

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

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

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW
ADDENDUM**

| | |
|---------------------|---|
| NDA 21-073 | SUBMISSION DATE: July 13, 1999 |
| BRAND NAME: | ACTOS™ |
| GENERIC NAME: | Pioglitazone, 15 mg, 30 mg, 45 mg tablets |
| REVIEWER: | Xiaoxiong (Jim) Wei, Ph.D. |
| SPONSOR: | Takeda America, Inc. Princeton, New Jersey |
| TYPE OF SUBMISSION: | Amendment (Dissolution Specification) |

SYNOPSIS:

On July 13, 1999, the sponsor submitted additional data in support of dissolution specification of Q= [REDACTED]. An initial recommendation was that specification be set at [REDACTED] based on the data that the sponsor provided from the bioavailability and scale-up lots. In this submission, the sponsor provided additional dissolution data from several development lots on stability study and 3 commercial lots for launch. Based on the current data, the following dissolution method and specification is recommended to the sponsor:

Apparatus: USP Apparatus 2 (paddle), [REDACTED]
 Medium: HCL-0.3 M KCL buffer, pH 2.0, 900 ml
 Assay: [REDACTED]
 Specification: Q= [REDACTED]

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-073, Amendment (Pioglitazone /ACTOS™) submitted on July 13, 1999. The above recommended dissolution specification should be sent to the sponsor as appropriate,

/S/ [REDACTED]

Xiaoxiong (Jim) Wei, Ph.D.
 Division of Pharmaceutical Evaluation II
 Office of Clinical Pharmacology and Biopharmaceutics

RD/ FT initialed by Hae-Young Ahn, Ph.D., Team Leader [REDACTED]

/S/ [REDACTED]

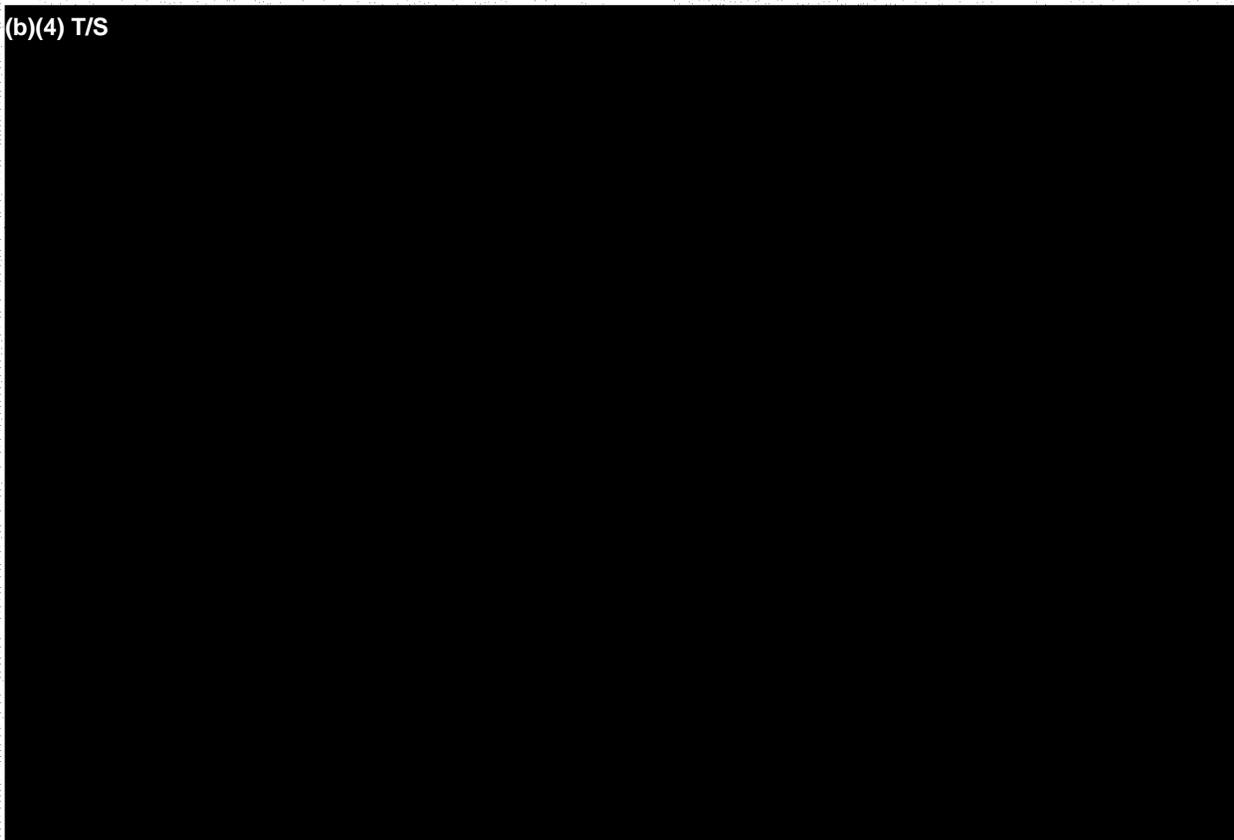
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CC: NDA 21-073 (orig., 1 copy), HFD-510(Weber, Ysem), HFD-850 (Lesko, Huang), HFD-870 (Wei, Ahn, M. Chen), CDR (Barbara Murphy).

