

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-842**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

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NDA: 21-842	Submission Date(s): 10/27/04; 1/13/05; 3/11/05, 7/11/05
Brand Name	—
Generic Name	Pioglitazone Hydrochloride and Metformin Hydrochloride Tablets
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM Division	Division of Metabolic and Endocrine Drug Products
Sponsor	Takeda
Submission Type	505 (b) (2)
Formulation; Strength(s)	15 mg/ 500 mg; 15 mg/ 850 mg Oral tablets
Indication	Treatment of Type 2 Diabetes Mellitus

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## **I Executive Summary**

Takeda has developed a fixed-dose combination tablet containing pioglitazone and metformin.

The efficacy and safety of the concomitant use of pioglitazone and metformin has previously been evaluated in 2 controlled clinical trials (NDA 21-073). Concomitant administration of the separate commercial pioglitazone and metformin tablets in adult patients with type 2 diabetes was approved by the FDA in 1999 as a part of the original marketing approval of pioglitazone.

Pioglitazone is approved for once-daily administration at doses of 15, 30 and 45 mg. Metformin is available in 500, 850, and 1000 mg tablets and is approved for individualized treatment up to a maximum daily dose of 2550 mg in adults. Typically metformin is administered twice per day with meals.

To aid in the approval of this application the sponsor has submitted the following pharmacokinetic studies: 2 Bioequivalence studies (OPTIMET004 and OPTIMET005) and 1 food effect study (OPTIMET006). There was also inclusion of in vitro dissolution method and results. There were no clinical studies done with the to-be marketed combination product and the pharmacokinetic studies were designed to bridge the proposed combination tablets to the clinical safety and efficacy database supporting the use of pioglitazone in combination with metformin existing under the approved NDA.

### **A Recommendation**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the NDA 21-842 for \_\_\_\_\_ tablets and finds it acceptable. Recommendations and labeling comments should be sent to the sponsor as appropriate.

CPB briefing was held on 8/11/05 and the attendees were Hank Malinowski, John Hunt, Hae-Young Ahn and Jayabharathi Vaidyanathan

### **B Phase 4 Commitments**

None.

## C Summary of CPB Findings

The summary of results from the 3 studies is provided below.

### *Bioequivalence:*

The 2 bioequivalence studies examined the relative rate and extent of exposure of the combination tablet formulation, (15 mg/ 500 mg and 15 mg/ 850 mg) to concomitant dosing of Actos<sup>®</sup> (pioglitazone 15 mg) + Glucophage<sup>®</sup> (metformin 500 mg) and Actos<sup>®</sup> (pioglitazone 15 mg) + Glucophage<sup>®</sup> (metformin 850 mg) tablets respectively in healthy subjects under fasting conditions. Results of both studies indicated that the bioequivalence was demonstrated for the pioglitazone and metformin components in terms of AUC and C<sub>max</sub>.

### *Food effect:*

The food effect study demonstrated that after administration of the combination tablet (15 mg/ 850 mg), the rate and extent of pioglitazone was not changed in the fed state as compared to the fasted state. On the other hand, administration of combination tablet with food caused a 13% decrease in AUC and about 30% decrease in C<sub>max</sub> of metformin from the formulation. The observed effects from the combination tablet were similar to those observed for the individual drugs.

### *Dissolution:*

Multipoint dissolution data from three batches of the to-be-marketed strengths was included for evaluation. Results indicate that the method was appropriate for The method and specifications are:

Medium: Buffer, pH 2.5, 37°C, 900 ml

Apparatus: Type 2 (paddles)

Speed: 50 rpm

Specifications: NLT — (Q) of the label claim of pioglitazone dissolved in 30 min.

NLT — (Q) of the label claim of metformin dissolved in 30 min.

## II **QBR**

### A General Attributes

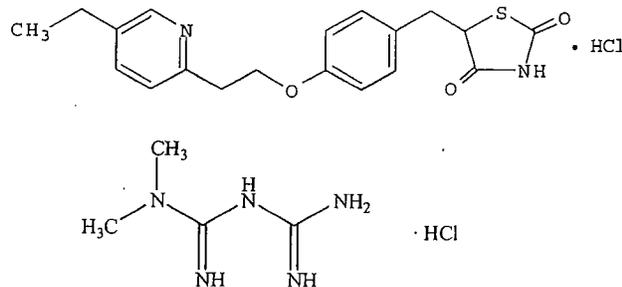
What are the highlights of the chemistry and physico-chemical properties of

tablets contain 2 oral antihyperglycemic drugs used in type 2 diabetes: pioglitazone hydrochloride and metformin hydrochloride. Pioglitazone ([(+)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride) (Figure 1) belongs to a different chemical class and has a different pharmacological

action than the sulfonylureas, biguanide, or the  $\alpha$ -glucosidase inhibitors. The molecule contains one asymmetric center, and the synthetic compound is a racemate. The two enantiomers of pioglitazone interconvert in vivo. Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of  $C_{19}H_{20}N_2O_3S \cdot HCl$  and a molecular weight of 392.90.

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) (Figure 1) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white crystalline powder with a molecular formula of  $C_4H_{11}N_5 \cdot HCl$  and a molecular weight of 165.62.

**Figure 1: Chemical structure of pioglitazone (top) and metformin (bottom).**



**What is the proposed mechanism (s) of action and therapeutic indication?**

ACTOPLUS MET combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone hydrochloride, a member of thiazolidinedione class, and metformin hydrochloride, a member of the biguanide class.

Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma ( $PPAR\gamma$ ).  $PPAR$  receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of  $PPAR\gamma$  nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Metformin hydrochloride is a biguanide antihyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

ACTOPLUS MET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone.

## What is the proposed dose and dosage form?

Proposed starting dose of ACTOPLUS MET will be based on the patient's current regimen of pioglitazone and/or metformin. ACTOPLUS MET is proposed to be given in divided daily doses with meals to reduce the gastrointestinal side effects associated with metformin.

### *Starting dose for patients inadequately controlled on metformin monotherapy:*

Based on the usual starting dose of pioglitazone (15-30 mg daily), ACTOPLUS MET is proposed to be initiated at either the 15 mg/500 mg or 15 mg/850 mg tablet strength once or twice daily, and gradually titrated after assessing adequacy of therapeutic response.

### *Starting dose for patients inadequately controlled on pioglitazone monotherapy:*

Based on the usual starting doses of metformin (500 mg twice daily or 850 mg daily), ACTOPLUS MET is proposed to be initiated at either the 15 mg/500 mg twice daily or 15 mg/850 mg tablet strength once daily, and gradually titrated after assessing adequacy of therapeutic response.

### *Starting dose for patients switching from combination therapy of pioglitazone plus metformin as separate tablets:*

ACTOPLUS MET is proposed to be initiated with either the 15 mg/500 mg or 15 mg/850 mg tablet strengths based on the dose of pioglitazone and metformin already being taken.

## **B     General Clinical Pharmacology**

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

No clinical studies with the drug product were performed in support of this submission. Consistent with the requirements for a 505 (b) (2) application, the clinical pharmacology studies were performed to demonstrate the bioequivalence of the combined drug product to the commercially available reference products.

Two doses of the pioglitazone/metformin fixed dose tablet (15 mg/500 mg and 15 mg/850 mg) were evaluated in 2 bioequivalence studies, the highest dose was evaluated in a food-effect study. All clinical pharmacology studies evaluated 2 formulations of the fixed-dose combination product, a — formulation and a formulation that contained — pioglitazone. The latter formulation was identified as suitable for commercial development. Therefore this review will focus on the bioequivalence and the effect of food on the — formulation.

## **C     Intrinsic Factors**

The effects of various intrinsic factors (e.g., hepatic, renal, gender, elderly) were provided in the original NDA for each drug.

## D Extrinsic Factors

Is there any drug-drug interaction between pioglitazone and metformin?

No drug interaction study was submitted in the current submission. Drug-drug interaction between pioglitazone and metformin was conducted under the original NDA submission for Actos. The current package insert for Actos has the following statement under Drug Interactions section:

Metformin: Co-administration of a single dose of metformin (1000 mg) and Actos after 7 days of Actos did not alter the pharmacokinetics of the single dose of metformin.

## E General Biopharmaceutics

What is the formulation of \_\_\_\_\_ tablets?

Two drug strengths were selected for the development, containing 15 mg of pioglitazone hydrochloride and either 500 mg or 850 mg of metformin hydrochloride in an immediate-release oral tablet. The compositions for the two dosage forms are shown in Table 1.

**Table 1: Composition of \_\_\_\_\_ tablets**

Component	Reference to Quality Standard	Function	Formula (mg/tablet)	
			15 mg + 500 mg	15 mg + 850 mg
Pioglitazone Hydrochloride (as Pioglitazone)	In-house Standard	Drug Substance	(15.0)	(15.0)
Microcrystalline Cellulose	NF	—		
Metformin Hydrochloride	In-house Standard	Drug Substance	500.0	850.0
Microcrystalline Cellulose	NF	/	/	/
Povidone	USP	/	/	/
Croscarmellose Sodium	NF	/	/	/
Magnesium Stearate	NF USP	/	/	/
Hypromellose 2910	USP	/	/	/
Polyethylene Glycol 8000	NF	/	/	/
Talc	USP	/	/	/
Titanium Dioxide	USP	/	/	/
Total tablet Weight			657.0	1100.0

Is the dissolution method appropriate for \_\_\_\_\_ tablets?

