CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-925

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW-2

NDA: 21-925	Submission Date(s): 5/20/06
Brand Name	DUETACT
Generic Name	Pioglitazone Hydrochloride and glimepiride Tablets
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCP Division	DCP-2
ORM Division	Division of Metabolic and Endocrine Products
Sponsor	Takeda
Submission Type	505 (b) (2)
Formulation; Strength(s)	30 mg/ 2 mg; 30 mg/ 4 mg ; [redacted] Oral tablets
Indication	Treatment of Type 2 Diabetes Mellitus

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I Executive Summary

The concomitant use of pioglitazone and glimepiride is approved under NDA 21-073. NDA 21-925 does not contain any new clinical trials with the fixed dose combination tablets. The original submission to the NDA 21-925 included bioequivalence studies for the combination tablet strengths (30 mg/2 mg; 30 mg/4 mg pioglitazone/glimepiride respectively) comparing to the commercial tablets given concomitantly and a food effect study. Results from these studies demonstrated that 30 mg/2 mg and 30 mg/4 mg were bioequivalent to the commercially available Actos and Amaryl tablets given concomitantly.

Takeda has submitted an NDA amendment for Duetact combination tablets on 4/20/06. This NDA amendment includes another bioequivalence study

An age-associated decrease in dissolution of pioglitazone was found from the combination tablets of all combinations. Therefore, the sponsor is proposing to change the packaging to bottles with desiccant and to tighten the dissolution specifications for pioglitazone for all the combination tablets, 30 mg/2 mg, 30 mg/4 mg

A Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the information provided in the NDA 21-925 for Duetact tablets. Recommendation may be sent as appropriate.

The results indicate that with increase in age of the tablets there is a significant reduction in the bioavailability of pioglitazone from the combination tablet. However the tightening of the dissolution specifications does not address the concern whether the tablets that are close to expiry date and meet the sponsor's newly proposed specifications will be bioequivalent to the freshly manufactured tablets.

B Phase 4 Commitments

None.

C Summary of CPB Findings

II QBR

A General Attributes

Not applicable. See clinical pharmacology review of original NDA.

B General Clinical Pharmacology

Not applicable. See clinical pharmacology review of original NDA.

C Intrinsic Factors

Not applicable. See clinical pharmacology review of original NDA.

D Extrinsic Factors

Not applicable. See clinical pharmacology review of original NDA.

4 Page(s) Withheld

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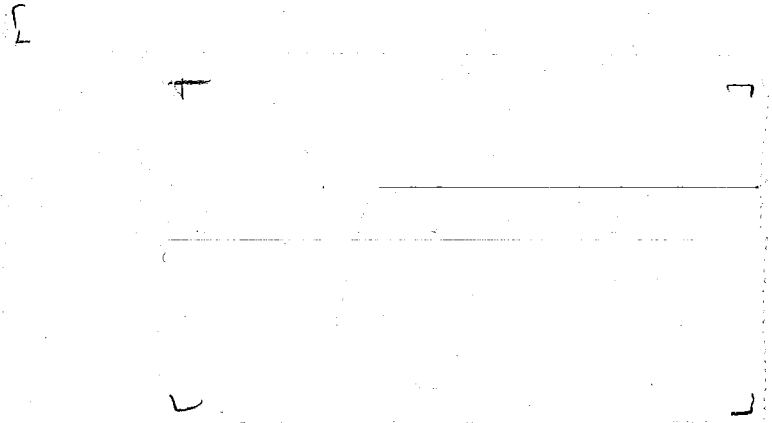

Similar dissolution profiles trends were observed with the strengths of pioglitazone/glimepiride (30 mg/2 mg and 30 mg/4 mg). In response to these data, the proposed commercial packaging for the tablets is being amended by the sponsor too include only the use of bottles with desiccant. In addition the dissolution specification acceptance criteria have been tightened to not less than of the drug to be released in 15 min for pioglitazone.

Dissolution specification for pioglitazone

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

Proposed method:
Specifications: NLT (Q) of the label claim of pioglitazone dissolved in 15 min.
There is no change in the dissolution medium and method. Since the dissolution is a stability issue please refer to chemistry review for details on stability.

Conclusions:

- The first BE studies submitted with the original NDA used about tablets for the all combinations (30 mg/2 mg, 30 mg/4 mg .
- The second BE study was conducted later using the same batch of the (about old at the time of study). Using tablets, the combination was lower than individual tablets in pioglitazone in AUC and Cmax. It is most likely that the strengths will have the similar reductions in BA with time since all the combinations were in blister packages and similar age-related decrease in dissolution was observed.
- The sponsor claims that it is due to moisture trapped within the Therefore, they propose the packaging change and tightening the dissolution spec (Q= in 30 min to Q= in 15 min) for all the tablet strengths.
- However, since there is no link between dissolution profiles and bioavailability, there is no information to address whether tablets meeting the proposed new

dissolution specification at the close expiry date will be bioequivalent to freshly manufactured tablets.

F Analytical

Not applicable. See clinical pharmacology review of original NDA.

III Labeling Recommendations

Labeling recommendations will be done pending clinical decision.

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/s/

Jayabharathi Vaidyanathan
7/11/2006 08:46:53 AM
BIOPHARMACEUTICS

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7/11/2006 09:31:04 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-925	Submission Date(s): 6/28/05
Brand Name	[redacted]
Generic Name	Pioglitazone Hydrochloride and glimepiride Tablets
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCP Division	DCP-2
ORM Division	Division of Metabolic and Endocrine Products
Sponsor	Takeda
Submission Type	505 (b) (2)
Formulation; Strength(s)	30 mg/ 2 mg; 30 mg/ 4 mg ; [redacted] 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 glimepiride.

The efficacy and safety of the concomitant use of pioglitazone and glimepiride has previously been evaluated in 2 controlled clinical trials (NDA 21-073). Concomitant administration of the separate commercial pioglitazone and glimepiride 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. glimepiride is available in 2, 4, and 8 mg tablets and is approved for individualized treatment up to a maximum daily dose of 8 mg in adults. Typically glimepiride is administered once with meals while pioglitazone can be administered regardless of meals.

To aid in the approval of this application the sponsor has submitted [redacted] bioequivalence studies and 1 food effect study. 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 glimepiride existing under the approved NDA.

A Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the information provided in the NDA 21-925 for [redacted] tablets and finds it acceptable. Recommendations and labeling comments should be sent to the sponsor as appropriate.

Jaya Vaidyanathan, Ph.D.
OCPB/DCPB2

A clinical pharmacology briefing was held for NDA 21-925 on April 7, 2006; the attendees were H. Malinowski, H. Ahn, A. Rahman, J. Vaidyanathan and R. Misbin.

FT signed by Hae-Young Ahn, Ph.D., Team Leader 4/ 7 /06

B Phase 4 Commitments

None.

C Summary of CPB Findings

The summary of results from the clinical pharmacology studies is provided below.