Code: ~~AE~~ AP

TABLE 4

(b)(4) T/S



APPEARS THIS WAY ON ORIGINAL

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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

| | |
|----------------------------|--|
| NDA 21-073 | SUBMISSION DATE: 01-15-1999, 03-31-1999, 04-05-1999, 04-06-1999 |
| BRAND NAME: | ACTOS™ |
| GENERIC NAME: | Pioglitazone, 15 mg, 30 mg, 45 mg tablets |
| REVIEWER: | Xiaoxiong (Jim) Wei, Ph.D. |
| SPONSOR: | Takeda America, Inc. Princeton, New Jersey |
| TYPE OF SUBMISSION: | NME, Code: 1P |

SYNOPSIS:

Pioglitazone (ACTOS™) has been developed as an oral antidiabetic agent, which belongs to thiazolidinediones. It acts primarily by decreasing insulin resistance. It is proposed to treat type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM).

The sponsor proposes to market three strengths of tablets, 15 mg, 30 mg and 45 mg of pioglitazone. However, the 45-mg tablets have not been used in clinical trial. The **bioequivalent studies** showed that these three strengths are bioequivalent.

The dosage sponsor proposes is an initial dosage of 30 mg once daily as monotherapy and 15 – 30 mg once daily for combination therapy with sulfonylureas, metformin and insulin. The dose can be increased based on therapeutic effect with maximum recommended dose of 45 mg/day.

Pharmacokinetic studies showed that it is rapidly absorbed and metabolized. Based on animal studies, two major metabolites, M-III and M-IV share its pharmacologic activity by 40 – 60% of parent compound (note: M-II is also active but the level is very low in human). At steady state, these two pharmacologically active metabolites reach serum concentrations equal to or greater than parent agent, pioglitazone. The sponsor has defined the parent drug, pioglitazone plus these two active metabolites, M-III and M-IV as the total active pioglitazone. The pioglitazone comprises about 20 – 25% of the total AUC. Pioglitazone and M-III, M-IV are highly bound to serum albumin. Pioglitazone is extensively metabolized by hydroxylation and oxidation mainly through CYP2C8 and 3A4. The drug is mainly excreted as metabolites in the bile and only 15 – 30% of the dose is recovered in the urine. The mean T_{1/2} for pioglitazone and the total pioglitazone ranges from 3-7 hours and 16 to 24 hours, respectively.

Special population studies showed that it may not be necessary to adjust dosage in renally impaired or hepatically impaired patients as well as in elderly patients. The pharmacokinetic parameters were 20 – 60% higher in females than in men, but these studies were not body-weight normalized.

Drug interaction studies between pioglitazone and digoxin, glipizide, warfarin, and metformin indicated that there were no significant changes in pharmacokinetic parameters. The potent CYP3A4 inhibitor, ketoconazole inhibited 85% of pioglitazone metabolism in vitro at the equal molar concentrations. However, the sponsor did not conduct some important drug

equal molar concentrations. However, the sponsor did not conduct some important drug interaction studies involving CYP3A4 such as ketoconazole, erythromycin.

Food may delay the T_{max} but may not affect the value of the total AUC.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-073 (Pioglitazone /ACTOS™) submitted on January 15, 1999. The overall Human Pharmacokinetic Section is acceptable to OCPB. However, OCPB requests Phase IV studies listed under Comments 2 and 3. This recommendation, comments (p. 17), and labeling comments (p. 18) should be sent to the sponsor as appropriate.