The sponsor has proposed the following dissolution method and specification.

Medium: \_\_\_\_\_ buffer, pH 2.5, 37°C, 900 ml

Apparatus: Type 2 (paddles)

Speed: 50 rpm

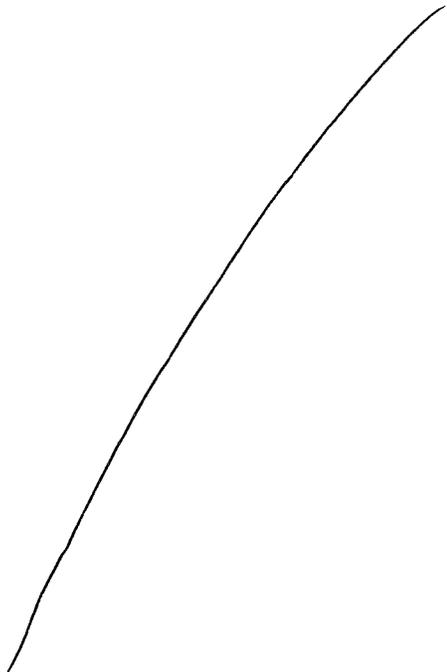
Specifications: NLT \_\_\_\_\_ (Q) of the label claim of pioglitazone dissolved in 30 min.

NLT \_\_\_\_\_ (Q) of the label claim of metformin dissolved in 30 min.

Justification was provided for the choice of media and speed used.

***Selection of dissolution medium:***

\_\_\_\_\_



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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

**Conclusions:**

- These results support the use of pH 2.5 as the dissolution medium for \_\_\_\_\_ tablets (15mg/500 mg and 15 mg/850 mg).
- pH 2.5 will be more helpful to discriminate between batches since it had slower dissolution rates of pioglitazone.
- Metformin is freely soluble in all pH.
- (Q) = \_\_\_\_\_, at 30 min is appropriate for pioglitazone and metformin.
- The use of paddle speed of 50 rpm is justified and is appropriate.
- There was no difference in dissolution rates using \_\_\_\_\_ media was used.
- We concur with the sponsor's proposed dissolution conditions of:  
Medium: pH 2.5 buffer; 900 ml \_\_\_\_\_  
Apparatus: Type 2 (paddles)  
Speed: 50 rpm  
Specifications: NLT \_\_\_\_\_ (Q) of the label claim of pioglitazone dissolved in 30 min.  
NLT \_\_\_\_\_ (Q) of the label claim of metformin dissolved in 30 min.

**Bioequivalence Study:**

**1) Is the combination tablet formulation of pioglitazone and metformin (15 mg/500 mg) bioequivalent to concomitant dosing of pioglitazone 15 mg and metformin 500 mg (15 mg + 500 mg) commercial tablets in healthy subjects?**

In order to determine the whether the combination tablet was bioequivalent to the commercial formulations, a single-center, open-label, randomized, 3-period crossover study was conducted in healthy adults (N=66 enrolled, 62 completed; age 18-55 yrs). Two different formulations of the combination tablets \_\_\_\_\_

\_\_\_\_\_ were evaluated. A 7-day washout period separated the 3 treatments. The 3 treatments were administered after an overnight fast. The treatments were:

A: Combination tablet \_\_\_\_\_ 15 mg pioglitazone/500 mg metformin.

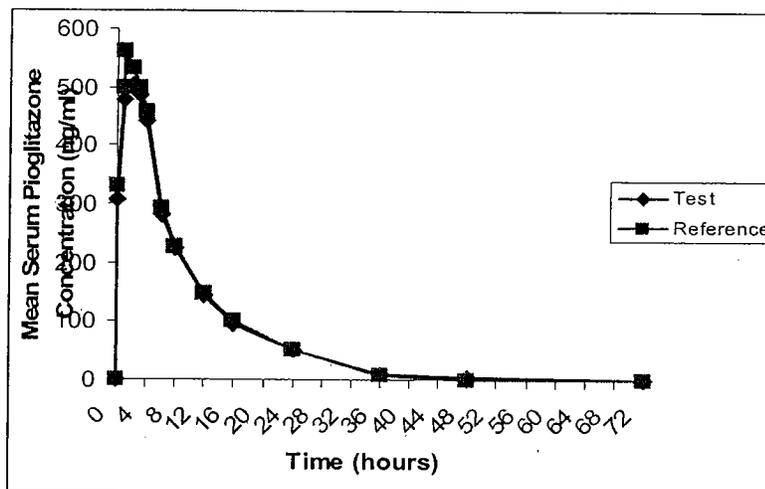
B: Combination tablet \_\_\_\_\_ 15 mg pioglitazone/500 mg metformin.

C: Commercial Actos 15 mg and 500 mg Glucophage tablets.

Since for commercial production the \_\_\_\_\_ formulation was chosen the review will focus only on the bioequivalence of the \_\_\_\_\_ formulation (Treatment A).

**Pioglitazone:** Concentrations of pioglitazone were similar after administration of both treatment regimens. The mean  $C_{max}$  occurred at 1.5 to 2 hr post dose. The mean serum concentration of pioglitazone from the combination tablet formulation and reference product is shown in Figure 4.

Figure 4: Mean pioglitazone serum concentration following administration of the combination and commercial tablets.



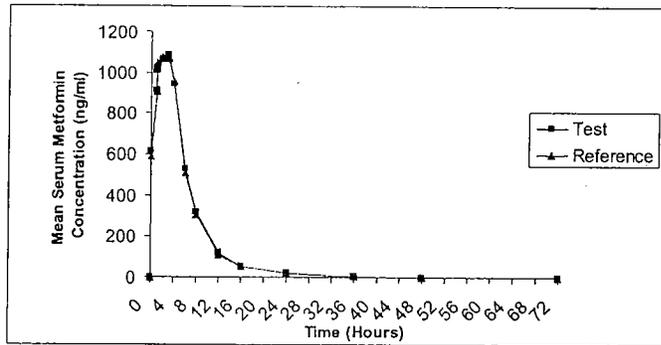
The summary of serum pioglitazone pharmacokinetic parameters is shown in Table 6. Based on AUC and  $C_{max}$  values, the bioavailability of pioglitazone following administration of the fixed-dose — tablet is equivalent to that observed following administration of separate commercial (Actos) tablets. The 90% CI of the geometric means for AUC(0-t), AUC<sub>inf</sub>, and  $C_{max}$  were (86.46-106.97%), (87.56-105.5%), and (83.5-106.59%) respectively.

Table 6: Summary statistics of pioglitazone PK parameters after administration of combination and commercial tablet.

Formulation	PK Parameter	Arithmetic Mean	Geometric Mean	Ratio	90% CI
Combination tablet — formulation) [Test]	AUC <sub>last</sub> (ng.hr/ml)	5069.7	4653.96	96.17	86.46-106.97
	AUC <sub>inf</sub> (ng.hr/ml)	5983.9	5224.00	96.11	87.56-105.50
	$C_{max}$ (ng/ml)	584.7	538.99	94.34	83.50-106.59
Commercial tablet [Reference]	AUC <sub>last</sub> (ng.hr/ml)	5087.7	4839.22		
	AUC <sub>inf</sub> (ng.hr/ml)	5809.6	5435.3		
	$C_{max}$ (ng/ml)	608.3	571.33		

**Metformin:** Concentrations of metformin were similar after administration of both treatment regimens. The mean  $C_{max}$  occurred at 2 to 3 hr post dose. The mean serum concentration of metformin from the combination tablet formulation and reference product (Glucophage) is shown in Figure 5.

**Figure 5: Mean metformin serum concentration following administration of the combination and commercial tablets.**



The summary of serum metformin pharmacokinetic parameters is shown in Table 7. Based on AUC and  $C_{max}$  values, the bioavailability of metformin following administration of the fixed-dose — tablet is equivalent to that observed following administration of separate commercial tablets. The 90% CI of the geometric means for AUC(0-t), AUC<sub>inf</sub>, and  $C_{max}$  were (92.89-112.38%), (93.94-113.35%), and (90.6-107.72%) respectively.

**Table 7: Summary statistics of metformin PK parameters after administration of combination and commercial tablet.**

Formulation	PK Parameter	Arithmetic Mean	Geometric Mean	Ratio	90% CI
Combination tablet — formulation) [Test]	AUC <sub>last</sub> (ng.hr/ml)	7610.0	7215.88	102.17	92.89-112.38
	AUC <sub>inf</sub> (ng.hr/ml)	7783.2	7419.16	103.19	93.94-113.35
	$C_{max}$ (ng/ml)	1202.9	1154.51	98.79	90.60-107.72
Commercial tablet [Reference]	AUC <sub>last</sub> (ng.hr/ml)	7433.0	7062.58		
	AUC <sub>inf</sub> (ng.hr/ml)	7599.0	7189.74		
	$C_{max}$ (ng/ml)	1214.5	1168.69		

**2) Is the combination tablet formulation of pioglitazone and metformin (15 mg/850 mg) bioequivalent to concomitant dosing of pioglitazone 15 mg and metformin 850 mg (15 mg + 850 mg) commercial tablets in healthy subjects?**

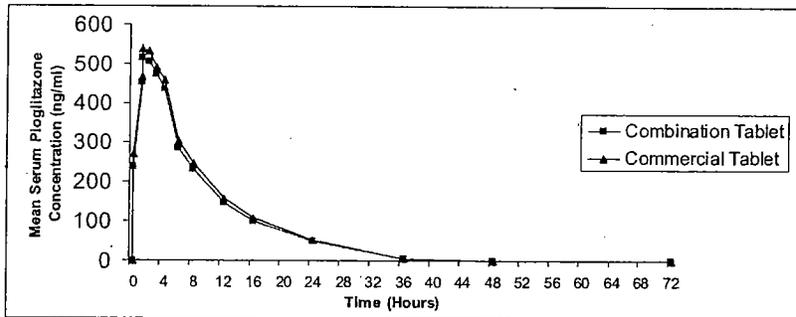
In order to determine the whether the combination tablet was bioequivalent to the commercial formulations, a single-center, open-label, randomized, 3-period crossover

study was conducted in healthy adults (N=66 enrolled, 62 completed; age 18-55 yrs). Two different formulations of the combination tablets (A and B) were evaluated. A 7-day washout period separated the 3 treatments. Blood was collected prior to dose administration and at definite time periods through 24 hours following dosing.