Bioequivalence:

Bioequivalence studies were conducted for all the [redacted] strengths of combination tablet. Results indicate that the pioglitazone and glimepiride from [redacted] 30 mg/2 mg and 30 mg/4 mg tablets were bioequivalent to Actos and Amaryl commercial tablets given concomitantly. [redacted]

Food effect:

Dissolution:

The proposed method is appropriate for [redacted]. The method and specifications are:

Pioglitazone:
Medium: Buffer, pH 2.5, 37°C, 900 ml
Apparatus: Type 2 (paddles)
Speed: 50 rpm
Specifications: NLT [redacted](Q) of the label claim of pioglitazone dissolved in 30 min.

Glimepiride:
Medium: Buffer, pH 6.8 buffer containing 0.2% SDS, 37°C, 900 ml
Apparatus: Type 2 (paddles)
Speed: 75rpm
Specifications: NLT [redacted](Q) of the label claim of glimepiride dissolved in 15 min.

II QBR

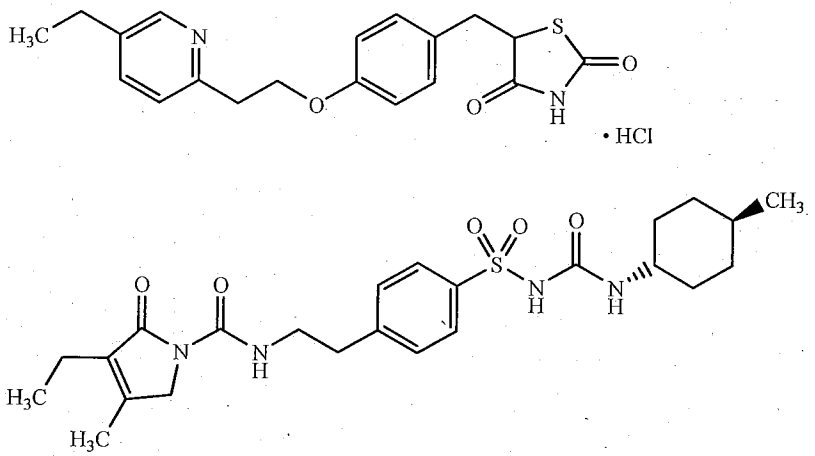
A General Attributes

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

contains 2 oral antihyperglycemic drugs used in type 2 diabetes; pioglitazone hydrochloride and glimepiride. Pioglitazone ([(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride) (Figure 1) belongs to thiazolidinedione class. 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 $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90.

Glimepiride 1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl] sulfonyl]-3-(*trans*-4-methylcyclohexyl)-urea belongs to the sulfonylurea class of oral anti-diabetic agents. The molecule is the trans-isomer with respect to the cyclohexyl substituents. Glimepiride is a white to yellowish-white crystalline, practically odorless powder that has a molecular formula of $C_{24}H_{34}N_4O_5S$ and a molecular weight of 490.62

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



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

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 glimepiride, a member of the sulfonylurea class. This is a 505 (b) (2) application. The proposed indication for the combination tablet is the same as that for the individual drugs.

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

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin.

[redacted] is indicated as an adjunct to diet and exercise as a once-daily combination therapy to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and a sulfonylurea or whose diabetes is not adequately controlled with a sulfonylurea alone.

What is the proposed dose and dosage form?

Based on the package insert, selection of the starting dose of [redacted] should be based on the patient's current regimen of pioglitazone and/or sulfonylurea. Those patients who may be more sensitive to antihyperglycemic drugs should be monitored carefully during dose adjustment. It is recommended that a single dose of [redacted] be administered orally once daily with the first main meal.

Starting dose for patients currently on glimepiride monotherapy
Based on the usual starting dose of pioglitazone (up to 30 mg daily), [redacted] may be initiated at 30 mg/2 mg or 30 mg/4 mg tablet strengths once daily, and adjusted after assessing adequacy of therapeutic response.

Starting dose for patients currently on pioglitazone monotherapy
Based on the usual starting doses of glimepiride (up to 2 mg once daily), [redacted] may be initiated at 30 mg/2 mg once daily, and adjusted after assessing adequacy of therapeutic response.

Starting dose for patients switching from combination therapy of pioglitazone plus glimepiride as separate tablets
[redacted] may be initiated with 30 mg/2 mg, 30 mg/4 mg [redacted] tablet strengths based on the dose of pioglitazone and glimepiride already being taken.

Starting dose for patients currently on a different sulfonylurea monotherapy or switching from combination therapy of pioglitazone plus a different sulfonylurea (e.g. glyburide, glipizide, chlorpropamide, tolbutamide, acetohexamide)
No exact dosage relationship exists between glimepiride and the other sulfonylurea agents. Therefore, based on the maximum starting dose of 2 mg glimepiride,

[redacted] should be limited initially to a starting dose of 30 mg/2 mg once daily, and adjusted after assessing adequacy of therapeutic response.

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. [redacted] doses of the pioglitazone/glimepiride fixed dose tablet (30 mg/2 mg, [redacted] were evaluated in [redacted] bioequivalence studies [redacted].

Does this combination drug prolong QT or QTc interval?

The sponsor has not submitted any study determining the effect of [redacted] on cardiac repolarization. However, both Actos® (pioglitazone) and Amaryl® (glimepiride) are approved drugs in the US and no reports of any adverse effects of these drugs due to their effect on cardiac repolarization has been reported thus far.

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 glimepiride?

Specific pharmacokinetic drug interaction studies with [redacted] have not been performed, although such studies have been conducted with the individual pioglitazone and glimepiride components. The proposed label has the following statement:

"Co-administration of pioglitazone (45 mg) and a sulfonylurea (5 mg glipizide) administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide". Glimepiride and glipizide [redacted] have similar metabolic pathways ([redacted] by CYP2C9); therefore, drug-drug interaction between pioglitazone and glimepiride is [redacted] unlikely.

E General Biopharmaceutics

What is the formulation of [redacted] tablets?

[redacted] tablets are a combination product containing either 30 mg + 2 mg, 30 mg + 4 mg or [redacted] of pioglitazone hydrochloride (as the free base) and glimepiride respectively. The composition of the tablets used in clinical pharmacology studies are shown in Table 1. The tablets used in clinical pharmacology studies are identical in composition to those intended for commercial distribution, with the exception that the commercial tablets will be debossed with the dose strength on one tablet face and 4833G on the other.

Table 1: Composition of [redacted] tablets

Component	Reference to Quality Standard	Function	Formula (mg/tablet) 30 mg + 2 mg	30 mg + 4 mg
Pioglitazone Hydrochloride Layer				
Pioglitazone hydrochloride (as Pioglitazone)	In-house standard			
[redacted]	USP			
[redacted]	NF			
[redacted]	NF			
[redacted]	NF			
[redacted]	USP			
Glimepiride Layer				
Glimepiride	In-house standard			
[redacted]	NF			
[redacted]	NF			
[redacted]	NF			
[redacted]	NF			
[redacted]	NF			
[redacted]	NF			
[redacted]	USP			
Total tablet weight (g)	[redacted]			

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Is the dissolution method appropriate for [redacted] tablets?

The dissolution method and specification proposed by the sponsor is shown in Table 2.