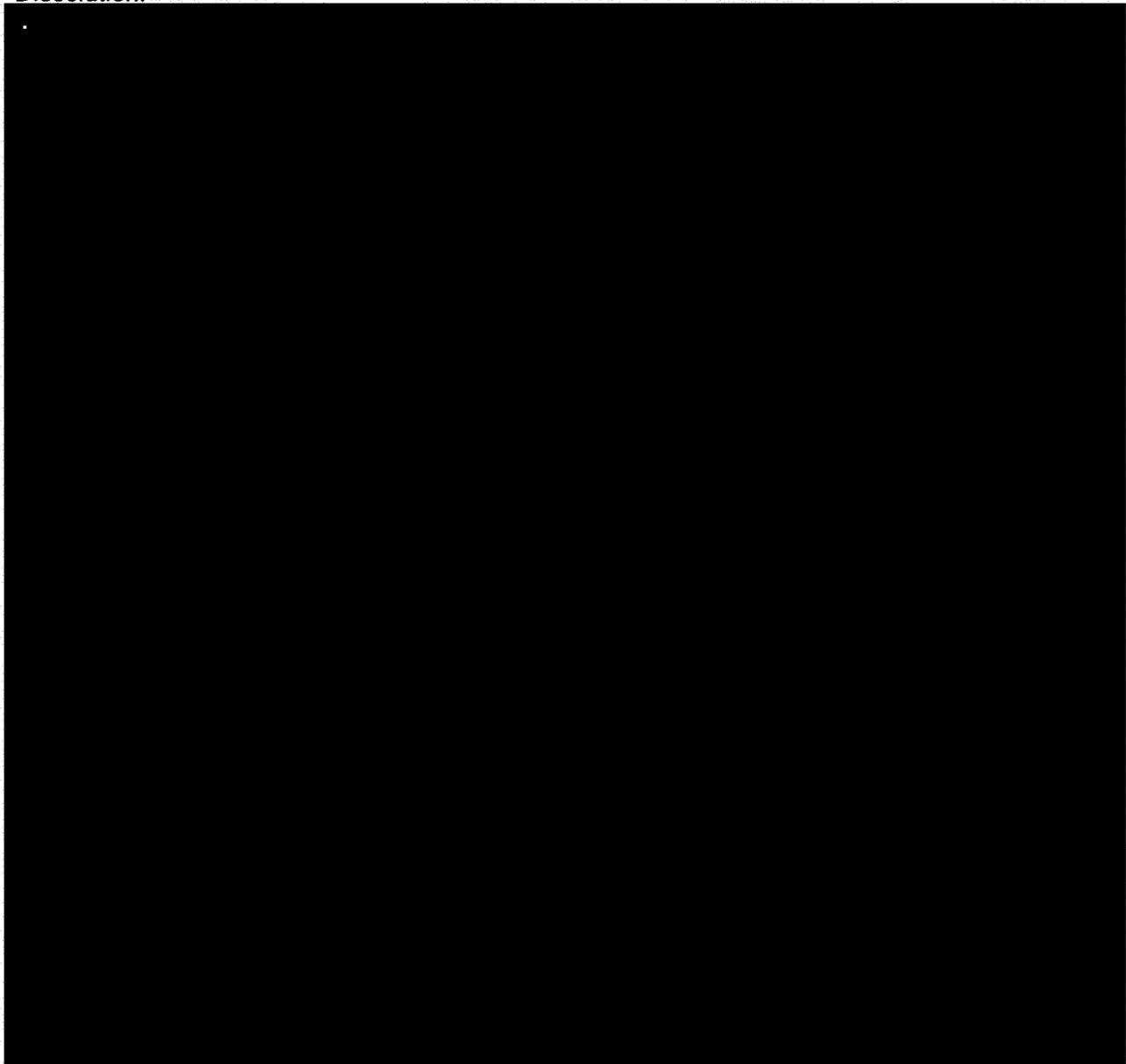
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Table 1: Composition of Commercial ACTOS™ Tablets

| Ingredient | Function | Composition (mg/tablet) | | |
|------------------------------------|----------|-------------------------|-------|-------|
| | | 15 mg | 30 mg | 45 mg |
| Pioglitazone hydrochloride | | | | |
| Lactose monohydrate, NF | | | | |
| Hydroxypropylcellulose calcium, NF | | | | |
| Carboxymethylcellulose calcium, NF | | | | |
| Magnesium stearate, NF | | | | |
| Total | | | | |

* Removed during manufacturing process.

Dissolution:



Bioequivalence

Two bioequivalence studies were conducted. The first BE study was performed to compare 1X30-mg tablet with 2 X 15-mg tablets in a single dose, two-period crossover study in 14 Japanese male adult subjects. These two formulations were found to be bioequivalent.

Table 2: PK Parameters of 1X30 mg and 2X15 mg Tablets

| PK Parameter | Pioglitazone/ ^a Total Active Pioglitazone Compounds | | | |
|--------------------------|--|---|--|-------------------------------|
| | Test Mean 1X30 mg Tablet (Treatment B) | Reference Mean 2X15 mg Tablet (Treatment A) | Ratio of LS Means Test/Reference | 90% Confidence Interval |
| C _{max} (ng/ml) | 1460±350 | 1470 ± 450 | 99 | 88.5 – 111.9 |
| | 1843 ± 381 | 1823 ± 475 | 101 | 90.3 – 114.1 |
| AUC:0-96h (µg.hr/ml) | 13.11 ± 3.59 | 12.78 ± 3.84 | 103 | 91.2 – 116.4 |
| | 50.26 ± 9.63 | 49.96 ± 1.07 | 101 | 89.4 – 107.6 |

^aTotal Active Pioglitazone Compounds: unchanged pioglitazone, metabolites II, III, IV.

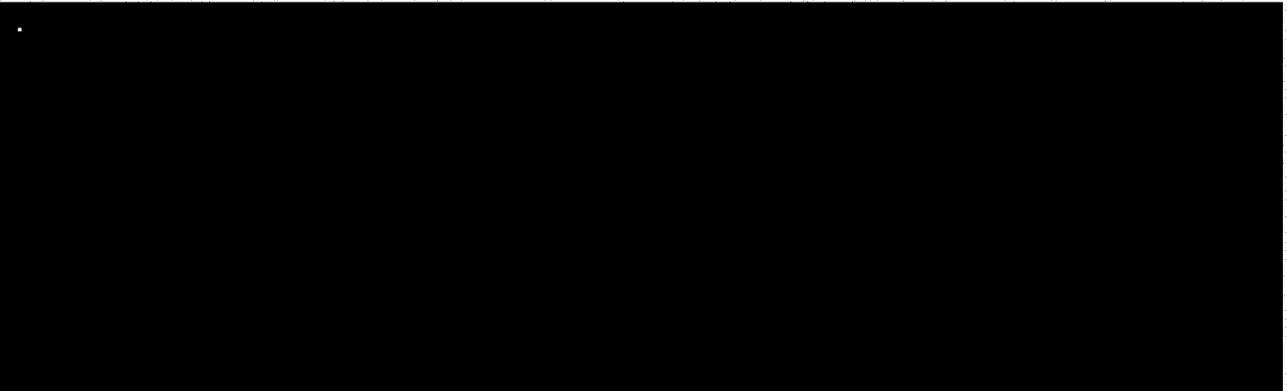
A single dose, open-label, two-treatment, two-period crossover bioequivalence study was conducted in 24 healthy male subjects ranging in age from 18 to 35 years in USA to evaluate whether one 45-mg tablet is bioequivalent to 3 of 15-mg tablets (volume 1.077-78, PNFP-018). These two formulations were found to be bioequivalent.