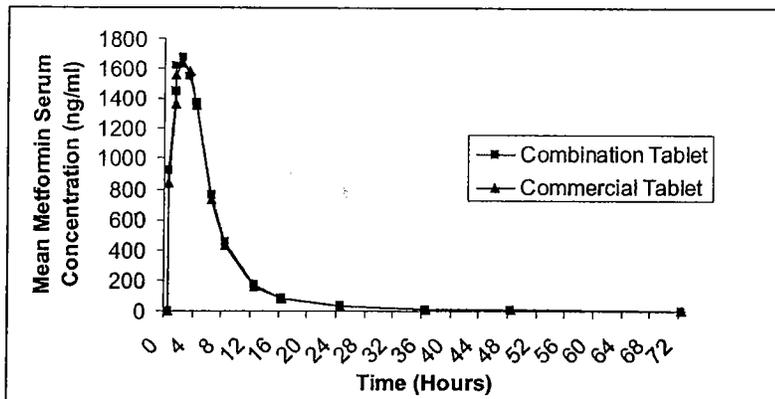
The 3 treatments were administered after an overnight fast. The treatments were:  
 A: Combination tablet — 15 mg pioglitazone/850 mg metformin.  
 B: Combination tablet — 15 mg pioglitazone/850 mg metformin.  
 C: Commercial Actos 15 mg and 850 mg Glucophage tablets.

The results indicate that bioequivalence of the combination tablet formulation relative to concomitant dosing of pioglitazone and metformin commercial tablets was demonstrated for the pioglitazone and metformin components in terms of  $AUC_{(0-\infty)}$ ,  $AUC_{(0-t)}$  and  $C_{max}$ . The results are summarized in the following figures and tables (Figures 6 and 7; Table 8 and 9).

**Figure 6: Mean pioglitazone serum concentration following administration of the combination and commercial tablets.**



**Figure 7: Mean metformin serum concentration following administration of the combination and commercial tablets.**



**Table 8: Summary statistics of pioglitazone PK parameters after administration of combination and commercial tablet.**

Formulation	PK Parameter	Arithmetic Mean	Geometric Mean	Ratio	90% CI
Combination tablet — formulation) [Test]	AUC <sub>last</sub> (ng.hr/ml)	4889.2	4584.98	94.54	84.56- 105.59
	AUC <sub>inf</sub> (ng.hr/ml)	5671.2	5098.10	94.56	85.42- 104.67
	C <sub>max</sub> (ng/ml)	569.3	529.15	97.23	85.29- 110.84
Commercial tablet [Reference]	AUC <sub>last</sub> (ng.hr/ml)	5186.7	4849.73		
	AUC <sub>inf</sub> (ng.hr/ml)	5957.3	5391.63		
	C <sub>max</sub> (ng/ml)	602.7	544.24		

**Table 9: Summary statistics of metformin PK parameters after administration of combination and commercial tablet.**

Formulation	PK Parameter	Arithmetic Mean	Geometric Mean	Ratio	90% CI
Combination tablet — formulation) [Test]	AUC <sub>last</sub> (ng.hr/ml)	11421.0	11012.8	102.45	94.27- 111.34
	AUC <sub>inf</sub> (ng.hr/ml)	11926.6	11343.73	102.56	94.44- 111.38
	C <sub>max</sub> (ng/ml)	1827.3	1751.06	101.69	93.05- 111.12
Commercial tablet [Reference]	AUC <sub>last</sub> (ng.hr/ml)	11192.9	10749.8		
	AUC <sub>inf</sub> (ng.hr/ml)	11568.8	11060.66		
	C <sub>max</sub> (ng/ml)	1797	1722.02		

**Conclusions:** Both rate and extent of pioglitazone and metformin absorption observed after single-dose administration of the — combination tablet (pioglitazone 15 mg/metformin 500 mg or pioglitazone 15 mg/metformin 850 mg ) were bioequivalent to those observed after administration of the separate commercial tablets (pioglitazone 15 mg + metformin 500 mg or pioglitazone 15 mg + metformin 850 mg) respectively. The conclusions are based on the findings that the 90% CI for the ratio of geometric means (test/reference) for AUC and C<sub>max</sub> were within the 80-125% interval.

## What is the effect of food on the bioavailability of —

A open-label, randomized, 2-sequence crossover study involving 28 healthy adults (age 18-55 yrs) was conducted to compare peak and total exposures of pioglitazone and metformin after administration of a single dose of the pioglitazone/metformin fixed-dose combination tablet when given under fasting conditions to when given with a high fat meal. This was a 4 way crossover study with both — formulations administered with and without food. A washout interval of 7 days separated the doses of the 4 study periods.

Pioglitazone levels rose quickly when administered under fasting conditions than with food. The  $T_{max}$  under fasting for pioglitazone was 1.5 to 2 h post dose under fasting while it was at 4 h post dose under fed conditions. Table 10 shows the PK analysis of the effect of food on the serum pioglitazone with the — formulation. The LS mean ratios (fed/fasted) for pioglitazone  $AUC_{(last)}$ ,  $AUC_{inf}$ , and  $C_{max}$  were 112.8%, 111%, and 104.5% respectively. The 90% CI were between 80-125% for all the three parameters indicating a lack of food effect.

**Table 10: Statistical analysis of pioglitazone PK parameters.**

Parameter (units)	N	Treatment	LS Mean	Test/Reference	LS Mean Ratio (%) (a)	90% CI of Ratio (%)
<b>— Formulation</b>						
$AUC_{(0-ttqc)}$ (hr·ng/mL) (b)	28	A	4760.0	B/A	112.8	(102.1, 124.7)
		B	5370.7			
$AUC_{(0-inf)}$ (hr·ng/mL) (b)	27	A	5289.4	B/A	111.0	(100.6, 122.4)
		B	5868.8			
$C_{max}$ (ng/mL) (b)	28	A	531.8	B/A	104.5	(92.8, 117.7)
		B	556.0			
$T_{max}$ (hr) (c)	28	A	1.63			
		B	3.48			
$\lambda_z$ (1/hr) (c)	27	A	0.099			
		B	0.109			

Where,

Treatment A: Pioglitazone 15 mg/metformin 850 mg — tablet (fasting).

Treatment B: Pioglitazone 15 mg/metformin 850 mg — tablet (fed).

(a) Ratio of LS mean of Treatment B/Treatment A.

(b) Natural logarithms of AUC and  $C_{max}$  were used in ANOVA.

(c) P-values for treatment effect were  $<0.001$  for  $T_{max}$  and  $P=0.060$  for  $\lambda_z$ .

Similarly metformin plasma concentrations also increased rapidly during fasting conditions than when given with food. The  $T_{max}$  occurred at 2 hr and 4 hr under fasting and fed conditions respectively. Table 11 shows the PK analysis of the effect of food on the serum metformin with the — formulation. The LS mean ratios (fed/fasted) for pioglitazone  $AUC_{(last)}$ ,  $AUC_{inf}$ , and  $C_{max}$  were 86.9%, 87.1%, and 71.9% respectively. The 90% CI were between 80-125% for AUC, however  $C_{max}$  fell below this interval thus indicating that the  $C_{max}$  was affected by food.

**Table 11: Statistical analysis of metformin PK parameters.**

Parameter (units)	N	Treatment	LS Mean	Test/Reference	LS Mean Ratio (%) (a)	90% CI of Ratio (%)
<b>— Formulation</b>						
AUC(0-t <sub>lqc</sub> ) (hr·ng/mL) (b)	28	A	11580.7	B/A	86.9	(81.2, 93.0)
		B	10063.8			
AUC(0-inf) (hr·ng/mL) (b)	24	A	12017.9	B/A	87.1	(80.9, 93.8)
		B	10472.6			
C <sub>max</sub> (ng/mL) (b)	28	A	1781.8	B/A	71.9	(63.4, 79.1)
		B	1281.3			
T <sub>max</sub> (hr) (c)	28	A	2.38			
		B	3.20			
λ <sub>z</sub> (1/hr) (c)	24	A	0.072			
		B	0.061			

**Conclusions:**

- Highest dose proposed for the combination tablet was studied in the food effect study.
- Due to the short half life of both metformin and pioglitazone and appropriate washout period between treatments the possible carry over effect is diminished.
- Administration of combination tablet with food caused a 13% decrease in AUC and about 30% decrease in C<sub>max</sub> of metformin in the — formulation. This extent of food effect is similar to that stated in the current Glucophage package insert that administration of Glucophage 850 mg with food caused a decrease in peak and total exposure of metformin by 40% and 25% respectively.
- However, since metformin is indicated to be given with meals, this combination tablet formulation is also proposed to be given with food.