Table 2: Dissolution specification for [redacted]

Dissolution (%)	
Pioglitazone HCl	Not less than [redacted] (Q) of the label claim of $C_{19}H_{20}N_2O_3S$ dissolved in 30 min
Glimepiride	Not less than [redacted] (Q) of the label claim of $C_{24}H_{34}N_4O_5S$ dissolved in 15 min
Test Method:	
Medium	Pioglitazone HCl: 900 mL of pH 2.0 potassium chloride buffer Glimepiride: 900 mL of pH 6.8 sodium phosphate buffer containing 0.2% SDS.
Apparatus	Pioglitazone HCl: USP apparatus 2, 50 rpm Glimepiride: USP apparatus 2, 75 rpm

Source: Section 3.2.P.5.3 of Module 3.

Selection of dissolution medium:

The dissolution condition used for pioglitazone was the same as that used for the approved commercial Actos tablet:
Dissolution medium: 900 ml; pH 2.0 potassium chloride buffer
Apparatus: USP apparatus 2
Speed: 50 rpm.

The dissolution conditions approved for Amaryl (USP apparatus 2, 50 rpm, 900 ml pH 7.8 sodium phosphate buffer) were used during initial formulation development. After completion of formulation development, the dissolution method for glimepiride was altered to provide robust and discriminating method for use in specification testing for the proposed commercial combination tablet. The sponsor used USP apparatus 2, 75 rpm, 37C and 900 ml of pH 6.8 sodium phosphate buffer containing 0.2% SDS. The sponsor provided justification for the inclusion of surfactant in the media as follows:

The sponsor generated dissolution profiles for gliempiride in pH 6.8 phosphate buffer containing 0.05%, 0.1% and 0.2% SDS at paddle speed of 75 rpm (Table 3).

Table 3: Dissolution profiles for glimepiride in [redacted] tablets (30/2 mg; 30/4 mg, [redacted] with various SDS concentration media.

Tablets strength	SDS concentration	Dissolution (%), (range)			
		0 min	10 min	15 min	20 min
30mg + 2mg (Z593101)*	0.05%	0.0	58.1 (57.2-58.6)	61.7 (61.1-62.1)	64.0 (62.5-65.3)
	0.1%	0.0	84.1 (83.0-84.8)	89.3 (87.9-90.1)	92.6 (91.0-93.7)
	0.2%	0.0	89.7 (86.9-92.5)	93.7 (91.7-96.4)	95.9 (92.4-100.9)
30mg + 4mg (Z593201)*	0.05%	0.0	45.3 (44.9-45.7)	46.9 (45.8-47.6)	46.8 (46.4-47.1)
	0.1%	0.0	74.1 (72.5-75.7)	79.8 (78.8-80.9)	82.4 (81.1-83.0)
	0.2%	0.0	90.4 (88.8-92.0)	96.1 (94.7-97.7)	98.5 (96.1-100.2)
[redacted]					

* ( ): Lot No.

As seen from the table, use of SDS < 0.2% resulted in release of about [redacted] by 20 min for the combination tablets containing glimepiride 4 mg. Use of 0.2% SDS resulted in over [redacted] of glimepiride dissolution by 15 min. Therefore use of 0.2% SDS is acceptable and has adequate discriminatory power. The proposed dissolution specification for pioglitazone and glimepiride is acceptable.

Bioequivalence Study:

1) Is the combination tablet formulation of pioglitazone and glimepiride (30 mg/2 mg) bioequivalent to concomitant dosing of pioglitazone 30 mg and glimepiride 2 mg (30 mg + 2 mg) commercial tablets in healthy subjects?

An open-label, randomized, 2-treatment, 4-period, 2 sequence, crossover replicate study was conducted in healthy subjects (35 enrolled; 32 completed) under fasting conditions. A washout of 7 days separated the 4 single doses. Blood samples were collected in each period at specified time points up to 72 h post dose. The two treatments were:
Treatment A: pioglitazone 30 mg/glimepiride 2 mg fixed dose combination tablet
Treatment B: 1 pioglitazone 30 mg commercial tablet administered concomitantly with 1 glimepiride 2 mg commercial tablet.

The AUCinf and Cmax of pioglitazone after administration of [redacted] were bioequivalent to that observed after concomitant administration of the separate

commercial pioglitazone and glimepiride tablets. The 90% CI of the least square means of both AUCinf and Cmax were within the 80% to 125% interval. However, the 90% CI of AUC0-t fell slightly below the prespecified limit (78.5-88.3), Table 4. The Tmax was similar for the two treatments.

Table 4: Comparison of geometric least square means of pioglitazone Cmax, AUC0-t, AUCinf for test and reference products under fasting conditions

Pioglitazone	AUC0-t	AUCinf	Cmax
Test product Mean (N=65) (range)	8758.42 (3016-23229)	9896 (3241-23673)	1006.71 (352-2140)
Reference product mean (N=67) (range)	10333.10 (3605-22052)	11099.06 (1011-23629)	1009.72 (292-2050)
% Ratio	83.27	89.04	96.20
90% CI	78.50-88.33	81.33-97.49	88.62-104.0

The systemic exposure of glimepiride after administration of [redacted] was bioequivalent to that observed after concomitant administration of the separate commercial pioglitazone and glimepiride tablets. The 90% CI of the least square means of AUC0-t, AUCinf and Cmax were within the 80% to 125% interval (Table 5).

Table 5: Comparison of geometric least square means of glimepiride Cmax, AUC0-t, AUCinf for test and reference products under fasting conditions

Glimepiride	AUC0-t	AUCinf	Cmax
Test product Mean (N=65) (range)	844.27 (330-1996)	884.07 (341-2011)	167.1 (57-319)
Reference product mean (N=65) (range)	838.89 (346-1813)	858.66 (355-1824)	186.92 (74-320)
% Ratio	100.0	102.4	88.60
90% CI	95.4-104.7	97.8-107.2	82.5-95.20

2) Is the combination tablet formulation of pioglitazone and glimepiride (30 mg/4 mg) bioequivalent to concomitant dosing of pioglitazone 30 mg and glimepiride 4 mg (30 mg + 4 mg) commercial tablets in healthy subjects?

An open-label, randomized, 2-treatment, 4-period, 2 sequence, crossover replicate study was conducted in healthy subjects (38 enrolled; 36 completed) under fasting conditions. A washout of 7 days separated the 4 single doses. Blood samples were collected in each period at specified time points up to 72 h post dose. The two treatments were:
Treatment A: pioglitazone 30 mg/glimepiride 4 mg fixed dose combination tablet
Treatment B: 1 pioglitazone 30 mg commercial tablet administered concomitantly with 1 glimepiride 4 mg commercial tablet.

The AUCinf and Cmax of pioglitazone after administration of [redacted] were bioequivalent to that observed after concomitant administration of the separate commercial pioglitazone and glimepiride tablets. The 90% CI of the least square means of both AUCinf and Cmax were within the 80% to 125% interval. The Tmax was similar for the two treatments. The systemic exposure of glimepiride after administration of [redacted] was bioequivalent to that observed after concomitant administration of the separate commercial pioglitazone and glimepiride tablets. The 90% CI of the least square means of AUC0-t, AUCinf and Cmax were within the 80% to 125% interval (Table 6).

Table 6: Pharmacokinetic analysis results for serum Pioglitazone and Gimepiride.

