CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-073/S-020

Trade Name: Actos

Generic Name: pioglitazone HCL

Sponsor: Takeda Pharmaceuticals North America, Inc.

Approval Date: November 26, 2003

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APPLICATION NUMBER:

NDA 21-073/S-020

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative and Correspondence Document(s)	X

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APPLICATION NUMBER:

NDA 21-073/S-020

APPROVAL LETTER

NDA 21-073/S-020

Takeda Pharmaceuticals North America, Inc.
Attention: Mary Jo Pritza, MPH, PharmD.
Regulatory Affairs Manager
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Ms. Pritza:

Please refer to your supplemental new drug application dated January 24, 2003, received January 27, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos® (pioglitazone HCl) Tablets, 15 mg, 30 mg and 45 mg.

We acknowledge receipt of your submissions dated July 22, August 13, and November 3, and 7, 2003.

This supplement provides for documentation to support multiple labeling changes to the **CLINICAL PHARMACOLOGY** section, (**Clinical Studies** subsection to include revisions of Actos in combination with metformin, a sulfonylurea, or insulin), **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE and ADMINISTRATION** sections, of the package insert.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted on November 26, 2003.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission
should be designated "FPL for approved supplement NDA 21-073/S-020." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure (package insert labeling – 30 pages)

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

/s/

David Orloff
11/26/03 04:07:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-073/S-020

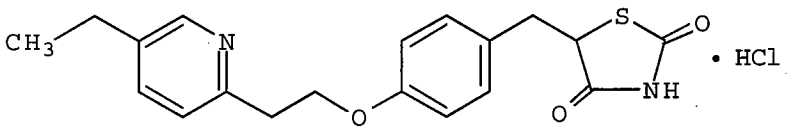
APPROVED LABELING

ACTOS®
(pioglitazone hydrochloride) Tablets

DESCRIPTION

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidine-dione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert in vivo. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



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 daltons. It is soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

ACTOS is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. 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.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (> 99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. In vivo studies of pioglitazone in combination with P450 inhibitors and substrates have been performed (see Drug Interactions). Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated with ACTOS showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

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

Special Populations

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see PRECAUTIONS, Hepatic Effects).

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS improved glycemic control in both males and females. In controlled clinical trials, hemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Drug-Drug Interactions

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Oral Contraceptives: Co-administration of ACTOS (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinyl estradiol AUC (0-24h) and C_{max} respectively. There were no significant changes in norethindrone AUC (0-24h) and C_{max}. In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown.

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS had no significant effect on fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

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.

Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS showed no significant effect on ranitidine pharmacokinetics.

Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73 - 0.95) for C_{max} and 0.88 (0.80 - 0.96) for AUC. In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

Ketoconazole: Co-administration of ACTOS for 7 days with ketoconazole 200 mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06 - 1.23) for C_{max}, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for C_{min}.

Atorvastatin Calcium: Co-administration of ACTOS for 7 days with atorvastatin calcium (LIPITOR®) 80 mg once daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 0.69 (0.57 - 0.85) for C_{max}, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for C_{min}. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for C_{max}, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for C_{min}.

Theophylline: Co-administration of ACTOS for 7 days with theophylline 400 mg administered twice daily resulted in no change in the pharmacokinetics of either drug.

Cytochrome P450: See **PRECAUTIONS**

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by ACTOS results in lower plasma glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of ACTOS appear to persist for at least one year. In controlled clinical trials, ACTOS in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15 mg, 30 mg, and 45 mg ACTOS dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in patients treated with ACTOS than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with ACTOS compared to placebo (Table 1).

Table 1 Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (24 weeks and 16 weeks) and metformin (24 weeks and 16 weeks), the results were generally consistent with the data above. In placebo-controlled trials, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL in patients treated with ACTOS. A similar pattern of results was seen in 24-week combination therapy studies of ACTOS with sulfonylurea or metformin.

In a combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for patients treated with ACTOS was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of

7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed. A similar pattern of results was seen in a 24-week combination therapy study with ACTOS with insulin.

Clinical Studies

Monotherapy

In the U.S., three randomized, double-blind, placebo-controlled trials with durations from 16 to 26 weeks were conducted to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week dose-ranging study, 408 patients with type 2 diabetes were randomized to receive 7.5 mg, 15 mg, 30 mg, or 45 mg of ACTOS, or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) at endpoint compared to placebo (see Figure 1, Table 2).

Figure 1 shows the time course for changes in FPG and HbA_{1c} for the entire study population in this 26-week study.