Table 3: PK Parameters of 1X45 mg and 3X15 mg Tablets

| PK Parameter | Pioglitazone/ ^a Total Active Pioglitazone Compounds | | | |
|--------------------------|--|---|--|-------------------------------|
| | Test Mean 1X45 mg Tablet (Treatment B) | Reference Mean 3X15 mg Tablet (Treatment A) | Ratio of LS Means Test/Reference | 90% Confidence Interval |
| C _{max} (ng/ml) | 1482 ± 499.7 | 1681 ± 496.0 | 88.2 | 79.7 - 96.6 |
| | 1865 ± 605.3 | 2108 ± 588.7 | 88.5 | 80.1 – 96.9 |
| T _{max} (hour) | 3 (2 – 5) | 3 (2 – 4) | 98.8 | 90.2 – 107 |
| | 4 (3 – 5) | 4 (2 – 5) | 101 | 94.4 – 108 |
| AUC:0-∞ (µg.hr/ml) | 13.85 ± 5.0 | 15.06 ± 4.51 | 92.0 | 83.9 – 100 |
| | 56.90 ± 15.56 | 62.54 ± 18.56 | 91.0 | 84.4 – 97.5 |

^aTotal Active Pioglitazone Compounds: unchanged pioglitazone, metabolites III, IV.

Analytical Methodology



CLINICAL PHARMACOLOGY

Pharmacokinetics (PK):

What are the basic PK parameters?
 Is the variability in PK in patients similar or different from healthy volunteers?
 What is the effect of food and how dose it influence dosing recommendations?
 Are there active/toxic metabolites, do they accumulate?

Single Dosing versus Multiple Dosing:

Single dose PK studies (P-5232-0001 and CPH-001, 002, 003) were performed during the development of pioglitazone. The single dose study (P-5232-001, USA study) was a double blind, placebo controlled, randomized single dose tolerance trial. It was conducted in 37 healthy male subjects (weight ranging from 60.9 – 93.2 kg); 24 subjects for pioglitazone and 13 subjects for placebo using 2-mg capsules for 2, 18 mg doses and 5-mg capsules for 30, 45, and 60 mg doses. Only unchanged pioglitazone was measured for the determination of PK parameters. The results showed that PK profile is linear in range from 2 to 60 mg (Table 5).

Table 5. PK parameters of unchanged pioglitazone following single doses of pioglitazone

| Parameter | 2 mg | 18 mg | 30 mg | 45 mg | 60 mg |
|-------------------------------|-------------|--------------|-------------|--------------|--------------|
| C _{max} (ng/ml) | 101 ± 8.08 | 818 ± 112 | 1070 ± 184 | 1577 ± 813 | 1938 ± 686 |
| T _{max} (hr) | 2.13 ± 1.31 | 1.25 ± 0.645 | 2.0 ± 1.41 | 2.63 ± 1.60 | 2.63 ± 1.11 |
| AUC _{0-∞} (µg.hr/ml) | 0.65 ± 0.16 | 6.40 ± 1.08 | 7.90 ± 0.87 | 14.00 ± 6.48 | 19.00 ± 8.93 |
| T _{1/2} (hr) | 3.32 | 5.13 | 4.81 | 5.29 | 6.93 |

In study CPH-001-002 conducted in Japan, five different single doses of 5, 15, 30, 45, 60 mg of tablets were administered in 5 subgroups of healthy male subjects (age: 20-50 yr., body weight: 90-120% of standard weight). Both unchanged pioglitazone and total active compounds were determined for PK profiles. The results showed that PK parameters are in Table 6.

Table 6. PK profile of Pioglitazone and Total Active Compounds following single doses of pioglitazone

| Parameter/ | 5 mg | 15 mg | 30 mg | 45 mg | 60 mg |
|-----------------------|-------------|--------------|--------------|---------------|----------------|
| Cmax (ng/ml) | 300 ± 8.08 | 900 ± 200 | 1500 ± 300 | 1900 ± 400 | 3000 ± 600 |
| | 300 ± 8.08 | 1100 ± 200 | 1900 ± 400 | 2400 ± 400 | 3700 ± 600 |
| Tmax (hr) | 1.5 ± 0.4 | 1.6 ± 0.5 | 1.9 ± 0.5 | 2.4 ± 0.8 | 1.9 ± 1.0 |
| | 2.1 ± 1.0 | 2.3 ± 0.3 | 2.3 ± 0.4 | 2.9 ± 0.9 | 2.5 ± 1.1 |
| AUC 0-∞ (µg.hr/ml) | 2.61 ± 0.70 | 6.50 ± 1.00 | 13.90 ± 3.10 | 18.30 ± 4.90 | 22.20 ± 2.40 |
| | 5.00 ± 0.50 | 26.20 ± 2.10 | 57.70 ± 9.30 | 75.60 ± 16.70 | 103.00 ± 23.50 |
| T1/2 (hr) | 6.0 ± 1.9 | 5.0 ± 0.6 | 2.9 ± 0.6 | 3.5 ± 1.4 | 5.2 ± 0.2 |
| | N/D | 15.4 ± 3.4 | 20.4 ± 3.1 | 20.3 ± 1.5 | 18.3 ± 3.4 |

In the study CPH-003, the 15-mg tablet was administered in a single dose study. PK parameters were similar to Study CPH-001/002.

