study Design

This was an open-label, randomized, three-period, period-balanced, crossover study. Each subject received one of the following three treatments in each study session:

Regimen A: single dose of a combination tablet of rosiglitazone/metformin (4/500 mg) orally administered, fasting

Regimen B: single dose of a combination tablet of rosiglitazone/metformin (4/500 mg) orally administered, after a standard FDA high fat breakfast

Regimen C: concomitant dosing of rosiglitazone 4 mg tablet AND metformin 500 mg orally administered, after a standard FDA high fat breakfast

Subjects were assigned to one of six treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA) according to a randomization schedule prepared in advance of the study. There was a washout period of at least one week between study sessions. Pharmacokinetic sampling for measurement of plasma rosiglitazone and metformin was conducted at pre-dose and over a 24-hour period following dosing in each session. Study duration was approximately 7-8 weeks from screening through end of follow-up.

Study Population

Healthy male/female subjects between the ages of 18 and 65 years, weighing at least 50 kg (and within -20% to +35% of ideal weight based on height and body frame) were eligible for the study. The target sample size was 18 subjects.

Treatment and Administration

Study medication consisted of oral tablets, rosiglitazone maleate 4 mg plus metformin HCl 500 mg (Lot number NO1032), or commercially available rosiglitazone (Avandia®) and metformin (Glucophage®). Study medication was administered with 240 mL tepid water.

Evaluation Criteria

Safety Parameters

Clinical monitoring, adverse events and vital signs were evaluated.

Pharmacokinetic Parameters

Blood samples were collected at pre-dose and up to 24 hours post-dose in all three treatment sessions. Plasma samples were assayed for rosiglitazone (BRL-49653) and metformin using a method based on [redacted] analysis. The LLQ for the rosiglitazone and metformin assays were [redacted] respectively, using a 50 uL aliquot of plasma. [redacted] analysis was used to calculate the following pharmacokinetic parameters: AUC(0-inf), Cmax, T1/2, and Tmax for rosiglitazone and metformin. Descriptive statistics by regimen were presented for these pharmacokinetic parameters.

Statistical Methods

The primary pharmacokinetic endpoints were AUC and Cmax of rosiglitazone. Secondary endpoints included AUC, Cmax, and Tmax of metformin, and Tmax of rosiglitazone. Following $\log_e$ transformation, AUC(0-inf) and Cmax of rosiglitazone and metformin were analyzed separately by analysis of variance with terms for sequence, subject (sequence), period, and regimen. Point estimates and 90% confidence intervals were calculated for the ratio 4/500 mg rosiglitazone/metformin, high-fat breakfast : 4/500 mg rosiglitazone/metformin, fasting" (B:A) and "4/500 mg rosiglitazone/metformin, high-fat breakfast : 4+500 mg rosiglitazone/metformin, high-fat breakfast" (B:C). Tmax was analyzed non-parametrically and point estimates and 90% confidence intervals were derived for the comparisons of interest.

Subject Disposition and Key Demographic Data

Nineteen healthy male and female subjects were enrolled in this study, 1 subject was withdrawn prior to dosing due to a baseline event of syncope. A total of 18 subjects were dosed and all 18 completed the study. Demographic data for all treated subjects are summarized in the following table:

Parameter	Age (years)	Height (m)	Weight (kg)
n	18	18	18
Mean	35	1.71	75.0
SD	11.4	0.08	12.0
Range	19-60	1.59-1.90	50.7-98.1

44% Female, 56% Male
44% Black; 56% White

Safety Results

There were no deaths, serious adverse events or withdrawals due to adverse events (AEs) reported during this study. Summary details for the non-serious, treatment-emergent AEs reported during this study are listed by regimen in the table below:

	Regimen A	Regimen B	Regimen C	Total
Total Number of AEs	8	6	7	21
Most frequent AE = Diarrhea	2	2	2	6
Number of Subjects with AEs	8	3	6	10
Number of Subjects Exposed	18	18	18	18

Regimen Key: Regimen A = 4/500 mg rosiglitazone/metformin, fasting
Regimen B = 4/500 mg rosiglitazone/metformin, high-fat breakfast
Regimen C = 4 + 500 mg rosiglitazone + metformin, high-fat breakfast

There were no clinically significant changes in vital signs during this study.

Pharmacokinetics

Mean (SD) pharmacokinetic data for rosiglitazone and metformin are shown in the following table.