FIGURE 1 MEAN CHANGE FROM BASELINE FOR FPG AND HBA_{1c} IN A 26-WEEK PLACEBO-CONTROLLED DOSE-RANGING STUDY

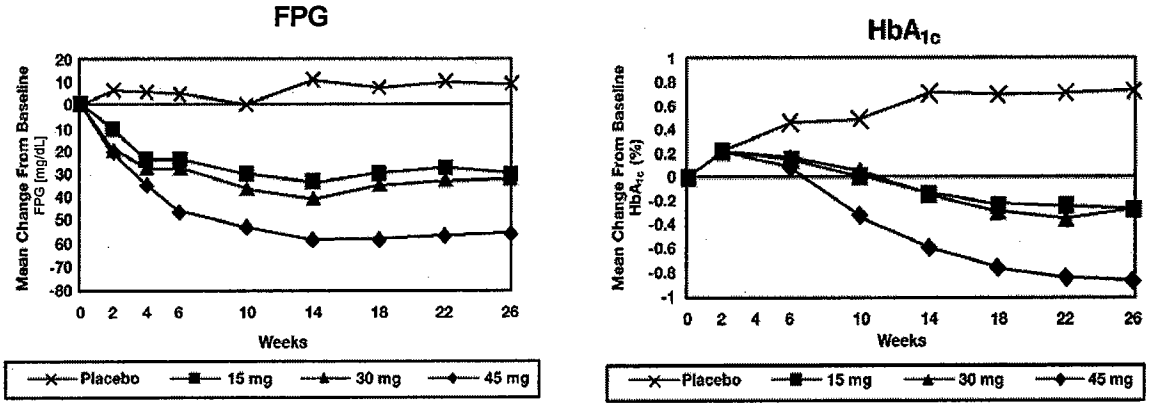


TABLE 2 SHOWS HbA_{1c} AND FPG VALUES FOR THE ENTIRE STUDY POPULATION.

Table 2 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Total Population				
HbA_{1c} (%)	N=79	N=79	N=85	N=76
Baseline (mean)	10.4	10.2	10.2	10.3
Change from baseline (adjusted mean[+])	0.7	-0.3	-0.3	-0.9
Difference from placebo (adjusted mean[+])		-1.0*	-1.0*	-1.6*
FPG (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	268	267	269	276
Change from baseline (adjusted mean[+])	9	-30	-32	-56
Difference from placebo (adjusted mean[+])		-39*	-41*	-65*

[+] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

THE STUDY POPULATION INCLUDED PATIENTS NOT PREVIOUSLY TREATED WITH ANTIDIABETIC MEDICATION (NAÏVE; 31%) AND PATIENTS WHO WERE RECEIVING ANTIDIABETIC MEDICATION AT THE TIME OF STUDY ENROLLMENT (PREVIOUSLY TREATED; 69%). THE DATA FOR THE NAÏVE AND PREVIOUSLY TREATED PATIENT SUBSETS ARE SHOWN IN TABLE 3. ALL PATIENTS ENTERED AN 8 WEEK WASHOUT/RUN-IN PERIOD PRIOR TO DOUBLE-BLIND TREATMENT. THIS RUN-IN PERIOD WAS ASSOCIATED WITH LITTLE CHANGE IN HbA_{1c} AND FPG VALUES FROM SCREENING TO BASELINE FOR THE NAÏVE PATIENTS; HOWEVER, FOR THE PREVIOUSLY-TREATED GROUP, WASHOUT FROM PREVIOUS ANTIDIABETIC MEDICATION RESULTED IN DETERIORATION OF GLYCEMIC CONTROL AND INCREASES IN HbA_{1c} AND FPG. ALTHOUGH MOST PATIENTS IN THE PREVIOUSLY-TREATED GROUP HAD A DECREASE FROM BASELINE IN HbA_{1c} AND FPG WITH ACTOS, IN MANY CASES THE VALUES DID NOT RETURN TO SCREENING LEVELS BY THE END OF THE STUDY. THE STUDY DESIGN DID NOT PERMIT THE EVALUATION OF PATIENTS WHO SWITCHED DIRECTLY TO ACTOS FROM ANOTHER ANTIDIABETIC AGENT.