In the study CPH-001/002 and 003, multiple doses were also administered to several subgroups in different doses. In CPH001/002, three arms of repeated dosing tests were performed as follows: a repeated once-daily dosing of 30 mg for 8 days, twice-daily dosing of 30 mg for 6 days and once-daily dosing of 60 mg for 8 days. In CPH-003, a repeated once daily dosing of 15 mg for 8 days was conducted.

Table 7. PK of Pioglitazone and Total Active Compounds for Study CPH-001/002

| Pioglitazone/ Total Active Compound | | Cmax (µg/ml) | Tmax (hr) | ^b AUC ₀₋₂₄ (µg.hr/ml) | T1/2 (hr) |
|--|-------|-----------------|-----------|--|--------------|
| 30 mg/day, qd; n=6 | Day 1 | 1.7±0.3 | 2.9±1.2 | 14.2 ± 4.6 | 4.9±1.3 |
| | | 2.1±0.2 | 3.3±1.0 | 58.0±11.2 | 17.4±2.3 |
| | Day 9 | 1.7±0.3 | 3.0±0.5 | 15.3±4.0 | 4.9±0.9 |
| | | 3.4±0.5 | 3.7±1.3 | 57.5±10.3 | 20.5±6.0 |
| 60 mg/day, bid; n=6 | Day 1 | 1.6±0.3 | 3.3 ± 0.8 | 12.8±3.7 | 4.2±1.1 |
| | | 2.1±0.2 | 4.3 ± 1.5 | 59.1±16.1 | 17.5±3.1 |
| | Day 9 | 1.9±0.4 | 2.4 ± 0.6 | 14.9±6.1 | 3.9±1.0 |
| | | 5.6±1.2 | 3.0±1.3 | 93.7±25.1 | 24.2±5.8 |
| 60 mg/day, qd; n=6 | Day 1 | 3.5±0.5 | 3.3±1.4 | 20.0±0.4 | 2.1±0.3 |
| | | 4.7±0.5 | 4.2±1.0 | 113.2±14.5 | 16.1±2.7 |
| | Day 9 | 2.8±0.6 | 3.8±1.3 | 24.4±4.5 | 3.8±0.5 |
| | | 6.6±0.9 | 5.3±2.1 | 113.5±14.1 | 22.6±2.0 |

^aTotal Active Pioglitazone Compounds: unchanged pioglitazone, M-II, M-III, and M-VI.

^bDay 1: AUC (0 - ∞ h); Day 9: AUC (0-24).

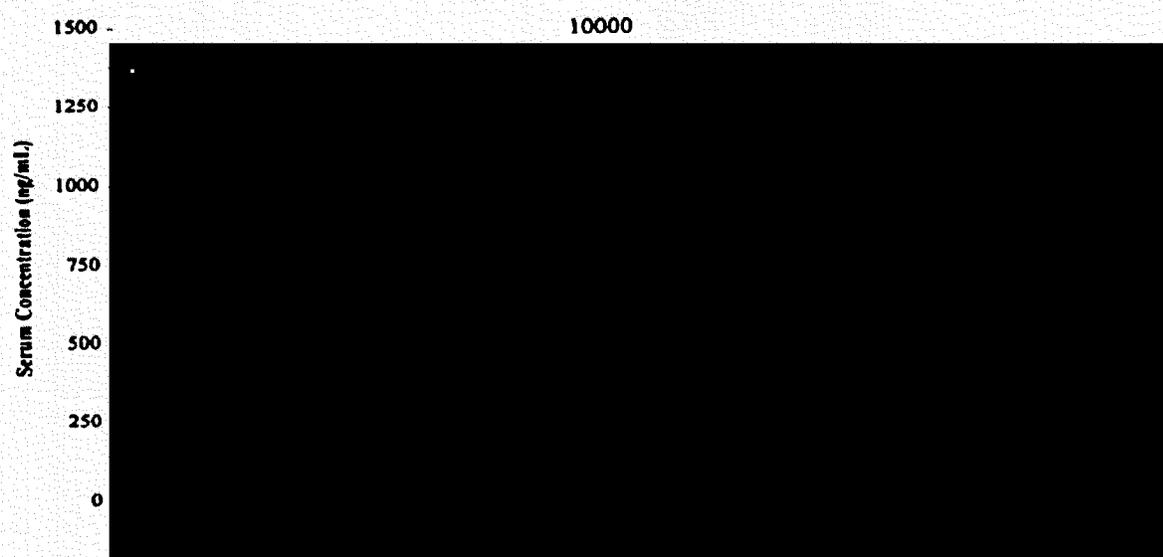
Table 8. PK parameter for Study CPH-003

| Pioglitazone/ Total Active Compound | | C _{max} (µg/ml) | T _{max} (hr) | AUC ₀₋₂₄ (µg.hr/ml) | T _{1/2} (hr) |
|--|-------|-----------------------------|-----------------------|-----------------------------------|--------------------------|
| 15 mg/day, qd, n=6 | Day 1 | 0.7±0.2 | 2.3±1.1 | 4.9 ± 0.8 | 1.8 |
| | | 0.9±0.2 | 3.7±1.3 | 23.5±1.8 | 18.6±4.1 |
| | Day 9 | 0.7±0.1 | 2.5±0.9 | 4.8±0.4 | 3.3±0.4 |
| | | 1.5±0.1 | 3.1±1.1 | 22.6±1.4 | 16.2±2.8 |