	AUC0-t	AUCinf	Cmax
Pioglitazone			
Test product Mean (N=71) (range)	9592.99 (3486-15497)	10421.89 (4531-18444)	1094.56 (341-1760)
Reference product mean (N=71) (range)	10841.32 (4678-22970)	11800.83 (4915-23512)	1166.93 (629-1960)
% Ratio	88.19	87.74	92.80
90% CI	83.62-93.01	83.46-92.25	87.24-98.72
Glimepiride			
Test product Mean (N=66) (range)	2270.52 (711-16156)	2433.56 (735-19874)	307.89 (120-617)
Reference product mean (N=68) (range)	2272.21 (789-17555)	2369.54 (813-21006)	356.48 (130-826)
% Ratio	100.38	102.07	85.77
90% CI	95.01-106.04	96.66-107.79	80.31-91.58

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F Analytical

Have the analytical methods been sufficiently validated?

Yes.

The concentrations of unchanged pioglitazone in human serum were measured by validated liquid chromatography/tandem mass spectrometry methods, while high performance liquid chromatographic method was used for glimepiride. The validated concentration ranges were ——— ng/ml for pioglitazone and ——— ng/ml for glimepiride. The mean intra- and inter- assay precision of the QC samples were ——— at lower limit of quantitation) for both pioglitazone (Table 11 and 12) and glimepiride (Table 13 and 14).

Table 11: Intra-Assay quality control sample statistics for pioglitazone

Nominal Concentration	2000	1000	75.0	2000	1000	75.0	2000	1000	74.9
Average Concentration	2215	987	74.3	2207	1030	73.6	2166	977	74.0
Standard Deviation	63.6	40.0	2.45	56.8	18.3	0.881	112	30.0	1.30
Precision (%)	2.9%	4.1%	3.3%	2.6%	1.8%	1.2%	5.2%	3.1%	1.8%
Accuracy (%)	110.8%	98.7%	99.1%	110.3%	103.0%	98.1%	108.3%	97.7%	98.8%
N	6	6	6	6	6	6	6	6	6

Table 12: Inter-Assay quality control sample statistics for pioglitazone

Nominal Concentrations	2000	1000	74.9
Average Concentrations	2079	938	75.5
SD	151	51.9	5.39
Precision (%)	7.3%	5.3%	7.1%
Accuracy (%)	103.9%	98.8%	100.3%
N	46	46	46

Table 13: Intra-Assay quality control sample statistics for glimepiride

Nominal conc.	1.00	3.00	250	400 ng/ml
Mean	0.95	2.90	246	385
SD	0.03	0.058	5.19	5.43
Precision CV%	3.13	2.0	2.13	1.4
N	18	18	18	18

Table 14: Inter-Assay quality control sample statistics for glimepiride

Nominal concentration	1.00	3.00	250	400 ng/ml
Mean	0.955	2.99	253	395
S.D.	0.0869	0.141	10.4	15
%CV	9.1	4.7	4.1	3.8
Theoretical	95.5	99.7	101.2	98.8
%Bias	-4.5	-0.3	1.2	-1.3
n	18	30	30	30

III Labeling Recommendations

Pharmacokinetics and Drug Metabolism

Absorption and Bioavailability:

Bioequivalence studies were conducted following a single dose of the 30 mg/2 mg, 30 mg/4 mg tablets and concomitant administration of Actos (30 mg and (2 mg or 4 mg) under fasting conditions in healthy subjects.

The area under the curve (AUC) and maximum concentration (Cmax) of both pioglitazone and glimepiride component from 30 mg/2 mg and 30 mg/4 mg were bioequivalent to Actos 30 mg concomitantly administered with (2 mg or 4 mg respectively).

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B Individual Study Synopsis

1) Bioequivalence study

Title of Study: An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 2 mg When Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet	
Name of Sponsor: Takeda Global Research & Development Center, Inc. (TGRD)	
Name of Finished Product: AD-4833SU (pioglitazone 30 mg/glimepiride 2 mg fixed-dose combination product)	
Investigator: [redacted]	**Study Center:** [redacted]
Publication Based in This Study: None	
Study Period: 9 October 2004 to 2 November 2004	**Phase of Development:** Phase 1
OBJECTIVES **Primary:** To determine the bioequivalence of pioglitazone and glimepiride when administered concomitantly as separate commercial tablets and as a fixed-dose combination tablet. **Secondary:** To evaluate the safety of pioglitazone and glimepiride when administered concomitantly as separate commercial tablets and as a fixed-dose combination tablet.	
METHODS This was a single-center, open-label, randomized, 2-treatment, 4-period, crossover, replicate-design study. Healthy subjects were randomly assigned to 1 of 2 treatment sequences in which they received a single oral dose of each treatment: AD-4833SU (pioglitazone 30 mg/glimepiride 2 mg fixed-dose combination product) and the concomitant administration of the commercially available pioglitazone 30 mg and glimepiride 2 mg tablets. The sequences of treatments were such that upon completion of the study each subject had received both treatments twice. During each period, blood samples were collected at specified time points up to 72 hours posttreatment for the measurement of serum pioglitazone and glimepiride concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations. **Number of Subjects (Planned and Analyzed):** Planned: 36 subjects, 18 subjects per sequence. Pharmacokinetic parameters were calculated for all 35 subjects that enrolled. Data obtained from 34 subjects were sufficient to facilitate calculation of the pharmacokinetic parameters in at least 1 period for both treatments and were included in the statistical analyses. All 35 subjects were included in the safety evaluation.	
Diagnosis and Main Criteria for Inclusion: To qualify for study participation, subjects must have been healthy male subjects or nonpregnant, nonlactating female subjects aged 18 to 55 years, inclusive; been willing to sign the informed consent form; had clinical laboratory results within the reference ranges or that were acceptable to the investigator;	

Title of Study:

An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 2 mg When Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

weighed at least 110 pounds and had a body mass index (BMI) ≤30 kg/m^2; and had a negative hepatitis panel and human immunodeficiency virus (HIV) antibody test at Screening.

Test Product, Dose, Mode of Administration, and Lot Number:

Drug	Dose	Form	Route	Lot No.
AD-4833SU	pioglitazone 30 mg/ glimepiride 2 mg	fixed-dose combination product	oral	Z5931021

Duration of Treatment:

The total duration of the study for a subject who completed all treatments was approximately 26 days, including Baseline (Day -1). A washout interval of 7 days separated the 4 single doses.

Reference Therapy, Dose, Mode of Administration, and Lot Number:

Drug	Dose	Form	Route	Lot No.
ACTOS®	pioglitazone 30 mg	commercial tablet	oral	A10330
AMARYL®	glimepiride 2 mg	commercial tablet	oral	1075415

Criteria for Evaluation:

Pharmacokinetic:

For each subject, the following pharmacokinetic parameters were calculated for each study period from serum concentrations of unchanged glimepiride and pioglitazone according to the model-independent approach: area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration (AUC[0-tlqc]), area under the serum concentration-time curve from time 0 to infinity (AUC[0-inf]), maximum observed serum concentration (Cmax), the time at which Cmax occurred (Tmax), terminal phase elimination rate constant (λz), terminal elimination half-life (T1/2), and apparent oral clearance (CL/F).