Table 3 **Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study**

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Naïve to Therapy				
HbA_{1c} (%)	N=25	N=26	N=26	N=21
Screening (mean)	9.3	10.0	9.5	9.8
Baseline (mean)	9.0	9.9	9.3	10.0
Change from baseline (adjusted mean*)	0.6	-0.8	-0.6	-1.9
Difference from placebo (adjusted mean*)		-1.4	-1.3	-2.6
FPG (mg/dL)	N=25	N=26	N=26	N=21
Screening (mean)	223	245	239	239
Baseline (mean)	229	251	225	235
Change from baseline (adjusted mean*)	16	-37	-41	-64
Difference from placebo (adjusted mean*)		-52	-56	-80
Previously Treated				
HbA_{1c} (%)	N=54	N=53	N=59	N=55
Screening (mean)	9.3	9.0	9.1	9.0
Baseline (mean)	10.9	10.4	10.4	10.6
Change from baseline (adjusted mean*)	0.8	-0.1	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FPG (mg/dL)	N=54	N=53	N=58	N=56
Screening (mean)	222	209	230	215
Baseline (mean)	285	275	286	292
Change from baseline (adjusted mean*)	4	-32	-27	-55
Difference from placebo (adjusted mean*)		-36	-31	-59

* Adjusted for baseline and pooled center

In a 24-week placebo-controlled study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one ACTOS treatment group, patients received an initial dose of 7.5 mg once daily. After four weeks, the dose was increased to 15 mg once daily and after another four weeks, the dose was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second ACTOS treatment group, patients received an initial dose of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar manner. Treatment with ACTOS, as described, produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (see Table 4).

Table 4 Glycemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study

	Placebo	ACTOS 30 mg[+] Once Daily	ACTOS 45 mg[+] Once Daily
Total Population			
HbA_{1c} (%)	N=83	N=85	N=85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean[++])	0.9	-0.6	-0.6
Difference from placebo (adjusted mean[++])		-1.5*	-1.5*
FPG (mg/dL)	N=78	N=82	N=85
Baseline (mean)	279	268	281
Change from baseline (adjusted mean[++])	18	-44	-50
Difference from placebo (adjusted mean[++])		-62*	-68*

[+] Final dose in forced titration

[++] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA_{1c} and 238 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.2% and mean FPG was 243 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 2.3% and 2.6% and mean FPG of 63 mg/dL and 95 mg/dL, respectively. For patients who had been previously treated with antidiabetic medication (76%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.7% and mean FPG was 290 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean FPG of 55 mg/dL and 60 mg/dL, respectively. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (see Table 5).

Table 5 Glycemic Parameters in a 16-Week Placebo-Controlled Study

	Placebo	ACTOS 30 mg Once Daily
Total Population		
HbA_{1c} (%)	N=93	N=100
Baseline (mean)	10.3	10.5
Change from baseline (adjusted mean[+])	0.8	-0.6
Difference from placebo (adjusted mean[+])		-1.4*
FPG (mg/dL)	N=91	N=99
Baseline (mean)	270	273
Change from baseline (adjusted mean[+])	8	-50
Difference from placebo (adjusted mean[+])		-58*

[+] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA_{1c} and 240 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.4% and mean FPG was 254 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FPG of 62 mg/dL. For patients who had been previously treated with antidiabetic medication (60%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.6% and mean FPG was 287 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FPG of 46 mg/dL. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

Combination Therapy

Three 16-week, randomized, double-blind, placebo-controlled clinical studies and three 24-week randomized, double-blind, dose-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 8\%$) despite current therapy with a sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy.

ACTOS Plus Sulfonylurea Studies

Two clinical studies were conducted with ACTOS in combination with a sulfonylurea. Both studies included patients with type 2 diabetes on a sulfonylurea, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 560 patients were randomized to receive 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current sulfonylurea regimen. When compared to placebo at Week 16, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} by 0.9% and 1.3% and mean FPG by 39 mg/dL and 58 mg/dL for the 15 mg and 30 mg doses, respectively.

In the second study, 702 patients were randomized to receive 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current sulfonylurea regimen. The mean reductions from baseline at Week 24 in HbA_{1C} were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

The therapeutic effect of ACTOS in combination with sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea.

ACTOS Plus Metformin Studies

Two clinical studies were conducted with ACTOS in combination with metformin. Both studies included patients with type 2 diabetes on metformin, either alone or in combination with another diabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 328 patients were randomized to receive either 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current metformin regimen. When compared to placebo at Week 16, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} by 0.8% and decreased the mean FPG by 38 mg/dL.

In the second study, 827 patients were randomized to receive either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current metformin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

The therapeutic effect of ACTOS in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin.

ACTOS Plus Insulin Studies

Two clinical studies were conducted with ACTOS in combination with insulin. Both studies included patients with type 2 diabetes on insulin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 566 patients receiving a median of 60.5 units per day of insulin were randomized to receive either 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their insulin regimen. When compared to placebo at Week 16, the addition of ACTOS to insulin significantly reduced both HbA_{1c} by 0.7% and 1.0% and FPG by 35 mg/dl and 49 mg/dL for the 15 mg and 30 mg dose, respectively.