**F Analytical**

**Have the analytical methods been sufficiently validated?**

**Metformin**

A validated LC/MS/MS method for determination of metformin in human serum was used. The standard curve was in the range of 10 -3500 ng/ml. The quality control samples were 3000, 800, and 30 ng/ml. Intra-assay and inter-assay accuracy and precision were determined for the quality control samples. Data indicate that the quality control sample data met the criteria. Diluted quality control data also met the precision and accuracy criteria (Table 12).

**Table 12: Inter and intra assay quality control statistics.**

	QC 10.0 10 ng/ml	QC 30.0 30 ng/ml	QC 800.0 800 ng/ml	QC 3000.0 3000 ng/ml
<b>Inter-assay</b>				
Mean	9.15	29.5	792	3000
SD	0.627	1.96	21.1	227
%CV	6.9	6.6	2.7	7.6
N	24	26	26	26
<b>Intra-assay</b>				
Mean	9.66	32.7	808	3060
SD	0.223	0.579	10.4	34.3
%CV	2.3	1.8	1.3	1.1
N	6	6	6	6

Pioglitazone

A validated LC/MS/MS method for determination of pioglitazone, and its metabolites M1 and M1V in human serum was used. The standard curve was in the range of 25 -2500 ng/ml and the quality control samples were 2000, 1000, and 74.9 ng/ml for the drug and its metabolites. Results are summarized in Table 13.

**Table 13: Inter and intra assay quality control statistics.**

	QC 25.0 25 ng/ml	QC 74.9.0 74.9ng/ml	QC 1000.0 1000 ng/ml	QC 2000.0 2000 ng/ml
<b>Inter-assay</b>				
Mean	25.4	71.7	991	2000
SD	2.82	4.19	34.4	73.6
%CV	11.1	5.8	3.5	3.7
N	18	20	19	20
<b>Intra-assay</b>				
Mean	22.8	74.4	1020	2000
SD	1.19	1.63	22.8	63.4
%CV	5.2	2.2	2.2	3.2
N	18	20	19	20

22 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**B Individual Study Synopsis**

**1) Bioequivalence study 01-03-TL-OPTIMET-004**

**2.0 SYNOPSIS**

<b>Title of Study:</b> An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 500 mg When Administered as Commercial Tablets and as a Combination Product	
<b>Name of Sponsor:</b> Takeda Global Research & Development Center, Inc. (TGRD)	
<b>Name of Finished Product:</b> Pioglitazone/metformin fixed-dose combination tablet	
<b>Investigator:</b> —	<b>Study Center:</b> /
<b>Publication (reference):</b> None	
<b>Study Period:</b> 13 March 2004 to 31 March 2004	<b>Phase of Development:</b> Phase 1
<b>OBJECTIVES</b> <b>Primary:</b> To determine the bioequivalency of pioglitazone and metformin when administered as commercial tablets and as a fixed-dose combination tablet. <b>Secondary:</b> To evaluate the safety of pioglitazone and metformin when administered as commercial tablets and as a fixed-dose combination tablet.	
<b>METHODOLOGY</b> This was a single-center, open-label, randomized, 3-period crossover study. Subjects were randomized to 1 of 6 treatment sequences in which they received a single oral dose of each treatment: 15/500 mg pioglitazone/metformin fixed-dose combination — tablet, 15/500 mg pioglitazone/metformin fixed-dose combination — tablet, and a 15 mg pioglitazone commercial tablet coadministered with a 500 mg metformin commercial tablet. The 3 treatment periods were separated by a washout period of 7 days. During each period, blood samples were collected at specified times up to 72 hours posttreatment for the measurement of pioglitazone and metformin concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations.	
<b>Number of Subjects (Planned and Analyzed):</b> Planned: 66 subjects Analyzed: Pharmacokinetics — 62 subjects; Safety — 66 subjects.	
<b>Diagnosis and Main Criteria for Inclusion:</b> To qualify for study participation, subjects must have been healthy male subjects or nonpregnant, nonlactating female subjects 18 to 55 years of age, inclusive; been able to comprehend and willing to sign the informed consent form; had clinical laboratory results within the reference ranges or that were acceptable to the investigator; weighed at least 110 pounds and had a body mass index (BMI) $\leq 30$ kg/m <sup>2</sup> ; and had a negative hepatitis panel and human immunodeficiency virus (HIV) antibody test at Screening.	

<b>Title of Study:</b>	
An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 500 mg When Administered as Commercial Tablets and as a Combination Product	
<b>Test Product, Dose and Mode of Administration:</b>	
	<u>Lot Number</u>
Pioglitazone/metformin fixed-dose combination, 15 mg/500 mg — tablet, oral	Z5504041
Pioglitazone/metformin fixed-dose combination, 15 mg/500 mg - . tablet, oral	Z5506031
<b>Duration of Treatment:</b>	
The study duration was 19 days (three 1-day dosing periods separated by a 7-day washout period with a 3-day follow-up after the third period).	
<b>Reference Therapy, Dose and Mode of Administration:</b>	
	<u>Lot Number</u>
ACTOS® (pioglitazone HCl), 15 mg, tablet, oral	A10153
GLUCOPHAGE* (metformin HCl), 500 mg, tablet, oral	MHM43
<b>Criteria for Evaluation:</b>	
<b>Pharmacokinetics:</b>	
For each subject, the following pharmacokinetic parameters were calculated for each study period from serum concentrations of unchanged metformin and pioglitazone according to the model-independent approach: maximum observed serum concentration (C <sub>max</sub> ), the time at which C <sub>max</sub> occurred (T <sub>max</sub> ), terminal-phase elimination rate constant (λ <sub>z</sub> ), area under the serum concentration-time curve from time 0 to time of last quantifiable concentration (AUC[0-t <sub>lqc</sub> ]), area under the serum concentration-time curve from time 0 to infinity (AUC[0-inf]), terminal elimination half-life (T <sub>1/2</sub> ), and apparent oral clearance (CL/F).	
<b>Safety:</b>	
Safety variables included AEs, clinical laboratory test results, vital signs, ECGs, and physical examinations.	
<b>Statistical Methods:</b>	
<i>Pharmacokinetic Measures:</i> An analysis of variance (ANOVA) with fixed effects for sequence, period, and treatment and random effect for subject nested within sequence was the primary analysis performed on T <sub>max</sub> , λ <sub>z</sub> , and the natural logarithms of AUC(0-t <sub>lqc</sub> ), AUC(0-inf), and C <sub>max</sub> of pioglitazone and metformin. The possibility of unequal carryover effect was also examined by including carryover effect in the aforementioned model. The 90% confidence intervals (CIs) for the ratio of the least-squares (LS) mean of the pioglitazone/metformin fixed-dose combination tablets / — relative to the LS mean of coadministered pioglitazone and metformin tablets (reference treatment) were calculated. If the 90% CIs for AUC(0-t <sub>lqc</sub> ), AUC(0-inf), and C <sub>max</sub> of pioglitazone and metformin were within the (80%, 125%) interval, bioequivalence between test and reference treatments was claimed.	
<b>SUMMARY OF RESULTS</b>	
<b>Subject Disposition:</b>	
A total of 66 subjects (mean age of 31.3 years), including 29 male subjects and 37 female subjects, were enrolled in the study; 62 (93.9%) subjects, including 28 males and 34 female subjects, completed the study. Four subjects discontinued the study early: 1 subject withdrew voluntarily; 1 subject withdrew because of an AE (mild allergic reaction); 1 subject withdrew because the subject became pregnant; and 1 subject was withdrawn because of a protocol violation.	

**Title of Study:**

An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 500 mg When Administered as Commercial Tablets and as a Combination Product

**Pharmacokinetic Results:**

Based on the primary analysis of AUC and  $C_{max}$  exposure to pioglitazone and metformin following administration of the fixed-dose combination — tablet was similar to that observed following coadministration of the separate commercial pioglitazone and metformin tablets. For both pioglitazone and metformin, the 90% CIs of the LS mean ratios of AUC(0-t<sub>lqc</sub>), AUC(0-inf), and C<sub>max</sub> were within the 80% to 125% range for bioequivalence.

With regard to the — tablet, exposure to pioglitazone and metformin was also similar to that observed following coadministration of the separate commercial pioglitazone and metformin tablets. As with the — tablet, the 90% CIs of the LS mean ratios for AUC(0-t<sub>lqc</sub>), AUC(0-inf), and C<sub>max</sub> for both pioglitazone and metformin were within the 80% to 125% bioequivalence range.

In addition, there were no statistically significant differences observed in treatment comparisons of T<sub>max</sub> and λ<sub>z</sub> for pioglitazone or metformin, and there were no notable differences between the treatments with respect to T<sub>1/2</sub> or CL/F.