		Pharmacokinetic Parameter			
Regimen	N	AUC(0-inf) (ng.h/mL)	Cmax (ng/mL)	Tmax* (h)	T1/2 (h)
Rosiglitazone					
A	18	1405 (321)	270 (58)	0.98 (0.48-4.02)	3.53 (0.75)
B	18	1335 (302)	209 (37)	2.56 (1.48-4.02)	3.50 (0.65)
C	18	1328 (339)	212 (47)	1.53 (0.50-3.98)	3.51 (0.78)
Metformin					
A	18	6098 (1653)	909 (247)	3.00 (1.48-4.03)	3.52 (0.63)
B	18	5745 (1150)	762 (150)	3.96 (1.97-5.98)	3.31 (0.42)
C	18	5684 (1221)	756 (150)	3.03 (1.02-4.03)	3.37 (0.61)

* = Median and range presented for Tmax

Regimen Key: Regimen A = 4/500 mg rosiglitazone/metformin, fasting
Regimen B = 4/500 mg rosiglitazone/metformin, high-fat breakfast
Regimen C = 4 + 500 mg rosiglitazone + metformin, high-fat breakfast

Point estimates and 90% confidence intervals for AUC(0-inf), Cmax, and Tmax are shown in the following table:

Parameter	Comparison	Point Estimate	90% CI
ROSIGLITAZONE			
AUC(0-inf)	B : A	0.95	(0.91, 0.99)[a]
Cmax	B : A	0.78	(0.73, 0.83)[a]
Tmax	B – A	1.51 h	(1.03 h, 1.82 h)[b]
AUC(0-inf)	B : C	1.01	(0.97, 1.05)[a]
Cmax	B : C	0.99	(0.93, 1.06)[a]
Tmax	B – C	0.25 h	(-0.02 h, 0.73 h)[b]
METFORMIN			
AUC(0-inf)	B : A	0.95	(0.90, 1.01)[a]
Cmax	B : A	0.85	(0.79, 0.92)[a]
Tmax	B – A	0.51 h	(0.01 h, 1.02 h)[b]
AUC(0-inf)	B : C	1.01	(0.95, 1.08)[a]
Cmax	B : C	1.01	(0.94, 1.09)[a]
Tmax	B – C	0.48 h	(-0.04 h, 0.99 h)[b]

a = Ratio of adjusted geometric means between formulations
b = Estimated median difference between formulations

Regimen Key: Regimen A = 4/500 mg rosiglitazone/metformin, fasting
Regimen B = 4/500 mg rosiglitazone/metformin, high-fat breakfast
Regimen C = 4 + 500 mg rosiglitazone + metformin, high-fat breakfast

In the combination tablet, rosiglitazone AUC(0-inf) was similar when administered with or without food as the 90% confidence interval was within the bioequivalence assessment range (0.80,1.25). Rosiglitazone Cmax decreased (22%), and Tmax was delayed (1.5 h), as expected, when administered with food. Rosiglitazone T1/2 values were similar (approximately 3.50 h) across all 3 regimens.

Metformin AUC(0-inf) was similar when administered with or without food in the combination tablet. When administered with food. Cmax decreased (15%). and Tmax was slightly delayed (0.5 h). Metformin T1/2 values were similar (approximately 3.40 h) across all 3 regimens.

Under fed conditions, the pharmacokinetics of rosiglitazone and metformin were similar after concomitant administration or administration of the combination tablet. Since the 90% confidence intervals for AUC(0-inf) and Cmax for both rosiglitazone and metformin were within the bioequivalence range (0.80, 1.25), the combination tablet formulation is bioequivalent to concomitantly administered rosiglitazone and metformin commercial tablets under fed conditions.

Conclusion

Food had no effect on the AUC(0-inf) of both rosiglitazone and metformin when administered in the combination tablet. However, compared to the fasted state, Cmax was lower and Tmax prolonged for both rosiglitazone and metformin under fed conditions.

Under fed conditions, the combination tablet formulation was bioequivalent to concomitantly administered rosiglitazone and metformin commercial tablets.

Dosing with combination formulations of rosiglitazone 4 mg plus metformin 500 mg under fed or fasting conditions, as well as concomitant dosing with rosiglitazone 4 mg plus metformin 500 mg under fed conditions, was well tolerated.