In the second study, 690 patients receiving a median of 60.0 units per day of insulin received either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current insulin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively.

The therapeutic effect of ACTOS in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin.

INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS

ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects

ACTOS, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure (see Information for Patients). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during these clinical trials; ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular).

In one 16-week U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin was compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. In a 24-week dose-controlled study in which ACTOS was co-administered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event.

Analysis of data from these studies did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

PRECAUTIONS

General

ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular: In U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with ACTOS as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with ACTOS in combination with insulin (see WARNINGS). Patients with NYHA Class III and IV cardiac status were not studied in these ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with ACTOS, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema: ACTOS should be used with caution in patients with edema. In all U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients and appears to be dose related (see ADVERSE REACTIONS). In postmarketing experience, reports of initiation or worsening of edema have been received.

Weight Gain: Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (Table 6). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6 Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with ACTOS

		Control Group (Placebo)	ACTOS 15 mg	ACTOS 30 mg	ACTOS 45 mg
		Median (25^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)
Monotherapy		-1.4 (-2.7/0.0) n=256	0.9 (-0.5/3.4) n=79	1.0 (-0.9/3.4) n=188	2.6 (0.2/5.4) n=79
Combination Therapy	Sulfonylurea	-0.5 (-1.8/0.7) n=187	2.0 (0.2/3.2) n=183	3.1 (1.1/5.4) n=528	4.1 (1.8/7.3) N=333
	Metformin	-1.4 (-3.2/0.3) n=160	N/A	0.9 (-.3/3.2) n=567	1.8 (-0.9/5.0) N=407
	Insulin	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.3 (0.9/6.3) n=522	4.1 (1.4/6.8) N=338

Note: Trial durations of 16 to 26 weeks

Ovulation: Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an

increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hepatic Effects:
In pre-approval clinical studies worldwide, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 4700 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.
In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pioglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and cases of liver failure, liver transplants and death during postmarketing clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT > 3 times the upper limit of normal) compared to placebo, and cases of reversible jaundice were reported.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up, which may include more frequent liver enzyme monitoring. If serum transaminase levels are

increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

There are no data available to evaluate the safety of ACTOS in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. ACTOS should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests

FPG and HbA_{1c} measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional (see PRECAUTIONS, General, Hepatic Effects and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients

It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on ACTOS should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions
In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3A4 substrate (see CLINICAL PHARMACOLOGY, Metabolism and Drug-Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility
A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with ACTOS (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology
Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy
Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers
Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breastfeeding woman.

Pediatric Use
Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use
Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

In worldwide clinical trials, over 5900 patients with type 2 diabetes have been treated with ACTOS. In U.S. clinical trials, over 4700 patients have received ACTOS, over 3300 patients have been treated for 6 months or longer, and over 450 patients for one year or longer.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 7.

Table 7

Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

IN A 16-WEEK, PLACEBO-CONTROLLED ACTOS PLUS INSULIN TRIAL (N=379), 10 PATIENTS TREATED WITH ACTOS PLUS INSULIN DEVELOPED DYSPNEA AND ALSO, AT SOME POINT DURING THEIR THERAPY, DEVELOPED EITHER WEIGHT CHANGE OR EDEMA. SEVEN OF THESE 10 PATIENTS RECEIVED DIURETICS TO TREAT THESE SYMPTOMS. THIS WAS NOT REPORTED IN THE INSULIN PLUS PLACEBO GROUP.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see

PRECAUTIONS, General, Hypoglycemia and DOSAGE and ADMINISTRATION, Combination Therapy).

In U.S. double-blind studies, anemia was reported in ≤ 2% of patients treated with ACTOS plus sulfonylurea, metformin or insulin (see PRECAUTIONS, General, Hematologic).

In monotherapy studies, edema was reported for 4.8% of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of

patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see PRECAUTIONS, General, Edema).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with ACTOS appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have rarely been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see PRECAUTIONS, Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L. Six of these patients continued to receive ACTOS, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c} which is a better indicator of long-term glycemic control than FPG alone. HbA_{1c} reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOS for a period of time adequate to evaluate change in HbA_{1c} (three months) unless glycemic control deteriorates.

Monotherapy

ACTOS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of ACTOS, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ACTOS.

Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose

The dose of ACTOS should not exceed 45 mg once daily in monotherapy or in combination with sulfonylurea, metformin, or insulin.