**Pharmacokinetic Analysis for Serum Pioglitazone and Metformin**

Parameter (a) (units)	N	Treatment	LS Mean	Test/ Reference	LS Mean Ratio (%) (b)	90% CI for Ratio (%)
<b>Pioglitazone</b>						
AUC(0-t <sub>lqc</sub> ) (hr·ng/mL)	62	A	4715.6	A/C	97.7	(91.0, 104.9)
	62	B	4830.4	B/C	100.1	(93.2, 107.4)
	62	C	4827.1			
AUC(0-inf) (hr·ng/mL)	51	A	5756.4	A/C	102.5	(97.6, 107.6)
	48	B	5729.6	B/C	102.0	(97.0, 107.2)
	54	C	5617.1			
C <sub>max</sub> (ng/mL)	63	A	540.9	A/C	95.0	(86.2, 104.7)
	62	B	550.1	B/C	93.1	(84.4, 102.6)
	63	C	569.5			
<b>Metformin</b>						
AUC(0-t <sub>lqc</sub> ) (hr·ng/mL)	62	A	7257.8	A/C	102.6	(97.9, 107.5)
	62	B	7248.0	B/C	102.5	(97.8, 107.4)
	62	C	7073.4			
AUC(0-inf) (hr·ng/mL)	59	A	7436.1	A/C	102.8	(98.1, 107.6)
	58	B	7478.2	B/C	103.3	(98.6, 108.3)
	59	C	7236.5			
C <sub>max</sub> (ng/mL)	63	A	1160.1	A/C	99.0	(94.8, 103.4)
	62	B	1160.1	B/C	99.0	(94.8, 103.4)
	63	C	1171.5			

Source: End-of-Text Tables 14.2.5 and 14.2.7.

Treatment A: Pioglitazone 15 mg/metformin 500 mg fixed-dose combination — tablet.

Treatment B: Pioglitazone 15 mg/metformin 500 mg fixed-dose combination — tablet.

Treatment C: One 15 mg pioglitazone tablet coadministered with one 500 mg metformin tablet.

(a) Natural logarithms of AUC and C<sub>max</sub> were used in the ANOVA with treatment, period, and sequence as fixed effects and subject within sequence as a random effect.

(b) Ratio is LS mean of Treatment A or B/LS mean of Treatment C.

<b>Title of Study:</b>						
An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 500 mg When Administered as Commercial Tablets and as a Combination Product						
<b>Safety Results:</b>						
A total of 22 of 66 subjects experienced 1 or more AEs during the study, and 15 of these 22 subjects experienced 1 or more AEs that were considered possibly or probably related to study drug. One subject experienced a treatment-emergent AE (facial edema) considered definitely related to study drug. All AEs were mild or moderate in severity.						
The greatest number of AEs occurred after administration of the combination — tablet (11 subjects, 17.2%). Three of these events (2 mild headaches, 1 mild allergic reaction) were treated with medication (2 acetaminophen, 1 antihistamine). No SAEs were reported and no deaths occurred during the study. One subject discontinued the study because of an AE (mild allergic reaction). No clinically significant abnormal laboratory values, changes in vital signs, ECG or physical examination findings were reported in the study.						
<b>AEs in 2 or More Subjects in Any Treatment Group</b>						
System Organ Class AE Preferred Term	Treatment					
	A N=64		B N=64		C N=63	
	n	%	n	%	n	%
Any event	8	(12.5)	11	(17.2)	8	(12.7)
<b>Gastrointestinal disorders</b>						
Abdominal pain	3	(4.7)	2	(3.1)	0	(0.0)
Diarrhea	3	(4.7)	1	(1.6)	0	(0.0)
<b>Nervous system disorders</b>						
Dizziness	2	(3.1)	1	(1.6)	1	(1.6)
Headache	0	(0.0)	3	(4.7)	2	(3.2)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>						
Pharyngolaryngeal pain	0	(0.0)	0	(0.0)	2	(3.2)
<b>Skin and Subcutaneous Tissue Disorders</b>						
Pruritis	0	(0.0)	2	(3.1)	0	(0.0)
Source: Table 14.3.1.2.						
Treatment A: Pioglitazone 15 mg/metformin 500 mg combination — tablet.						
Treatment B: Pioglitazone 15 mg/metformin 500 mg combination — tablet.						
Treatment C: One 15 mg pioglitazone tablet coadministered with one 500mg metformin tablet.						

<b>Title of Study:</b>	
An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 500 mg When Administered as Commercial Tablets and as a Combination Product	
<b>CONCLUSIONS:</b>	
Peak and total exposures (C <sub>max</sub> and AUCs) of pioglitazone and metformin observed after single-dose administration of the — fixed-dose combination tablets (pioglitazone 15 mg/metformin 500 mg) were bioequivalent to those observed after administration of the separate commercial tablets (pioglitazone 15 mg tablet and metformin 500 mg tablet). In addition, the 2 fixed-dose combination tablet formulations were safe and well tolerated as administered in this study.	
These conclusions are based on these findings:	
<ul style="list-style-type: none"> <li>• The 90% CIs of the LS mean ratios (test/reference) for AUC(0-t<sub>1/2</sub>), AUC(0-inf), and C<sub>max</sub> were within the 80% to 125% interval required to establish bioequivalency between the fixed-dose combination — tablets and the separate commercial tablets.</li> <li>• The safety profile for all treatments was similar based on the occurrence of AEs and clinical laboratory, vital sign, ECGs, and physical examination findings.</li> </ul>	
<b>Date of Report:</b>	
03 August 2004	

2) Bioequivalence study 01-03-TL-OPTIMET-005

<b>Title of Study:</b> An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 850 mg When Administered as Commercial Tablets and as a Combination Product	
<b>Name of Sponsor:</b> Takeda Global Research & Development Center, Inc. (TGRD)	
<b>Name of Finished Product:</b> Pioglitazone/metformin fixed-dose combination tablet	
<b>Investigator:</b> —	<b>Study Center:</b> /
<b>Publication (reference):</b> None	
<b>Study Period:</b> 27 March 2004 to 14 April 2004	<b>Phase of Development:</b> Phase I
<b>OBJECTIVES</b>	
<b>Primary:</b> To determine the bioequivalency of pioglitazone and metformin when administered as commercial tablets and as a fixed-dose combination tablet.	
<b>Secondary:</b> To evaluate the safety of pioglitazone and metformin when administered as commercial tablets and as a fixed-dose combination tablet.	
<b>METHODOLOGY</b>	
This was a single-center, open-label, randomized, 3-period crossover study. Subjects were randomized to 1 of 6 treatment sequences in which they received a single oral dose of each treatment: 15/850 mg pioglitazone/metformin fixed-dose combination tablet, 15/850 mg pioglitazone/metformin fixed-dose combination — tablet, and a 15 mg pioglitazone commercial tablet coadministered with an 850 mg metformin commercial tablet. The 3 treatment periods were separated by a washout period of 7 days. During each period, blood samples were collected at specified times up to 72 hours posttreatment for the measurement of metformin and pioglitazone concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations.	

<b>Title of Study:</b> An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 850 mg When Administered as Commercial Tablets and as a Combination Product	
<b>Number of Subjects (Planned and Analyzed):</b> Planned: 66 subjects Analyzed: Pharmacokinetics — 60 subjects; Safety — 64 subjects.	
<b>Diagnosis and Main Criteria for Inclusion:</b> To qualify for study participation, subjects must have been healthy male subjects or nonpregnant, nonlactating female subjects aged 18 to 55 years, inclusive; been able to comprehend and willing to sign the informed consent form; had clinical laboratory results within the reference ranges or that were acceptable to the investigator; weighed at least 110 pounds and had a body mass index (BMI) $\leq 30$ kg/m <sup>2</sup> , and had a negative hepatitis panel and human immunodeficiency virus (HIV) antibody test at Screening.	
<b>Test Product, Dose and Mode of Administration:</b>	
	<u>Lot Number</u>
Pioglitazone/metformin fixed-dose combination, 15 mg/850 mg, — tablet, oral	Z3505021
Pioglitazone/metformin fixed-dose combination, 15 mg/850 mg — tablet, oral	Z3507031
<b>Duration of Treatment:</b> The study duration was 19 days (three 1-day dosing periods separated by a 7-day washout period with a 3-day follow-up after the third period).	
<b>Reference Therapy, Dose and Mode of Administration:</b>	
	<u>Lot Number</u>
ACTOS® (pioglitazone HCl), 15 mg, tablet, oral	A10153
GLUCOPHAGE® (metformin HCl), 850 mg, tablet, oral	MMMI5
<b>Criteria for Evaluation:</b>	
<b>Pharmacokinetics:</b> For each subject, the following pharmacokinetic parameters were calculated for each study period from serum concentrations of unchanged metformin and pioglitazone according to the model-independent approach: maximum observed serum concentration (C <sub>max</sub> ), the time at which C <sub>max</sub> occurred (T <sub>max</sub> ), terminal phase elimination rate constant ( $\lambda_z$ ), area under the serum concentration-time curve from time 0 to time of last quantifiable concentration (AUC[0-t <sub>lqc</sub> ]), area under the serum concentration-time curve from time 0 to infinity (AUC[0-inf]), terminal elimination half-life (T <sub>1/2</sub> ), and apparent oral clearance (CL/F).	
<b>Safety:</b> Safety variables included AEs, clinical laboratory test results, vital signs, ECGs, and physical examinations.	