Safety:

Safety variables included AEs, clinical laboratory test results, vital signs, ECGs, and physical examinations.

Statistical Methods:

Pharmacokinetic Measures:

Statistical analyses were performed on Tmax, λz, and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax for pioglitazone and glimepiride. The statistical model used in this replicate crossover study was based on the Food and Drug Administration (FDA) guidance entitled *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence*. The model included fixed effects for sequence, period, and treatment with different intrasubject variability for each treatment. Carryover effect was also explored by adding this factor into the aforementioned model.

Within the framework of these models, the 90% confidence intervals (CIs) for the ratio (test/reference) of the least-squares (LS) mean of AD-4833SU (Treatment A) relative to the LS mean of the concomitantly administered pioglitazone and glimepiride commercial tablets (Treatment B) were calculated for AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and glimepiride. The test treatment was considered bioequivalent to the reference treatment if the 90% CIs of these ratios were within 80% to 125%.

Title of Study:

An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 2 mg When Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

SUMMARY OF RESULTS

Subject Disposition:

A total of 35 healthy subjects (mean age of 31.3 years), including 22 male and 13 female subjects, were randomly assigned to treatment at 1 study site. Thirty-two subjects (91.4 %), including 19 male and 13 female subjects, completed the study. Three subjects discontinued the study early: 2 subjects withdrew voluntarily and 1 subject withdrew because of AEs.

Pharmacokinetic Results:

The systemic exposures to pioglitazone and glimepiride after administration of AD-4833SU were bioequivalent to exposures observed after concomitant administration of the separate commercial pioglitazone and glimepiride tablets. The 90% CIs of the LS mean ratios for AUC(0-inf) and Cmax of pioglitazone and AUC(0-inf), AUC(0-tlqc), and Cmax of glimepiride were within the 80% to 125% interval. The 90% CI of the LS mean ratio for AUC(0-tlqc) of pioglitazone fell slightly below the 80% to 125% interval, as the 90% CI for this parameter was (77.48%, 87.17%).

The LS mean and median Tmax values for pioglitazone were approximately 2 hours for both treatments, and the LS mean λz values were 0.079 1/hr after treatment with AD-4833SU and 0.068 1/hr after concomitant administration of the commercial tablets. The LS mean and median Tmax values for glimepiride were between 2 and 2.6 hours for both treatments. The LS mean λz values were 0.103 1/hr after treatment with AD-4833SU and 0.128 1/hr after concomitant administration of the commercial tablets.

Pharmacokinetic Analysis Results for Serum Pioglitazone and Glimepiride

Parameter (a) (units)	N	Treatment	LS Mean	Test/ Reference	LS Mean Ratio (%) (b)	90% CI of Ratio (%)
Pioglitazone						
AUC(0-tlqc) (hr·ng/mL)	34	A	8055.277	A/B	82.18	(77.48, 87.17)
		B	9801.961			
AUC(0-inf) (hr·ng/mL)	32	A	9464.891	A/B	84.40	(80.24, 88.79)
		B	11213.669			
Cmax (ng/mL)	34	A	890.4	A/B	95.01	(87.53, 103.12)
		B	937.2			
Glimepiride						
AUC(0-tlqc) (hr·ng/mL)	34	A	775.806	A/B	99.41	(95.08, 103.93)
		B	780.424			
AUC(0-inf) (hr·ng/mL)	34	A	806.725	A/B	101.14	(96.62, 105.86)
		B	797.660			
Cmax (ng/mL)	34	A	156.75	A/B	88.14	(82.06, 94.68)
		B	177.84			

Source: Tables 14.2.3 and 14.2.5.
Treatment A: AD-4833SU (pioglitazone 30 mg/glimepiride 2 mg fixed-dose combination product).
Treatment B: 1 pioglitazone 30 mg commercial tablet administered concomitantly with 1 glimepiride 2 mg commercial tablet.
(a) Natural logarithms of AUCs and Cmax were used in the ANOVA modeling.
(b) Ratio is LS mean of Treatment A/LS mean of Treatment B.

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Title of Study:

An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 2 mg When Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

Safety Results:

The overall incidence of AEs was similar after administration of both treatments. Twelve of 35 subjects experienced 1 or more AE after treatment with AD-4833SU, and 10 of 34 subjects experienced 1 or more AE after administration of the commercial tablets. Headache and dizziness were the only AEs experienced by more than 2 subjects in either treatment group. All AEs were considered mild in severity. No serious adverse events (SAEs) were reported, and no deaths occurred during this study. One subject discontinued the study because of AEs (mild facial lesions and mild dizziness). There were no clinically important abnormal laboratory, vital sign, ECG, or physical examination findings.

AEs Reported by 2 or More Subjects in Any Treatment Group

System Organ Class Preferred Term	Treatment A N=35 n (%)	Treatment B N=34 n (%)
Any AE	12 (34.3)	10 (29.4)
Gastrointestinal Disorders		
Diarrhea	2 (5.7)	0 (0.0)
Flatulence	2 (5.7)	2 (5.9)
Nervous System Disorders		
Dizziness	4 (11.4)	4 (11.8)
Headache	3 (8.6)	5 (14.7)
Paraesthesia	2 (5.7)	0 (0.0)
Respiratory , Thoracic and Mediastinal Disorders		
Cough	2 (5.7)	0 (0.0)

Source: Tables 14.3.1.2
Treatment A: AD-4833SU (pioglitazone 30 mg/glimepiride 2 mg fixed-dose combination product).
Treatment B: 1 pioglitazone 30 mg commercial tablet administered concomitantly with 1 glimepiride 2 mg commercial tablet.

CONCLUSIONS:

Systemic exposures to pioglitazone and glimepiride after single-dose administration of AD-4833SU (pioglitazone 30 mg/glimepiride 2 mg fixed-dose combination product) were bioequivalent to exposures observed after concomitant administration of the commercially available pioglitazone 30 mg and glimepiride 2 mg tablets. Both treatments were safe and well tolerated as administered in this study.

These conclusions are based on the following findings:

- For pioglitazone, the 90% CIs of the LS mean ratios for AUC(0-inf) and Cmax were within the 80% to 125% interval.
- For glimepiride, the 90% CIs of the LS mean ratios for AUC and Cmax were within the 80% to 125% interval.
- There were no SAEs, deaths, or clinically important abnormal laboratory, vital sign, ECG, or physical examination findings.

Date of Report:

30 March 2005

2) Bioequivalence study

Title of Study: An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 4 mg When Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet	
Name of Sponsor: Takeda Global Research & Development Center, Inc. (TGRD)	
Name of Finished Product: AD-4833SU (pioglitazone 30 mg/glimepiride 4 mg fixed-dose combination product)	
Investigator: [redacted]	**Study Center:** [redacted]
Publication (reference): None	
Study Period: 16 October 2004 to 16 November 2004	**Phase of Development:** Phase 1

OBJECTIVES

Primary:

To determine the bioequivalence of pioglitazone and glimepiride when administered concomitantly as separate commercial tablets and as a fixed-dose combination tablet.

Secondary:

To evaluate the safety of pioglitazone and glimepiride when administered concomitantly as separate commercial tablets and as a fixed-dose combination tablet.