Dose adjustment in patients with renal insufficiency is not recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see PRECAUTIONS, General, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Liver enzyme

monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects).

THERE ARE NO DATA ON THE USE OF ACTOS IN PATIENTS UNDER 18 YEARS OF AGE; THEREFORE, USE OF ACTOS IN PEDIATRIC PATIENTS IS NOT RECOMMENDED.

No data are available on the use of ACTOS in combination with another thiazolidinedione.

HOW SUPPLIED

ACTOS is available in 15 mg, 30 mg, and 45 mg tablets as follows:

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:
NDC 64764-151-04 Bottle of 30
NDC 64764-151-05 Bottle of 90
NDC 64764-151-06 Bottle of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other, available in:
NDC 64764-301-14 Bottle of 30
NDC 64764-301-15 Bottle of 90
NDC 64764-301-16 Bottle of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:
NDC 64764-451-24 Bottle of 30
NDC 64764-451-25 Bottle of 90
NDC 64764-451-26 Bottle of 500

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

Rx only

Manufactured by:
Takeda Chemical Industries, Ltd.
Osaka, Japan

Marketed by:
Takeda Pharmaceuticals America, Inc.
475 Half Day Road
Lincolnshire, IL 60069
and
Eli Lilly and Company
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5012100-06-R Revised November 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-073/S-020

MEDICAL REVIEW(s)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 26, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-073/S-020
Actos (pioglitazone HCl) tablets
Combination use of the 45 mg dose with insulin, metformin, and sulfonylurea

SUBJECT: sNDA review issues and recommended action

Background

With the original approval of Actos in 1999, three dosage strengths, 15 mg, 30 mg, and 45 mg, were available for use as monotherapy in DM2. Only the 15 mg and 30 mg doses were approved for use in combination with other antidiabetic medications. This supplement includes the results of three separate 6-months studies of Actos 30 and 45 mg in combination with insulin, metformin, and sulfonylurea, respectively. In addition, the results of two drug-drug interaction studies were submitted. Changes to the labeling were proposed in multiple sections of the package insert, notably in Clin Pharm, Warning, Precautions, and Dosage and Administration. Additionally, based on the preponderance of clinical trial evidence, the sponsor proposes removing the recommendation for q2 month LFT monitoring during the first year of therapy, such that it now be recommended to check LFTs at baseline and periodically thereafter per clinical judgment. Drs. Misbin, Pian (OB) and Lao (OCPB) have conducted thorough reviews. This brief memo summarizes the basic conclusions of Dr. Misbin's review and lists the essence of the labeling changes to be approved at this time.

Clinical Efficacy and Safety

As above, three separate studies comparing the safety and efficacy of Actos 30 vs. 45 mg in combination with, individually, insulin, sulfonylurea, and metformin, were conducted. These studies were designed as superiority trials. Treatment group sizes were approximately 350 patients in 2 trials, and 415 patients in the metformin trial. With regard to efficacy, first of all, the mean effects (change from baseline in HbA1c) with 30 mg in combination with the three other therapies were consistent with the results of the trials reviewed as part of the original NDA. In all three trials, the efficacy of 45 mg was modestly superior (an additional lowering of 0.12-0.29 HbA1c percentage units) to that of 30 mg, though the difference was statistically significant only for the combination with insulin. Nevertheless, the results support reasonable expectation of a variable but real incremental lowering of HbA1c (i.e., improvement in glycemic control) with an increase in daily Actos dose from 30 to 45 mg in patients treated with the combinations of Actos plus either insulin, metformin, or SFU.

With regard to safety, not unexpectedly, with Actos 45 mg compared to 30 mg, there were slight further reductions in hemoglobin concentration, increased reporting of adverse events of CHF (total at 45 mg under 1%), and increased incidence of lower limb edema (variable relative to 30 mg across the trials, total at 45 mg ~15%). There were no new findings with regard to hepatic safety, and no additional reporting of hypoglycemia. Weight gain with 45 mg was greater than with 30 mg (~1 kg difference).

Dr. Misbin concludes that the 45 mg dose may be appropriate in combination with other antidiabetic drugs for patients not achieving adequate glycemic control on Actos 30 mg as part of the combination. I concur. The increased risk of fluid retention/edema, CHF, the reduction in Hgb and increased weight all need to be considered in the decision to increase Actos dose, whether as monotherapy or combination therapy. All the above side effects are monitorable. In the vast majority of patients, fluid retention is manageable with salt restriction, diuretics, and/or reduction in TZD dose.