**Title of Study:**

An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 850 mg When Administered as Commercial Tablets and as a Combination Product

**Statistical Methods:**

**Pharmacokinetic Measures:** An analysis of variance (ANOVA) with fixed effects for sequence, period, and treatment and random effect for subject nested within sequence was the primary analysis performed on  $T_{max}$ ,  $\lambda_z$ , and the natural logarithms of AUC(0-t<sub>lqc</sub>), AUC(0-inf), and C<sub>max</sub> of pioglitazone and metformin. The possibility of unequal carryover effect was also examined by including carryover effect in the aforementioned model. The 90% confidence intervals (CIs) for the ratio of the least-squares (LS) mean of the pioglitazone/metformin fixed-dose combination — tablets (test treatment) relative to the LS mean of coadministered pioglitazone and metformin tablets (reference treatment) were calculated. If the 90% CIs for AUC(0-t<sub>lqc</sub>), AUC(0-inf), and C<sub>max</sub> of pioglitazone and metformin were within the (80%, 125%) interval, bioequivalence between test and reference treatments was claimed.

**SUMMARY OF RESULTS****Subject Disposition:**

A total of 64 subjects (mean age of 32.0 years), including 35 male subjects and 29 female subjects, were randomly assigned to treatment in the study at 1 study site, and 60 (93.8 %) subjects, including 33 male and 27 female subjects, completed the study. Four subjects discontinued the study early: 2 subjects withdrew voluntarily; 1 subject was withdrawn because the subject became pregnant; and 1 subject was lost to follow up.

**Pharmacokinetic Results:**

Based on the primary analysis of AUC and C<sub>max</sub>, exposure to pioglitazone and metformin following administration of the fixed-dose combination — tablet was similar to that observed following coadministration of the separate commercial pioglitazone and metformin tablets. For both pioglitazone and metformin, the 90% CIs of the LS mean ratios of AUC(0-t<sub>lqc</sub>), AUC(0-inf), and C<sub>max</sub> were all within the 80% to 125% range for bioequivalence. Similar results were obtained even when carryover effect was included in the ANOVA model.

With regard to the — tablet, exposure to pioglitazone and metformin was also similar to that observed following coadministration of the separate pioglitazone and metformin commercial tablets. As with the — tablet, the 90% CIs of the LS mean ratios for AUC(0-t<sub>lqc</sub>), AUC(0-inf), and C<sub>max</sub> for both pioglitazone and metformin were within the 80% to 125% bioequivalence range, even when carryover effect was included in the ANOVA model.

In addition, there were no statistically significant differences observed in treatment comparisons of  $T_{max}$  and  $\lambda_z$  for pioglitazone or metformin, and there were no significant differences between the treatments with respect to  $T_{1/2}$  or  $CL/F$ .

<b>Title of Study:</b>						
An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 850 mg When Administered as Commercial Tablets and as a Combination Product						
<b>Pharmacokinetic Analysis for Serum Pioglitazone and Metformin</b>						
Parameter (units) (a)	N	Treatment	LS Mean	Test/Reference	LS Mean Ratio (%) (b)	90% CI of Ratio (%)
<b>Pioglitazone</b>						
AUC(0-t <sub>lqc</sub> ) (hr·ng/mL)	60	A	4623.2	A/C	94.9	(90.0, 100.1)
	61	B	4782.9	B/C	98.2	(93.1, 103.5)
	61	C	4870.9			
AUC(0-inf) (hr·ng/mL)	52	A	5432.9	A/C	94.9	(90.6, 99.3)
	54	B	5651.1	B/C	98.3	(94.0, 102.9)
	55	C	5747.9			
C <sub>max</sub> (ng/mL)	60	A	526.3	A/C	97.0	(89.9, 104.7)
	61	B	540.1	B/C	99.5	(92.3, 107.4)
	61	C	542.6			
<b>Metformin</b>						
AUC(0-t <sub>lqc</sub> ) (hr·ng/mL)	60	A	10999.7	A/C	102.5	(98.3, 106.8)
	61	B	10670.2	B/C	99.4	(95.4, 103.6)
	61	C	10735.5			
AUC(0-inf) (hr·ng/mL)	47	A	11382.1	A/C	102.8	(98.2, 107.5)
	48	B	11035.7	B/C	99.6	(95.3, 104.2)
	52	C	11074.8			
C <sub>max</sub> (ng/mL)	60	A	1751.3	A/C	101.8	(96.9, 106.9)
	61	B	1700.9	B/C	98.9	(94.1, 103.8)
	61	C	1720.7			
Source: End-of-Text Tables 14.2.5 and 14.2.7.						
Treatment A: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination — tablet.						
Treatment B: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination — tablet.						
Treatment C: One 15 mg pioglitazone tablet coadministered with one 850 mg metformin tablet.						
(a) Natural logarithms of AUC and C <sub>max</sub> were used in the ANOVA with treatment, period, and sequence as fixed effects and subject within sequence as a random effect.						
(b) Ratio is LS Mean of Treatment A or B/LS mean of Treatment C.						

<b>Title of Study:</b> An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 850 mg When Administered as Commercial Tablets and as a Combination Product						
<b>Safety Results:</b> A total of 25 of 64 subjects experienced 1 or more AEs during the study, and the frequencies of AEs were similar for all study treatments. Most of the AEs were gastrointestinal system disorders, and all AEs were mild or moderate in severity. Of the 25 subjects that experienced 1 or more AEs, 21 experienced AEs considered possibly or probably related to study drug. No subject experienced an AE that was considered definitely related to study drug. No subject withdrew from the study because of an AE. No serious adverse events (SAEs) were reported and no deaths occurred during the study. No clinically significant abnormal laboratory values, changes in vital signs, or ECG or physical examination findings were reported in this study.						
<b>AEs in 2 or More Subjects in Any Treatment Group</b>						
	<b>Treatment</b>					
	<b>A</b>		<b>B</b>		<b>C</b>	
	<b>N=62</b>		<b>N=63</b>		<b>N=61</b>	
<b>System Organ Class</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>AE Preferred Term</b>						
Any event	10	(16.1)	10	(15.9)	11	(18.0)
<b>Gastrointestinal disorders</b>						
Abdominal pain	3	(4.8)	4	(6.3)	5	(8.2)
Diarrhea	1	(1.6)	1	(1.6)	3	(4.9)
Loose stools	3	(4.8)	2	(3.2)	1	(1.6)
Nausea	2	(3.2)	3	(4.8)	1	(1.6)
<b>Immune system disorders</b>						
Seasonal allergy	1	(1.6)	0	(0.0)	2	(3.3)
<b>Musculoskeletal and connective tissue disorders</b>						
Pain in extremity	0	(0.0)	0	(0.0)	2	(3.3)
<b>Nervous system disorders</b>						
Headache	2	(3.2)	4	(6.3)	1	(1.6)
Source: End-of-Test Table 14.3.1.2.						
Treatment A: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination — tablet.						
Treatment B: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination — tablet.						
Treatment C: One 15 mg pioglitazone tablet coadministered with one 850 mg metformin tablet.						

<b>Title of Study:</b> An Open-Label, Randomized, 3-Period Crossover Study to Determine the Bioequivalency of Pioglitazone 15 mg and Metformin 850 mg When Administered as Commercial Tablets and as a Combination Product	
<b>CONCLUSIONS:</b> Peak and total exposures (C <sub>max</sub> and AUCs) of pioglitazone and metformin observed after single-dose administration of the — fixed-dose combination tablets (pioglitazone 15 mg/metformin 850 mg) were bioequivalent to those observed after administration of the separate commercial tablets (pioglitazone 15 mg tablet and metformin 850 mg tablet). In addition, the 2 fixed-dose combination tablet formulations were safe and well tolerated as administered in this study. These conclusions are based on these findings:	
<ul style="list-style-type: none"> <li>For both pioglitazone and metformin, the 90% CIs of the LS mean ratios (test/reference) for AUC(0-12h), AUC(0-inf), and C<sub>max</sub> were within the 80% to 125% interval required to establish bioequivalency between the fixed-dose combination — tablets and the separate commercial tablets.</li> <li>The safety profile for all treatments was similar based on the occurrence of AEs and clinical laboratory, vital sign, ECG, and physical examination findings.</li> </ul>	
<b>Date of Report:</b> 11 August 2004	

3) Food Effect study 01-03-TL-OPTIMET-006

<b>Title of Study:</b> An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetic Profile of Pioglitazone and Metformin when Administered as a Combination Product	
<b>Name of Sponsor:</b> Takeda Global Research & Development Center, Inc. (TGRD)	
<b>Name of Finished Product:</b> Pioglitazone/metformin fixed-dose combination tablet	
<b>Investigator:</b> /	<b>Study Center:</b> /
<b>Publication (reference):</b> None	
<b>Study Period (years):</b> 3 April 2004 to 27 April 2004	<b>Phase of Development:</b> Phase 1
<b>OBJECTIVES</b>	
<b>Primary:</b> To compare the peak and total exposures of pioglitazone and metformin after administration of a single dose of the pioglitazone/metformin fixed-dose combination tablet when given under fasting conditions to when given with a high-fat meal.	
<b>Secondary:</b> To evaluate the safety of the pioglitazone/metformin fixed-dose combination tablet when given under fasting conditions and when given with a high-fat meal.	
<b>METHODOLOGY</b>	
This was a single-center, open-label, randomized, 2-sequence crossover study involving 4 treatments:	
<ul style="list-style-type: none"> <li>• Treatment A: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination  tablet (during a fast).</li> <li>• Treatment B: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination  tablet (with food).</li> <li>• Treatment C: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination  tablet (during a fast).</li> <li>• Treatment D: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination  tablet (with food).</li> </ul>	
Subjects were randomly assigned to 1 of 2 treatment sequences as follows:	
<ul style="list-style-type: none"> <li>• Sequence I: Treatment A, B, C, D.</li> <li>• Sequence II: Treatment B, A, D, C.</li> </ul>	