METHODS

This was a single-center, open-label, randomized, 2-treatment, 4-period, crossover, replicate-design study. Healthy subjects were randomly assigned to 1 of 2 treatment sequences in which they received a single oral dose of each treatment: AD-4833SU (pioglitazone 30 mg/glimepiride 4 mg fixed-dose combination product) and the concomitant administration of the commercially available pioglitazone 30 mg and glimepiride 4 mg tablets. The sequences of treatments were such that upon completion of the study each subject had received both treatments twice. During each period, blood samples were collected at specified times up to 72 hours posttreatment for the measurement of serum pioglitazone and glimepiride concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.

Number of Subjects (Planned and Analyzed):

Planned: 38 subjects, 19 subjects per sequence.
Analyzed: Pharmacokinetics—37 subjects; Safety—38 subjects.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been healthy male subjects or nonpregnant, nonlactating female subjects aged 18 to 55 years, inclusive; been 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) ≤ 30 kg/m^2; and had a negative hepatitis panel and human immunodeficiency virus (HIV) antibody test at Screening.

Title of Study:

An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 4 mg When Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

Test Product, Dose, Mode of Administration, and Lot Number:

Drug	Dose	Form	Route	Lot No.
AD-4833SU	pioglitazone 30 mg/ glimepiride 4 mg	fixed-dose combination product	oral	Z5932021

Duration of Treatment:

The total duration of the study for a subject who completed all treatments was approximately 26 days, including Baseline (Day -1). A washout interval of 7 days separated the 4 single doses.

Reference Therapy, Dose, Mode of Administration, and Lot Number:

Drug	Dose	Form	Route	Lot No.
ACTOS®	pioglitazone 30 mg	commercial tablet	oral	A10330
AMARYL®	glimepiride 4 mg	commercial tablet	oral	1074614

Criteria for Evaluation:

Pharmacokinetic:

For each subject, the following pharmacokinetic parameters were calculated for each study period from serum concentrations of unchanged glimepiride and pioglitazone according to the model-independent approach: area under the serum concentration-time curve from time 0 to the time of last quantifiable concentration (AUC[0-tlqc]), area under the serum concentration-time curve from time 0 to infinity (AUC[0-inf]), maximum observed serum concentration (Cmax), the time at which Cmax occurred (Tmax), terminal phase elimination rate constant (λz), terminal elimination half-life (T1/2), and apparent oral clearance (CL/F).

Safety:

Safety variables included AEs, clinical laboratory test results, vital signs, ECGs, and physical examinations.

Statistical Methods:

Pharmacokinetic Measures:

Statistical analyses were performed on Tmax, λz, and natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax for pioglitazone and glimepiride. The statistical model used in this replicate crossover study was based on the Food and Drug Administration (FDA) guidance entitled *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence*. The model included fixed effects for sequence, period, and treatment with different intrasubject variability for each treatment. Carryover effect was explored by adding each factor independently into the aforementioned model. Group effect was also explored by adding group and group×treatment interaction terms into the model.

Within the framework of these models, the 90% confidence intervals (CIs) for the ratio (test/reference) of the least-squares (LS) mean of AD-4833SU (Treatment A) relative to the LS mean of the concomitantly administered pioglitazone and glimepiride commercial tablets (Treatment B) were calculated for AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and glimepiride. The test treatment was considered bioequivalent to the reference treatment if the 90% CIs of these ratios were within 80% to 125%.

Title of Study:

An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 4 mg When Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

SUMMARY OF RESULTS

Subject Disposition:

A total of 38 healthy subjects (mean age of 29 years), including 18 male subjects and 20 female subjects, were randomly assigned to treatment at 1 study site. Thirty-six subjects (94.7%), including 18 male subjects and 18 female subjects, completed the study. Two subjects discontinued the study early: 1 subject withdrew voluntarily for personal reasons, and 1 subject withdrew because of difficulties with the blood draws.

Pharmacokinetic Results:

Systemic exposures to pioglitazone and glimepiride after single-dose administration of AD-4833SU were bioequivalent to exposures observed after concomitant administration of the commercially available pioglitazone and glimepiride commercial tablets. For pioglitazone and glimepiride, the 90% CIs of the LS mean ratios for AUC(0-tlqc), AUC(0-inf), and Cmax were within the 80% to 125% interval.

The LS mean and median Tmax values for pioglitazone were between 1.5 and 2.2 hours for both treatments. The LS mean λz values were 0.081 1/hr after treatment with AD-4833SU and 0.076 1/hr after concomitant administration of the commercial tablets. The LS mean and median Tmax values for glimepiride were between 2.5 and 2.7 hours for both treatments. The LS mean λz values were 0.0755 1/hr after treatment with AD-4833SU and 0.0858 1/hr after concomitant administration of the commercial tablets.

Pharmacokinetic Analysis Results for Serum Pioglitazone and Glimepiride

Parameter (a) (units)	N	Treatment	LS Mean	Test/ Reference	LS Mean Ratio (%) (b)	90% CI of Ratio (%)
Pioglitazone						
AUC(0-tlqc) (hr·ng/mL)	37	A	9248.849	A/B	87.03	(82.50, 91.81)
		B	10627.333			
AUC(0-inf) (hr·ng/mL)	36	A	10319.654	A/B	87.51	(83.17, 92.08)
		B	11792.436			
Cmax (ng/mL)	37	A	1058.7	A/B	92.29	(86.76, 98.17)
		B	1147.1			
Glimepiride						
AUC(0-tlqc) (hr·ng/mL)	37	A	1835.121	A/B	100.51	(95.52, 105.77)
		B	1825.751			
AUC(0-inf) (hr·ng/mL)	36	A	1950.192	A/B	101.67	(96.58, 107.04)
		B	1918.079			
Cmax (ng/mL)	37	A	290.5	A/B	85.69	(80.60, 91.09)
		B	339.1			

Source: Table 14.2.3 and 14.2.5.
Treatment A: AD-4833SU (pioglitazone 30 mg/glimepiride 4 mg fixed dose combination product).
Treatment B: 1 pioglitazone 30 mg commercial tablet administered concomitantly with 1 glimepiride 4 mg commercial tablet.
(a) Natural logarithms of AUCs and Cmax were used in the analysis of variance (ANOVA) modeling.
(b) Ratio is LS mean of Treatment A/LS mean of Treatment B.

Title of Study:

An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 4 mg When Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

Safety Results:

The overall incidence of AEs was generally low during both treatments. Four of 38 subjects experienced 1 or more AE after treatment with AD-4833SU, and 9 of 37 subjects experienced 1 or more AE after treatment with the commercial tablets. Headache was the only AE experienced by more than 2 subjects in either treatment group, and all AEs were considered mild in severity. No serious adverse events (SAEs), deaths, or discontinuations due to AEs occurred during this study. There were no clinically important abnormal laboratory, vital sign, ECG, or physical examination findings.