^aTotal Active Pioglitazone Compounds: unchanged pioglitazone, M-II, M-III, and M-VI.

^bDay 1: AUC (0 - ∞ h); Day 9: AUC (0-24).

Figure 2. Pioglitazone and Metabolites Serum Concentration Profiles after a Single 30 mg Dose (Study CPH-050)



Healthy volunteers vs. patients:

A randomized, single blind, multiple-dose study (P-5232-0010) was conducted in three parallel groups of patients with mild-to-moderate NIDDM (N=30). Patients received 15 mg, 30 mg, or 60 mg daily for 14 days. Serum pioglitazone, and M-3, and M-4 concentrations were determined for samples taken following the dose on Day 14. The change in AUC₀₋₂₄ was proportional from 15 mg/day to 30mg/day; however, a less than proportional increase in AUC₀₋₂₄ was observed from 30 mg/day to 60mg/day.

Table 9. Average (± SD) PK parameters for pioglitazone and total active compounds following 14 days of treatment.

| Parameter | Treatment | | |
|--------------------------------|-------------|-------------|--------------|
| | 15 mg | 30 mg | 60 mg |
| Pioglitazone | | | |
| C _{max} (ng/ml) | 327 ± 106 | 715 ± 216 | 972 ± 266 |
| T _{max} (hr) | 2.1 ± 1.1 | 2.5 ± 1.2 | 2.6 ± 0.97 |
| AUC ₀₋₂₄ (µg.hr/ml) | 3.43 ± 1.26 | 7.65 ± 3.14 | 10.00 ± 3.40 |

| Total Active Compounds* | | | |
|--------------------------------|--------------|--------------|---------------|
| C _{max} (ng/ml) | 1052 ± 377 | 1940 ± 597 | 2884 ± 536 |
| T _{max} (hr) | 5.6 ± 4.0 | 5.4 ± 2.5 | 6.3 ± 3.2 |
| AUC ₀₋₂₄ (μg.hr/ml) | 18.00 ± 5.91 | 34.00 ± 9.58 | 52.00 ± 13.00 |

*Total Active Pioglitazone Compounds: unchanged pioglitazone, metabolites III, IV.

In this study, there were no Day 1 PK data and no control group (healthy subjects). On Day 14, AUC values in these patients' population were much lower than those from healthy volunteers (study CPH-001/002/003): 52 vs 113.5 for 60 mg/day, which decreased by 54.2%; 34 vs. 57.5 for 30 mg/day, decreased by 42.5% ; and 18 vs. 22.6 for 15 mg/day, decreased by 20.45%, which seems dose-dependent in the extent of decrease. The length of treatment is related to decrease in AUC, Since formulations were different in these studies, this reviewer can not draw any conclusion whether or not it is due to autoinduction or formulation changes. In healthy volunteers' studies, 2-60mg/day is well under linear range however, only patients' PK profiles showed it is less than proportional from 30mg/day to 60 mg/day. These studies were using different formulations and conducted in Japan and USA, respectively. In drug interaction studies, the PK difference in healthy volunteers and patients were minimal, in which the same formulation was used.

Absorption:

Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. The absolute bioavailability of pioglitazone (Actos™) in humans is not known. However, absolute bioavailability of Actos™ in rats and dogs are 54% and 34%, respectively.

A relative bioavailability of 45 mg tablets of pioglitazone versus 45 mg suspension was investigated in 24 healthy subjects (male: 13, female: 11) in a two period, crossover study. The relative bioavailability of 45-mg tablet over suspension is about 94.5%. Female subjects were found to have 20-50% higher C_{max} and AUC values for pioglitazone. However, this reviewer calculated the mean body weight of female subjects and found that it was about 23% less than the mean body weight of male subjects, which may explain the difference between genders in these PK parameters.

Table 9: Summary of the Mean PK Parameters of Total Active Compounds in the Tablet (Treatment B) and Suspension (Treatment A) Groups.