<b>Title of Study:</b>	
An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetic Profile of Pioglitazone and Metformin when Administered as a Combination Product	
<b>METHODOLOGY (continued)</b>	
The 4 treatment periods were separated by washout periods of 7 days. During each period, blood samples were collected at specified times up to 72 hours posttreatment for the measurement of pioglitazone and metformin concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory test results, vital signs, electrocardiograms (ECGs), and physical examination.	
<b>Number of Subjects (Planned and Analyzed):</b>	
Planned: 28 subjects (14 per sequence)	
Analyzed: Pharmacokinetics — 28 subjects for — tablet; 27 subjects for — tablet; Safety — 28 subjects for both tablets.	
<b>Diagnosis and Main Criteria for Inclusion:</b>	
To qualify for study participation, subjects must have been healthy: men or nonpregnant, nonlactating women; aged 18 to 55 years, inclusive; at least 110 lbs in weight with a body mass index (BMI) $\leq 30$ kg/m <sup>2</sup> ; been able to comprehend and willing to sign the informed consent form; had clinical laboratory results within the reference ranges or that were acceptable to the investigator and sponsor; had negative urine tests for selected substances of abuse at Screening and at check-in on Day -1; had a negative hepatitis panel at Screening; and had negative human immunodeficiency virus (HIV) antibody at Screening.	
<b>Test Product, Dose, and Mode of Administration:</b>	
	<u>Lot Number</u>
Pioglitazone/metformin fixed-dose combination, 15 mg/850 mg, — tablet, oral, with food	Z5505021
Pioglitazone/metformin fixed-dose combination, 15 mg/850 mg, — tablet, oral, with food	Z5507031
<b>Duration of Treatment:</b>	
The study duration was 25 days (four 1-day dosing periods separated by three 7-day washout periods with a 3-day follow-up after the last period).	
<b>Reference Therapy, Dose, and Mode of Administration:</b>	
	<u>Lot Number</u>
Pioglitazone/metformin fixed-dose combination, 15 mg/850 mg, — tablet, oral, during a fast	Z5505021
Pioglitazone/metformin fixed-dose combination, 15 mg/850 mg, — tablet, oral, during a fast	Z5507031
<b>Criteria for Evaluation:</b>	
<b>Pharmacokinetics</b>	
For each subject, the following pharmacokinetic parameters were calculated for each study period, whenever possible, from serum concentrations of unchanged pioglitazone and metformin, according to the model-independent approach: maximum observed serum concentration (C <sub>max</sub> ), time at which C <sub>max</sub> occurred (T <sub>max</sub> ), elimination rate constant ( $\lambda_z$ ), area under the serum concentration-time curve from time 0 to time of last quantifiable concentration (AUC[0-t] <sub>lc</sub> ), area under the serum concentration-time curve from time 0 to infinity (AUC[0-inf]), terminal elimination half-life (T <sub>1/2</sub> ), and apparent oral clearance (CL/F).	

<p><b>Title of Study:</b> An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetic Profile of Pioglitazone and Metformin when Administered as a Combination Product</p>
<p><b>Safety:</b> Safety variables included AEs, clinical laboratory test results, vital signs, ECGs, and physical examination.</p>
<p><b>Statistical Methods:</b> <i>Pharmacokinetic Measures:</i> An analysis of variance (ANOVA) with fixed effects for sequence, period, and treatment and random effect for subject nested within sequence was performed on T<sub>max</sub>, λ<sub>z</sub>, and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and C<sub>max</sub> for pioglitazone and metformin. The 90% confidence intervals (CIs) for the ratio of the least-squares (LS) mean of pioglitazone/metformin fixed-dose combination tablet — , under fed conditions relative to the LS mean of the pioglitazone/metformin fixed dose combination tablet — , under fasting conditions were calculated. The absence of a food effect on the metabolism of pioglitazone and metformin from either formulation was shown if the 90% CIs for AUC(0-tlqc), AUC(0-inf), and C<sub>max</sub> of pioglitazone and metformin were within the (80%, 125%) interval.</p>
<p><b>SUMMARY OF RESULTS</b></p> <p><b>Subject Disposition:</b> A total of 28 subjects (mean age of 32.7 years), including 15 male and 13 female subjects, were enrolled in the study, and 27 subjects, including 15 male and 12 female subjects, completed the study. One subject withdrew because of a protocol deviation.</p> <p><b>Pharmacokinetic Results:</b> With respect to the — formulation, the results of this study indicate a lack of food effect on total and peak exposure of pioglitazone and on the total exposure of metformin. For pioglitazone, the 90% CIs of the LS mean ratios of AUC(0-tlqc), AUC(0-inf), and C<sub>max</sub> were within the (80%, 125%) range. For metformin, the 90% CIs of the LS mean ratios for AUC(0-tlqc) and AUC(0-inf) were within the (80%, 125%) range. There was a food effect on the peak exposure of metformin; the 90% CI of the LS mean ratio for C<sub>max</sub> was (65.4%, 79.1%). Percent decreases in the exposures to metformin based on point estimate values were 13%, 13%, and 28% for AUC(0-tlqc), AUC(0-inf), and C<sub>max</sub>, respectively. Drug dosing with food resulted in prolongation of T<sub>max</sub> from approximately 1.6 to 3.5 hours for pioglitazone and from approximately 2.4 to 3.2 hours for metformin.</p> <p>For the — formulation, there was a lack of food effect on total exposure of pioglitazone and a lack of a significant food effect on peak exposure of pioglitazone. The 90% CIs of the LS mean ratios for AUC(0-tlqc) and AUC(0-inf) were within the (80%, 125%) range, and the 90% CI of the LS mean ratio for C<sub>max</sub> was (92.4%, 126.0%). There was a food effect on the total and peak exposures of metformin; the 90% CIs of the LS mean ratios of the pharmacokinetic parameters were not within the (80%, 125%) range. Percent decreases in the exposures to metformin based on point estimate values were 13%, 21%, and 30% for AUC(0-tlqc), AUC(0-inf), and C<sub>max</sub>, respectively. Drug dosing with food resulted in prolongation of T<sub>max</sub> from approximately 2.7 to 3.7 hours for pioglitazone and from approximately 2.5 to 3.6 hours for metformin.</p>

<b>Title of Study:</b>						
An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetic Profile of Pioglitazone and Metformin when Administered as a Combination Product						
<b>Effect of Food on the Pharmacokinetic Parameters of Serum Pioglitazone and Metformin</b>						
Parameter (units)	N	Treatment	LS Mean	Test/Reference	LS Mean Ratio (%) (a)	90% CI of Ratio (%)
<b>Pioglitazone - Formulation</b>						
AUC(0-tq) (hr·ng/mL) (b)	28	A	4760.0	B/A	112.8	(102.1, 124.7)
		B	5370.7			
AUC(0-inf) (hr·ng/mL) (b)	27	A	5289.4	B/A	111.0	(100.6, 122.4)
		B	5868.8			
Cmax (ng/mL) (b)	28	A	531.8	B/A	104.5	(92.8, 117.7)
		B	556.0			
<b>Pioglitazone - Formulation</b>						
AUC(0-tq) (hr·ng/mL) (b)	26	C	4815.7	D/C	102.0	(93.2, 111.7)
		D	4914.1			
AUC(0-inf) (hr·ng/mL) (b)	22	C	5735.0	D/C	94.9	(86.9, 103.6)
		D	5440.7			
Cmax (ng/mL) (b)	26	C	476.8	D/C	107.9	(92.4, 126.0)
		D	514.5			
<b>Metformin - Formulation</b>						
AUC(0-tq) (hr·ng/mL) (b)	28	A	11580.7	B/A	86.9	(81.2, 93.0)
		B	10063.8			
AUC(0-inf) (hr·ng/mL) (b)	24	A	12017.9	B/A	87.1	(80.9, 93.8)
		B	10472.6			
Cmax (ng/mL) (b)	28	A	1781.8	B/A	71.9	(65.4, 79.1)
		B	1281.3			
<b>Metformin - Formulation</b>						
AUC(0-tq) (hr·ng/mL) (b)	27	C	11884.5	D/C	86.7	(78.7, 95.4)
		D	10299.9			
AUC(0-inf) (hr·ng/mL) (b)	19	C	13251.5	D/C	78.8	(73.1, 85.0)
		D	10447.3			
Cmax (ng/mL) (b)	27	C	1804.9	D/C	70.0	(63.2, 77.6)
		D	1263.4			
Source: End-of-Test Tables 14.2.3 and 14.2.6.						
Treatment A: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination — tablet (during a fast).						
Treatment B: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination — tablet (with food).						
Treatment C: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination — tablet (during a fast).						
Treatment D: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination — tablet (with food).						
(a) Ratio is LS Mean of Treatment B/Treatment A or Treatment D/Treatment C.						
(b) Natural logarithms of AUC and Cmax were used in the ANOVA modeling.						

**Title of Study:**

An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetic Profile of Pioglitazone and Metformin when Administered as a Combination Product

**Safety Results:**

Twelve out of 28 subjects experienced 1 or more AEs during 1 or more treatment periods; 10 of these 12 subjects experienced 1 or more AEs that were considered possibly or probably related to study medication. The most frequent AEs were nausea (4 reports), abdominal pain, and loose stools (3 reports each). None of the AEs were considered definitely related to study drug and all AEs were mild in severity.