AEs Reported by 2 or More Subjects in Any Treatment Group

System Organ Class Preferred Term	Treatment A N=38 n (%)	Treatment B N=37 n (%)
Any AE	4 (10.5)	9 (24.3)
Gastrointestinal disorder		
Nausea	1 (2.6)	2 (5.4)
Nervous system disorders		
Headache	1 (2.6)	3 (8.1)
Tremor	0 (0.0)	2 (5.4)

Source: Tables 14.3.1.2.
Treatment A: AD-4833SU (pioglitazone 30 mg/glimepiride 4 mg fixed dose combination product).
Treatment B: 1 pioglitazone 30 mg commercial tablet administered concomitantly with 1 glimepiride 4 mg commercial tablet.

CONCLUSIONS:

Systemic exposures to pioglitazone and glimepiride after single-dose administration of AD-4833SU (pioglitazone 30 mg/glimepiride 4 mg fixed-dose combination product) were bioequivalent to exposures observed after concomitant administration of the commercially available pioglitazone 30 mg and glimepiride 4 mg tablets. Both treatments were safe and well tolerated as administered in this study.

These conclusions are based on the following findings:

- For pioglitazone and glimepiride, the 90% CIs of the LS mean ratios for AUC and Cmax were within the 80% to 125% interval.
- There were no SAEs, deaths, or clinically important abnormal laboratory, vital sign, ECG, or physical examination findings.

Date of Report:

31 March 2005

8 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

C OCPB Filing Memo

4.1.1 Office of Clinical Pharmacology and Biopharmaceutics

5 *New Drug Application Filing and Review Form*

5.1.1.1.1 ***General Information About the Submission***

	Information		Information
NDA Number	**21-925**	**Brand Name**	
OCPB Division (I, II, III)	**II**	**Generic Name**	**Pioglitazone/glimepiride**
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**	**30 mg/2 mg; 30 mg/4 mg, tablets**
		Dosing Regimen	**QD**
Date of Submission	**6/28/05**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**3/1/06**	**Sponsor**	**Takeda**
PDUFA Due Date	**4/29/06**	**Priority Classification**	**Standard**
5.1.1.2 **Division Due Date**	**3/29/06**		

5.1.1.2.1.1.1.1 Clin. Pharm. and Biopharm. Information

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

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	3	3	[redacted] vs. individual components
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X			Dissolution profile provided at only one media and speed.
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**4**	**4**	
5.2.1.1.1.1				

5.2.1.1.1.2 **Filability and QBR comments**

	"X" if yes	5.2.1.2.1.1.1.1.1 Comments
5.2.1.2		
5.2.1.3 **Application filable ?**	X	Reasons if the application is not filable (or an attachment if applicable)
5.2.1.4 **Comments sent to firm ?**		• **Please provide dissolution profile for glimepiride in pH 6.8 phosphate buffer containing 0.05%, 0.1% and 0.2% SDS using USP apparatus 2 at 75 rpm.**
5.2.1.5		• **Pleas submit bioanalytical reports No. 0221-04165; 0221-04167; and 0224-04168-2.**
QBR questions (key issues to be considered)		1) Does the proposed dosing combination address all the possible combination that patients may likely need? 2) Does food alter the bioavailability of actoplus sulf? 3) Is the combination formulation of pioglitazone and glimepiride (30 mg/2 mg, 30 mg/4 mg and [redacted]) bioequivalent to individual commercially available tablets? 4) Is the dissolution method appropriate for both pioglitazone and glimepiride? 5) Have the analytical methods been sufficiently validated?

Other comments or information not included above	**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 study.** Protocol: 01-04-TL-OPISU-002 Title of study: An open-label, randomized, 4-period crossover replicate study to determine the bioequivalency of pioglitazone 30 mg and glimepiride 4 mg when administered as separate commercial tablets and as a fixed dose combination tablet. **Clinical site:** **Analytical site:**
Primary reviewer Signature and Date	**Jaya bharathi Vaidyanathan, Ph.D.**
Secondary reviewer Signature and Date	**Hae-Young Ahn, Ph.D.**

Background:

On June 28, 2005, Takeda submitted NDA 21-925 for pioglitazone/glimepiride tablets mg for the treatment of type 2 diabetes. [redacted] strengths of the pioglitazone/glimepiride fixed-dose tablet (30 mg/2 mg 30 mg/4 mg [redacted] are proposed. Tablets used in clinical studies were identical in composition to those intended for commercial use. Four studies have been submitted under the clinical pharmacology section as follows.

- [redacted]
- An open-label, randomized, 4-period crossover replicate study to determine the bioequivalency of pioglitazone 30 mg and glmepiride 2 mg when administered as separate commercial tablets and as a fixed-dose combination tablet.
- An open-label, randomized, 4-period crossover replicate study to determine the bioequivalency of pioglitazone 30 mg and glimepiride 4 mg when administered as separate commercial tablets and as a fixed dose combination tablet.
- [redacted]

Findings:

Food-Effect study: Results indicate that exposures to pioglitazone and glimepiride are not altered in presence of food. There was a delay in Tmax and decrease in Cmax in presence of food for pioglitazone. There was not effect of glimepiride Cmax in presence of food.

The combination tablet is proposed to be taken once daily with the first main meal.

Bioequivalence studies: Based on AUC and Cmax values, the rate and extent of absorption of pioglitazone and glimepiride following administration of the pioglitazone 30 mg/glimepiride2 mg and pioglitazone 30 mg/glimepiride 4 mg dose of combination tablets were bioequivalent to that observed following co-administration of the separate commercial pioglitazone 30 mg + glimepiride 2 mg and pioglitazone 30mg + glimepiride 4 mg tablets respectively.

Proposed dissolution method:

Sponsor is proposing the approved dissolution conditions for pioglitazone while it is different for glimepiride.

Dissolution (%)	
Pioglitazone HCl	Not less than ___ (Q) of the label claim of $C_{19}H_{20}N_2O_3S$ dissolved in 30 min
Glimepiride	Not less than ___ (Q) of the label claim of $C_{24}H_{34}N_4O_5S$ dissolved in 15 min
Test Method:	
Medium	Pioglitazone HCl: 900 mL of pH 2.0 potassium chloride buffer Glimepiride: 900 mL of pH 6.8 sodium phosphate buffer containing 0.2% SDS.
Apparatus	Pioglitazone HCl: USP apparatus 2, 50 rpm Glimepiride: USP apparatus 2, 75 rpm

Source: Section 3.2.P.5.3 of Module 3.

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

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D DSI Audit Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 28, 2006

TO: Mary H. Parks, M.D.
Director
Division of Metabolic and Endocrine Products, DMEP

FROM: Michael F. Skelly, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-925 [redacted]
(pioglitazone HCl + glimepiride tablets, AD-4833SU),
Sponsored by Takeda

At the request of DMEP, the Division of Scientific Investigations audited the clinical and analytical portions of the following bioequivalence study, performed at [redacted] in [redacted], and [redacted] in [redacted], respectively.

Study 01-04-TL-OPISU-002: "An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride mg when Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

Following the inspection at [redacted] Form 483 was issued. Following the inspection at [redacted], there were no objectionable observations and no Form 483 was issued. The objectionable observation at [redacted] and our evaluation are as follows:

[redacted]:

1. The investigation was not conducted in accordance with the investigational plan, in that 6 of the 38 subjects did not have two negative serum hCG tests of which the first hCG test was conducted at least 7 days prior to the first dose, and the second before dosing. The first serum hCG tests for six subjects (1003, 1007, 1021, 1033, 1035, and 1037) were done only 2 or 3 days prior to the first dose.