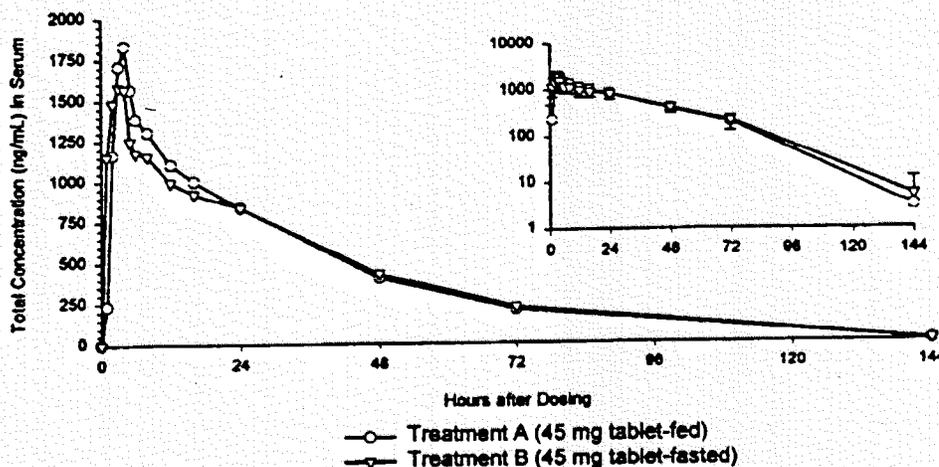
| PK Parameter | Test mean 45 mg tablet (Treatment B) | Reference Mean 45 mg suspension (Treatment A) | Test /Reference (%) | 90% Confidence Interval |
|-------------------------------|--------------------------------------|---|---------------------|-------------------------|
| C _{max} (ng/ml) | 1903 | 2448 | 78.7 | 64.3 – 89.6 |
| T _{max} (hours) | 4.02 | 5.00 | 96.9 | 89.7 – 104.1 |
| AUC _{0-∞} (ng.hr/ml) | 56946 | 60236 | 94.5 | 84.1 – 102.0 |
| T _{1/2} (hour) | 23.6 | 20.1 | 118 | 106.3 – 129.5 |

Food slightly delays the time to peak serum concentration to 3-4 hours, but does not alter the extent of absorption, which was examined in Study PNFP-036 in a single-dose, randomized, open-label, single center crossover trial with at least a 5-day washout between

dose administrations. Following oral administration of a 45 mg pioglitazone tablet with food (10 min after an ADA standardized breakfast containing 30% fat), the rate of absorption was slightly modified, with the mean C_{max} increased approximately 18% and the median T_{max} delayed approximately 1 hour compared to that observed in the absence of food. The mean AUC for pioglitazone were comparable between treatments, An examination of the composite serum profile of the parent and metabolites (total active compounds) demonstrated a pharmacokinetic profile similar to that of pioglitazone, with C_{max} increased approximately 18% when administered with food, while mean AUC values were comparable between treatments.

Since clinically pioglitazone will be administered chronically and doses will be selected for individual patients based upon therapeutic effect, this reviewer agrees with the sponsor that the small differences with and without food are not considered clinically relevant and the labeling for administration of pioglitazone with food is not necessary.

Figure 3. Mean Total Concentrations (ng/ml) of Pioglitazone, M-III, and M-IV in Serum, Comparing Treatment A versus Treatment B Subjects.

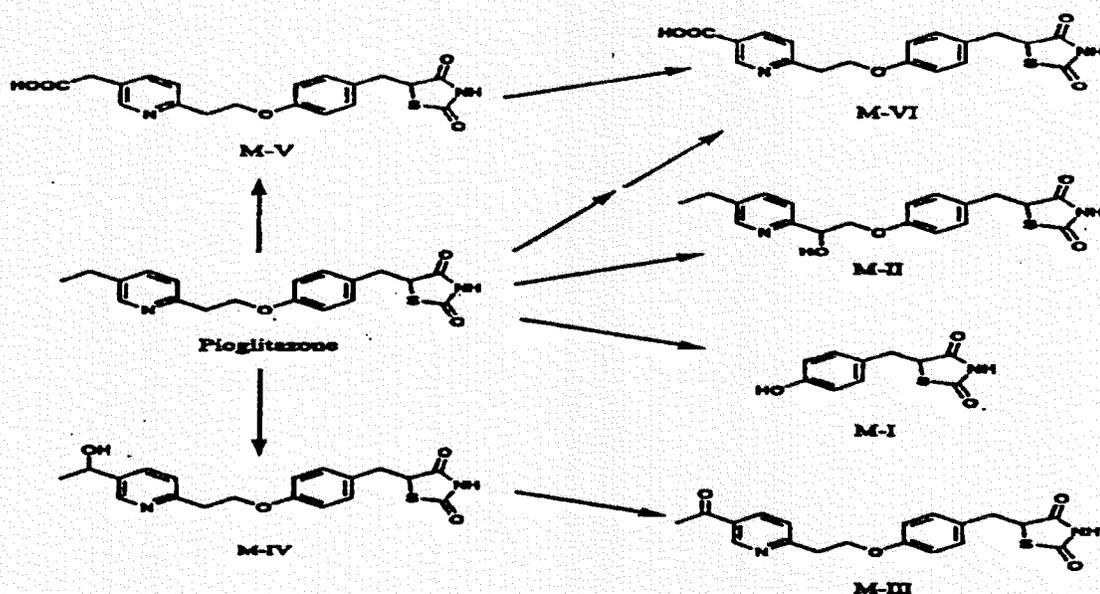


Distribution:

The mean apparent volume of distribution (V_d/F) of pioglitazone following single-dose administration is $0.62 + 0.39$ (mean + SD) L/kg of body weight. Pioglitazone is extensively bound (>99%) in human serum, principally to serum albumin. Pioglitazone was also found to be bound to other proteins, but with lower affinity. Metabolites III (M-III) and IV (M-IV) also are extensively bound (>98%) to serum albumin.