Overall, the incidence of AEs was similar during administration of both pioglitazone/metformin fixed-dose combination tablets under fasting or fed conditions (Treatment A: 3/28, 10.7%; Treatment B: 4/28, 14.3%; Treatment C: 4/27, 14.8%; Treatment D: 5/28, 17.9%). No SAEs were reported and no deaths occurred during the study.

No clinically significant abnormal laboratory values, changes in vital signs, ECGs, or physical examination findings were reported in the study.

**AEs in 2 or More Subjects in Any Treatment Group**

System Organ Class Preferred Term (a)	Treatment							
	A N=28		B N=28		C N=27		D N=28	
	n	%	n	%	n	%	n	%
Any adverse event	3	(10.7)	4	(14.3)	4	(14.8)	5	(17.9)
<b>Gastrointestinal Disorders</b>								
Abdominal pain	0	(0.0)	2	(7.1)	0	(0.0)	1	(3.6)
Loose stools	1	(3.6)	2	(7.1)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	2	(7.1)	1	(3.7)	1	(3.6)

Source: End-of-text Tables 14.3.1.2.

Treatment A: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination tablet (during a fast).

Treatment B: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination tablet (with food).

Treatment C: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination tablet (during a fast).

Treatment D: Pioglitazone 15 mg/metformin 850 mg fixed-dose combination tablet (with food).

(a) A subject who reported 2 or more AEs within the same preferred term was counted only once for that term.

**Title of Study:**

An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetic Profile of Pioglitazone and Metformin when Administered as a Combination Product

**CONCLUSIONS:**

The magnitude and the direction of the food-effect responses observed in the present study for the fixed-dose combination tablets were similar to those reported for marketed ACTOS (pioglitazone) and GLUCOPHAGE (metformin) tablets. As has been demonstrated in studies involving coadministration of the separate commercial pioglitazone and metformin tablets, both the — fixed-dose combination tablets were well tolerated.

These conclusions are based on the following findings:

- For the — tablet, the 90% CIs of the LS mean ratios (fed/fasted) for AUC(0-t<sub>lq</sub>c), AUC(0-inf), and C<sub>max</sub> for pioglitazone were all within the (80%, 125%) range. The 90% CIs of the LS mean ratios for AUC(0-t<sub>lq</sub>c) and AUC(0-inf) for metformin were within the (80%, 125%) range, and the 90% CI of the LS mean ratio for C<sub>max</sub> was (65.4%, 79.1%). Percent decreases in the exposures to metformin based on point estimate values were 13%, 13%, and 28% for AUC(0-t<sub>lq</sub>c), AUC(0-inf), and C<sub>max</sub>, respectively.
- For the — tablet, the 90% CIs of the LS mean ratios (fed/fasted) for AUC(0-t<sub>lq</sub>c) and AUC(0-inf) for pioglitazone were within the (80%, 125%) range, and the 90% CI for C<sub>max</sub> was (92.4%, 126.0%). The 90% CIs for AUC(0-t<sub>lq</sub>c), AUC(0-inf), and C<sub>max</sub> for metformin were not within the (80%, 125%) range. Percent decreases in the exposures to metformin based on point estimate values were 13%, 21%, and 30% for AUC(0-t<sub>lq</sub>c), AUC(0-inf), and C<sub>max</sub>, respectively.
- The incidence of AEs was low in all treatment groups and there were no clinically significant changes in clinical laboratory results, vital signs, or physical examination results during the study.

**Date of Report:**

24 August 2004

C OCPB Filing Memo

5.1.1 Office of Clinical Pharmacology and Biopharmaceutics				
6 New Drug Application Filing and Review Form				
6.1.1.1 General Information About the Submission				
	Information		Information	
NDA Number	21-842	Brand Name	Actoplusmet™	
OCPB Division (I, II, III)	II	Generic Name	Pioglitazone/metformin	
Medical Division	DMEDP	Drug Class	Thiazolidinedione/sulphonylurea	
OCPB Reviewer	Jayabharathi Vaidyanathan, Ph.D.	Indication(s)	Type 2 diabetes	
OCPB Team Leader	Hae-Young Ahn, Ph.D.	Dosage Form	15 mg/ 500mg; 15 mg/ 850 mg tablets	
		Dosing Regimen	QD	
Date of Submission	10/29//04	Route of Administration	Oral	
Estimated Due Date of OCPB Review	6/29/05	Sponsor	Takeda	
PDUFA Due Date	8/29/05	Priority Classification	Standard	
6.1.1.2 Division Due Date	8/1//05			
6.1.1.2.1.1.1 Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
6.2 Healthy Volunteers-				
single dose:				
multiple dose:				
6.2.1 Patients-				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	2	2	Actoplusmet vs. individual components
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>	X	1	1	
<b>Dissolution:</b>	X			Dissolution profile provided at only one media and speed.
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		3	3	
6.2.1.1.1.1				
6.2.1.1.1.2 Filability and QBR comments				
6.2.1.2	"X" if yes	6.2.1.2.1.1.1.1.1.1 Comments		
6.2.1.3 Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable)		
6.2.1.4 Comments sent to firm ?		<ul style="list-style-type: none"> <li>Please provide dissolution profiles in three different pH for three batches (12 tablets/batch) for each combination tablet strength.</li> </ul>		
6.2.1.5				
<b>QBR questions (key issues to be considered)</b>	<ol style="list-style-type: none"> <li>Does food alter the bioavailability of actoplusmet?</li> <li>Is the combination formulation of pioglitazone and metformin (15 mg/500 mg and 15 mg/850 mg) bioequivalent to individual commercially available tablets?</li> <li>Have the analytical methods been sufficiently validated?</li> </ol>			

Other comments or information not included above	<p>Since no clinical trial was conducted with the combination tablet strength proposed in this NDA submission, it is desirable to conduct DSI inspection on the pivotal BE studies.</p> <p><u>Protocol: 01-03-TL-OPIMET-004</u>  Title of study: An open-label, randomized, 3-period crossover study to determine the bioequivalency of pioglitazone 15 mg and metformin 500 mg when administered as commercial tablets and as a combination product</p> <p><u>Protocol: 01-03-TL-OPIMET-005</u>  Title of study: An open-label, randomized, 3-period crossover study to determine the bioequivalency of pioglitazone 15 mg and metformin 850 mg when administered as commercial tablets and as a combination product</p> <p><u>Clinical site:</u> _____  <u>Analytical site:</u> _____</p>
Primary reviewer Signature and Date	Jaya bharathi Vaidyanathan, Ph.D.
Secondary reviewer Signature and Date	Hae-Young Ahn, Ph.D.

Background:

On October 29, 2004, Takeda submitted NDA 21-842 for pioglitazone/metformin tablets mg for the treatment of type 2 diabetes. Two doses of the pioglitazone/metformin fixed-dose tablet (15 mg/500 mg and 15 mg/850 mg) are proposed. Tablets used in clinical studies were identical in composition to those intended for commercial use. The batch size of pilot scale production used in clinical studies was \_\_\_\_\_ tablets and \_\_\_\_\_ tablets for the 15 mg/metformin 500 mg and 15 mg/metformin 850 mg respectively which was 10% of the commercial batch size. Three studies have been submitted under the clinical pharmacology section as follows.

- An open-label, randomized, crossover, food-effect study was conducted to determine the effect of food on the exposure to pioglitazone and metformin after administration of the pioglitazone 15 mg/metformin 850 mg fixed-dose combination tablet.
- Open-label, randomized, crossover, bioequivalence study to assess the bioequivalence of the pioglitazone 15 mg/metformin 500 mg fixed-dose combination tablets to that of separate pioglitazone 15 mg and metformin 500 mg tablets.
- Open-label, randomized, crossover, bioequivalence study to assess the bioequivalence of the pioglitazone 15 mg/metformin 850 mg fixed-dose combination tablets to that of separate pioglitazone 15 mg and metformin 850 mg tablets.

Findings:

Food-Effect study: Based on AUC and Cmax values, there was an absence of food-effect on total and peak exposure to pioglitazone and on the total exposure of metformin. There was a decrease in Cmax of metformin in presence of food by 28%. Administration with food resulted in prolongation of Tmax from approximately 1.6 h to 3.5 h for pioglitazone and from approximately 2.4 to 3.2 h for metformin.

Bioequivalence studies: Based on AUC and Cmax values, the rate and extent of absorption of pioglitazone and metformin following administration of the pioglitazone 15 mg/metformin 500 mg and pioglitazone 15 mg/metformin 850 mg dose of combination tablets were bioequivalent to that observed following co-administration of the separate commercial pioglitazone 15 mg + metformin 500 mg and pioglitazone 15 mg + metformin 850 mg tablets respectively.

Proposed dissolution method:

Medium: — buffer, pH 2.5, 37C, 900 ml

Apparatus: Apparatus 2 (paddles)

Speed: 50 rpm

Tolerance specifications: NLT — (Q) of the label claim of pioglitazone dissolved in 30 min.

NLT — (Q) of the label claim of metformin dissolved in 30 min

**Conclusions:** The Clinical Pharmacology section of this application is filable.

**APPEARS THIS WAY  
ON ORIGINAL**

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this page is the manifestation of the electronic signature.**  
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/s/

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Jayabharathi Vaidyanathan  
8/23/2005 11:36:44 AM  
PHARMACOLOGIST

Hae-Young Ahn  
8/23/2005 01:24:11 PM  
BIOPHARMACEUTICS