Labeling

Changes to:

- Clinical Pharmacology, Drug-Drug Interactions regarding the extent of changes in PK of ethinyl estradiol in conjunction with Actos.
- Clinical Pharmacology, Clinical Studies regarding the efficacy results of the new studies of Actos 30 and 45 mg in combination with other agents.
- Warnings, Cardiac Failure and other Cardiac Effects to enumerate the results with regard to reporting of CHF as a serious AE.
- Precautions, Edema to state the apparent dose-relatedness of the incidence of edema in associations with Actos use.
- Precautions, Weight Gain to add information from the current studies to table 6 summarizing the effects of Actos on weight.
- Precautions, Hematologic to add a statement on the apparent dose-relatedness of the effect of Actos on hemoglobin concentration.
- Precautions, Hepatic effects and Information for patients regarding monitoring of LFTs in the first year
- Adverse Reactions to change the numbers of patients treated in controlled trials of Actos, to add information on mild to moderate hypoglycemia, and to amend information on laboratory abnormalities observed in patients treated with Actos.
- Dosage and Administration to imply that the 45 mg dose may be used in combination with SFU, metformin, or insulin.

Biopharmaceutics

As above, minor changes to labeling.

Pharmacology/Toxicology

No new data

Chemistry/ Microbiology

No new data.

DSI/Data Integrity

No inspections conducted

Financial disclosure
The financial disclosure information is in order per Dr. Misbin's review.

Recommendation
Approval with labeling changes as finalized with sponsor on 11-26-03

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/s/

David Orloff
11/26/03 04:02:43 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	**21073**	**APPLICATION TYPE:**	**NDA.....**
SPONSOR:	**Takeda**	**PROPRIETARY NAME:**	**Pioglitazone.....**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**ACTOS.....**
		ROUTE:	**Oral.....**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	**November 26, 2003.....**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
January 24, 2003		NDA supplement	
July 22, 2003		Safety update	
August 13, 2003	August 15, 2003	Safety data	
November 7, 2003	November 10, 2003	Most recent proposal for revised label	

The supplement contains data from three trials comparing 30 to 45 mg of ACTOS when used in combination with other antidiabetic agents. When all the results are viewed as a whole, the higher dose appears marginally more efficacious but associated with more adverse events related to fluid retention. There is also new post-marketing information about congestive heart failure and liver injury.

Recommendation:
The 45 mg dose should not be specifically indicated for use in combination with other agents, but the efficacy and safety data relating to this dose should be presented in the label.
The label should be updated regarding heart failure, liver injury, anemia.

Signed: **Medical Reviewer: Robert I Misbin MD** **Date: November 26, 2003 (drafted 11/12/03)**

Medical Team Leader: _____ **Date:** _____

Table of Contents

Executive Summary

I Recommendations:

The results of the new trials show that 45 mg of Actos is more efficacious than 30 mg in insulin-treated patients, but may to be associated with more congestive heart failure. The higher dose may be appropriate in some patients depending on individual circumstances. In metformin-treated patients, the larger dose probably had somewhat more efficacy but was also associated with more edema. Congestive heart failure was not reported in metformin-treated patients, perhaps because patients likely to develop CHF should not generally be treated with metformin because of the fear of lactic acidosis. In SFU-treated patients, the larger dose did not improve efficacy but was associated with more edema and CHF. The proposed label does not recommend the 45 mg dose for combination therapy in the dosage and Administration section. Instead, the Sponsor has apparently chosen (wisely in my judgment) to present the data from the three new trials without seeking a specific indication for the 45 mg dose. This lets physicians and patients can decide for themselves if the higher dose is appropriate.

The label should be updated regarding risk of congestive heart failure, [redacted] tumors and liver injury.

II Summary of Clinical Findings

Actos was originally approved in doses of 15 mg, 30 mg, and 45 mg. The 45 mg dose was approved only for monotherapy. For combination therapy, no data existed for doses higher than 30 mg. The Sponsor has submitted results of three trials comparing 30 mg and 45 mg in combination with insulin, sulfonylureas (SFU), and metformin (MET) respectively. These trials were 24 weeks in length, as opposed to the 16 week trials of combination therapy in the original NDA. As shown below, the mean change in HbA1c and FPG was greater at 45 mg than 30 mg in all trials, but the difference between the two doses was not always statistically significant.