One negative hCG test either 2 or 3 days prior to dosing, and another negative hCG test 1 day prior to dosing, provide adequate assurance that the 6 subjects were not pregnant. An earlier first hCG test would not have given better assurance that subjects were not pregnant at the time of dosing. This technical protocol violation did not compromise subject protection.

Additional Comment:

Subject #055 (acquisition number 1003), a 27-year-old female, had no glimepiride in her plasma for any sample in Period I, although there were expected concentrations of pioglitazone. [redacted] repeated the glimepiride assays to confirm the results. Our audits found no explanation for this aberrant outcome in the clinical, dosing, or analytical records. During the other replicate Period with the same two approved (reference) tablets, the expected concentrations of both drugs were present.

Conclusions:

DSI recommends that the clinical and analytical data from study 01-04-TL-OPISU-002 are acceptable for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly, Ph.D.
Pharmacologist

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Final Classification:

VAI - [redacted]
NAI - [redacted]

Recommendation: The data from study 01-04-TL-OPISU-002 are acceptable for review.

cc:
HFA-224
HFD-45/RF
HFD-48/Himaya
HFD-48/CF
DMEP (formerly HFD-510)/Weber
HFR- [redacted]
HFR- [redacted]
Drafted: MFS 2/28/06
Edits: JAO/MFS 2/28/06
DSI: [redacted] O:\BE\EIRCover\21925tak.piogli.doc
FACTS: 701252

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/s/

Amalia Himaya
2/28/2006 03:06:48 PM
CSO
Paper copy signed by Dr. Viswanathan on 2/28/06 and available upon request.

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/s/

Jayabharathi Vaidyanathan
4/7/2006 02:03:35 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/7/2006 02:59:37 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-925	Brand Name	[redacted]
OCPB Division (I, II, III)	II	Generic Name	Pioglitazone/glimepiride
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	30 mg/2 mg; 30 mg/4 mg; [redacted] tablets
		Dosing Regimen	QD
Date of Submission	6/28/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	3/1/06	Sponsor	Takeda
PDUFA Due Date	4/29/06	Priority Classification	Standard
Division Due Date	3/29/06		

Clin. Pharm. and Biopharm. Information

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

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	3	3	[redacted] vs. individual components
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X			Dissolution profile provided at only one media and speed.
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4	4	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable)
Comments sent to firm ?		• **Please provide dissolution profile for glimepiride in pH 6.8 phosphate buffer containing 0.05%, 0.1% and 0.2% SDS using USP apparatus 2 at 75 rpm.** • **Pleas submit bioanalytical reports No. 0221-04165; 0221-04167; and 0224-04168-2.**
QBR questions (key issues to be considered)		1) Does the proposed dosing combination address all the possible combination that patients may likely need? 2) Does food alter the bioavailability of actoplus sulf? 3) Is the combination formulation of pioglitazone and glimepiride (30 mg/2 mg, 30 mg/4 mg and [redacted] bioequivalent to individual commercially available tablets? 4) Is the dissolution method appropriate for both pioglitazone and glimepiride? 5) Have the analytical methods been sufficiently validated?

Other comments or information not included above	**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 study.** Protocol: 01-04-TL-OPISU-002 Title of study: An open-label, randomized, 4-period crossover replicate study to determine the bioequivalency of pioglitazone 30 mg and glimepiride 4 mg when administered as separate commercial tablets and as a fixed dose combination tablet. Clinical site [redacted] Analytical site [redacted]
Primary reviewer Signature and Date	Jaya bharathi Vaidyanathan, Ph.D.
Secondary reviewer Signature and Date	Hae-Young Ahn, Ph.D.

Background:

On June 28, 2005, Takeda submitted NDA 21-925 for pioglitazone/glimepiride tablets mg for the treatment of type 2 diabetes. [redacted]trengths of the pioglitazone/glimepiride fixed-dose tablet (30 mg/2 mg 30 mg/4 mg [redacted] are proposed. Tablets used in clinical studies were identical in composition to those intended for commercial use. Four studies have been submitted under the clinical pharmacology section as follows.

- [redacted]
- An open-label, randomized, 4-period crossover replicate study to determine the bioequivalency of pioglitazone 30 mg and glmepiride 2 mg when administered as separate commercial tablets and as a fixed-dose combination tablet.
- An open-label, randomized, 4-period crossover replicate study to determine the bioequivalency of pioglitazone 30 mg and glimepiride 4 mg when administered as separate commercial tablets and as a fixed dose combination tablet.
- [redacted]

Findings:

[redacted]

Bioequivalence studies: Based on AUC and Cmax values, the rate and extent of absorption of pioglitazone and glimepiride following administration of the pioglitazone 30 mg/glimepiride2 mg and pioglitazone 30 mg/glimepiride 4 mg dose of combination tablets were bioequivalent to that observed following co-administration of the separate commercial pioglitazone 30 mg + glimepiride 2 mg and pioglitazone 30mg + glimepiride 4 mg tablets respectively.

Proposed dissolution method:
Sponsor is proposing the approved dissolution conditions for pioglitazone while it is different for glimepiride.

Dissolution (%)	
Pioglitazone HCl	Not less than [redacted](Q) of the label claim of $C_{19}H_{20}N_2O_3S$ dissolved in 30 min
Glimepiride	Not less than [redacted](Q) of the label claim of $C_{24}H_{34}N_4O_5S$ dissolved in 15 min
Test Method:	
Medium	Pioglitazone HCl: 900 mL of pH 2.0 potassium chloride buffer Glimepiride: 900 mL of pH 6.8 sodium phosphate buffer containing 0.2% SDS.
Apparatus	Pioglitazone HCl: USP apparatus 2, 50 rpm Glimepiride: USP apparatus 2, 75 rpm

Source: Section 3.2.P.5.3 of Module 3.

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

Proposed Labeling:

[redacted]
(pioglitazone hydrochloride and glimepiride) tablets

DESCRIPTION

[redacted] (pioglitazone hydrochloride and glimepiride) tablets contain two oral antihyperglycemic agents used in the management of type 2 diabetes: pioglitazone hydrochloride and glimepiride. The concomitant use of pioglitazone and a sulfonylurea, the class of drugs that includes glimepiride, has been previously approved based on clinical trials in patients with type 2 diabetes inadequately controlled on a sulfonylurea. Additional efficacy and safety information about pioglitazone and glimepiride monotherapies may be found in the prescribing information for each individual drug.

Pioglitazone hydrochloride is an oral antihyperglycemic agent that acts primarily by decreasing insulin resistance. Pioglitazone is used in the management of type 2 diabetes. Pharmacological studies indicate that pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone improves glycemic control while reducing circulating insulin levels.

Pioglitazone (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, biguanides, or the α-glucosidase inhibitors. The molecule contains one asymmetric center, and the synthetic compound is a racemate. The two enantiomers of pioglitazone interconvert in vivo. The structural formula is as shown:

29 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Jayabharathi Vaidyanathan
8/22/2005 12:33:53 PM
PHARMACOLOGIST

Hae-Young Ahn
8/22/2005 01:48:23 PM
BIOPHARMACEUTICS