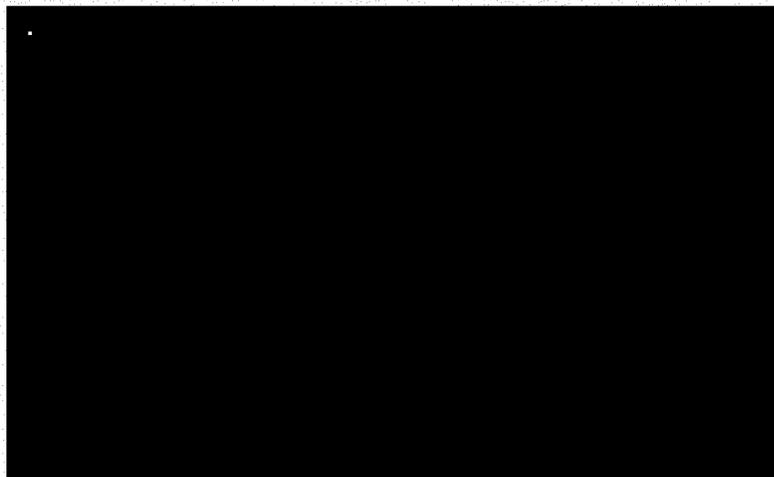
Metabolism:

The metabolic pathways of pioglitazone have been determined as below in humans.



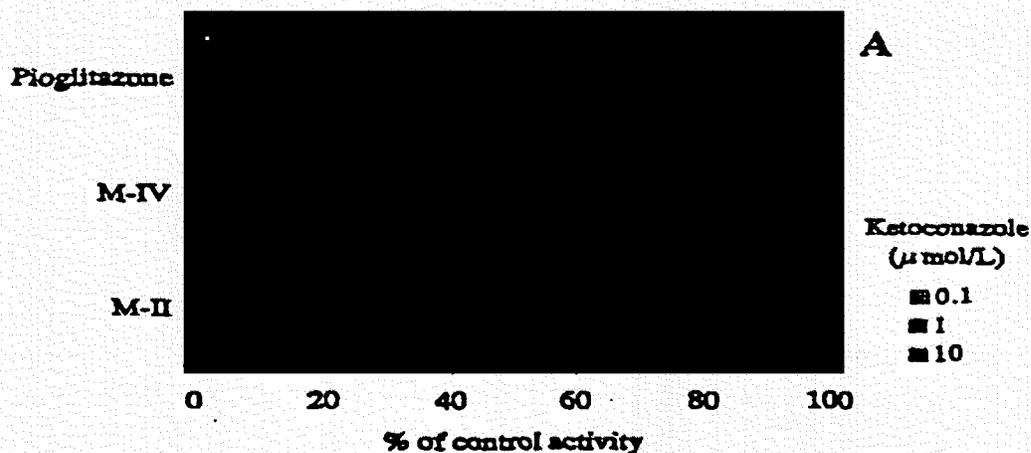
The sponsor conducted some in vitro drug metabolism studies using cDNA expressed CYP cell lines, human liver microsomes with probe substrates as activity index, and some inhibitory drugs such as ketoconazole. Based on cDNA expressed CYP studies, the sponsor concluded CYP1A1 and CYP2C8 are the major isoforms, whereas CYP3A4, CYP2C9, CYP2C19, CYP2D6 are minor enzymes.

Figure 4. In Vitro Metabolism of pioglitazone by Specific CYP Expressed B-Lymphoblastoid Cell Microsomes. Pioglitazone hydroxylation (10 μ M) was incubated with CYP expressing microsomes (2.5 pmol P450/ml) in the presence of NADPH-generating system at 37°C for 120min (mean value, n=2).



Based on the correlation study, the major isoforms were identified to be CYP2C8 and 3A4. However, there are no details in this submission how the correlation studies performed. In addition, the specific CYP3A4 inhibitor, ketoconazole inhibited pioglitazone metabolism by 65 to 85% at the same concentrations to pioglitazone, which is a striking evidence that CYP3A4 may contribute the metabolism of pioglitazone significantly. Since the submission did not have a detailed description on these in vitro studies, this reviewer can't comment on why these studies did not accord to each other in results.

The following figure showed that the effect of ketoconazole on the metabolism of pioglitazone was examined with 10 $\mu\text{mol/L}$ of pioglitazone and 1 mg protein/mL of human liver microsomes. Ketoconazole with the final concentration ranging 0.1 to 10 $\mu\text{mol/L}$ demonstrated a concentration-dependent and potent inhibitory effect on pioglitazone metabolism with both M-II and M-IV formation being inhibited by approximately 65 -85 % at the concentration of 10 $\mu\text{mol/L}$.



Elimination:

Following oral administration, approximately 15 to 30% of the dose was recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted as metabolites, principally M-V, and their conjugates. The data from animal studies suggests that part of the oral dose may be excreted into the bile either unchanged or as metabolites and possibly then reabsorbed.

The mean serum half-life of pioglitazone and total active pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone is a slowly cleared compound with an apparent clearance, CL/F , calculated to be 5-7 L/hr.

V. Special Populations:

What are the changes in the special populations?
Do special populations and disease state patients (renal, hepatic) require adjustment in their initial dosage regimens?