Changes in HbA1c and FPG when 30 mg or 45 mg of Actos is used in combination with Insulin, Sulfonylureas (SFU) and Metformin (MET): Change at 24 weeks for ITT

	HbA1c, %				FPG, mg/dl		
	Insulin	SFU	MET		Insulin	SFU	MET
30 mg	-1.17	-1.55	-0.80		-32	-52	-38
45 mg	-1.46*	-1.67	-1.01		-46*	-56	-51*

Trial 343 - Actos with Insulin:

Significant reductions from baseline HbA1c, FPG and insulin doses were observed in both groups. There was a small difference in favor of 45 mg with respect to reduction in HbA1c, FPG, and insulin dose. Reporting of edema and hypoglycemia were the same at both doses. Decreases in hemoglobin were slightly greater at 45mg. Mean rises in CPK of 12-13% were similar at both doses.

	30mg (n=345)	45mg (n=345)
HbA1c, % units	-1.17	-1.46*
FPG, mg/dl	-32	-46*
Insulin dose, units	-4.5	-7.3
Triglyceride,%	-4.7	-5.9
FFA mg/dl	-0.94	-2.13*
Hypoglycemic events	44%	48%
Lower limb Edema	13.6%	13.9%
Hemoglobin g/dL	-0.40	-0.55
Congestive Heart Failure (as serious adverse event)	0.3%	0.9%

Trial 341- Actos with sulfonylureas (SFU)

This was a 24 week trial of 30-mg vs 45 mg of Actos in patients who had been on a stable dose of an SFU for at least 30 days at screening. Randomization was preceded by a run-in of 2-4 weeks. During the trial, patients were instructed to alter their dose of SFU. Mean HbA1c at baseline was 9.82% in the group randomized to 30 mg and 9.86% in the group randomized to 45 mg.

There was no difference between 30 and 45 mg with respect to reduction in HbA1c, FPG, or triglyceride. However, weight gain appeared to be somewhat greater at 45 mg than on 30 mg. Reporting of hypoglycemic events (mostly mild) was the same at both doses.

One patient discontinued because of CHF at 30 mg and three patients at 45 mg. Reports of edema were greater at 45 mg than at 30 mg. Decreases in hemoglobin and shift in CPK from normal to elevated were similar at both doses.

	30mg (n=351)	45mg (n=351)
HbA1c, % units	-1.55	-1.67
FPG, mg/dl	-52	-56
TG,%	-9.6	-5.7
Body weight, kg	4.3	5.6
Hypoglycemic events	46%	49%
Discontinuation		
CHF	0.3	0.9
Edema	0.0	0.6
Lower limb Edema	5.7%	12.3%
Hemoglobin g/dL	-0.49	-0.68

Trial 342 - Actos with Metformin

This was a double; blind study comparing 30 and 45 mg of Actos in patients who had been on stable dose of metformin for at least 30 days The duration of blinded therapy was 24 weeks. This was preceded by a one-week single blind placebo run-in. Patients continued their previous dose of metformin during the study. This dose averaged 1700 mg f[illegible] and 1500 mg for [illegible] Antidiabetic medications other than metformin (54% of patients) were discontinued at screening.

	30mg (n=411)	45mg (n=416)
HbA1c, % units	-0.80	-1.01
FPG	-38	-51*
Triglyceride, %	-7	-13*
FFA, mg/dl	-2.5	-3.7*
Body weight, kg	1.44	3.31
Lower limb Edema	2.9%	11.3%
Hemoglobin g/dL	-0.37	-0.55

Update on Safety

Congestive Heart Failure/Edema – The results of the new studies show a dose-dependent increase in edema/congestive failure with Actos.

Hepatic Safety – Results of new studies fail to demonstrate any risk to the liver from taking Actos.

Anemia - The results of the new studies show a dose-dependent decrease in hemoglobin and hematocrit.

Review:

I Introduction and Background

Actos (pioglitazone) was approved in July 1999. Although three dosage strengths were approved, 15, 30, and 45 mg, only the 15 and 30 mg doses were labeled to be used in combination with other antidiabetic medications. The 45-mg dose was labeled for use as monotherapy only. As a condition of approval, Takeda made a phase 4 commitment to perform trials comparing 30 mg and 45 mg of pioglitazone in combination with insulin, sulfonylureas (SFU) and metformin.

This submission contains results from three controlled clinical trials of 30 vs 45 mg of pioglitazone in combination with insulin, sulfonylureas (SFU) and metformin. Additional safety data were also submitted regarding the risk of liver abnormalites and exacerbation of congestive heart failure (CHF).

II Clinically relevant findings from review from other disciplines - NA

III Pharmocokinetic and Pharmacodynamics NA

IV Description of Clinical Sources – electronic submissions

V Clinical Review Methods

Regulatory statements regarding submission of documents

The Sponsor submitted debarment and financial disclosure documents on January 24, 2003. I have examined these documents and found them to be acceptable. The debarment statement indicated that had not and will not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act.

The following financial disclosure information has been signed 11/11/02 and submitted January 24, 2003:

1 Form OMB No. 0910-0396. The applicant certifies that Takeda has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study.

2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in Takeda. below.

3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment

VI Review of Efficacy

Study 343 – Actos plus insulin.

This was a 24 week, randomized, double blind trial of 30 mg vs 45 mg of Actos in patients who had been on a stable dose of insulin for 30 days. Randomization was preceded by a 2-week screening period and one-week placebo lead-in. Oral antidiabetic agents, if present, were discontinued at screening.

The median dose of insulin at baseline was 60 units. Subjects were not allowed to increase their insulin dose but were allowed to decrease the insulin dose if necessitated by safety concerns. Patients were 55% male, mean age 56 years, 64% white, Mean height 171 cm, mean weight 97 kg. Mean HbA1c at baseline was 9.86% in the group randomized to 30 mg and 9.71 in the group randomized to 45 mg. The trial medication was Actos 30 mg with Actos 15 mg or Actos 15 mg placebo. The dose was given without reference to time of day,

Summary of major findings:

Significant reductions from baseline in HbA1c, FPG and insulin dose was observed in both groups. There was a small difference in favor of 45 mg with respect to reduction in HbA1c, FPG, and insulin dose. Reporting of edema and hypoglycemia were the same at both doses. Decreases in hemoglobin were slightly greater at 45mg. A mean rise in CPK of 12-13% was similar at both doses.

	30mg (n=345)	45mg (n=345)
HbA1c, % units	-1.17	-1.46*
FPG, mg/dl	-32	-46*
Insulin dose, units	-4.5	-7.3
Triglyceride,%	-4.7	-5.9
FFA mg/dl	-0.94	-2.13*
Hypoglycemic events	44%	48%
Lower limb Edema	13.6%	13.9%
Hemoglobin g/dL	-0.40	-0.55
Congestive Heart Failure (as serious adverse event)	0.3%	0.9%

Efficacy:

As shown in the following table, there were significant reductions in HbA1c observed in both groups by week 4. From week 8 and beyond the reduction was greater at 45 mg than at 30 mg. The statistically significant ($p<0.05$) reduction from baseline is indicated by "c" and greater reduction at 45 than at 30 mg is indicated by "d"

Table 11.4.1.1.1: Mean Values and Least Squares Mean Change From Baseline for HbA_{1c} (%) by Visit (LOCF) — ITT Population

Visit	Mean Values (%)		Least Squares Mean Change from Baseline (%)	
	30 mg QD Pioglitazone + Insulin (N= 345)	45 mg QD Pioglitazone + Insulin (N= 345)	30 mg QD Pioglitazone + Insulin (N= 345)	45 mg QD Pioglitazone + Insulin (N= 345)
Baseline				
N[a]	328	328	328	328
Mean/LS Mean	9.87	9.69	9.86	9.68
SE	0.086	0.081	0.084	0.085
Week 4				
N[b]	324	325	324	325
Mean/LS Mean Change	9.35	9.14	-0.49[c]	-0.55[c]
SE	0.087	0.079	0.044	0.044
Week 8				
N[b]	327	328	327	328
Mean/LS Mean Change	8.95	8.60	-0.89[c]	-1.08[c,d]
SE	0.090	0.080	0.062	0.062
Week 12				
N[b]	328	328	328	328
Mean/LS Mean Change	8.66	8.29	-1.17[c]	-1.39[c,d]
SE	0.090	0.084	0.070	0.070
Week 16				
N[b]	328	328	328	328
Mean/LS Mean Change	8.61	8.18	-1.20[c]	-1.51[c,d]
SE	0.094	0.087	0.075	0.075
Week 20				
N[b]	328	328	328	328
Mean/LS Mean Change	8.60	8.17	-1.23[c]	-1.50[c,d]
SE	0.094	0.089	0.077	0.078
Week 24 (Endpoint)				
N[b]	328	328	328	328
Mean/LS Mean Change	8.65	8.23	-1.17[c]	-1.46[c,d]
SE	0.095	0.092	0.080	0.081

Consistent with the data for HbA1c, FPG decreased in both arms. From week 4 and beyond the reduction was greater at 45 mg than at 30 mg.

Based on a response of at least 30 mg/dl reduction in FPG, the response rate was 62% at 45 mg vs 56% at 30 mg.

Table 11.4.1.2.1: Mean Values and Least Squares Mean Change From Baseline in FPG (mg/dL) by Visit (LOCF) — ITT Population				
	Mean Values (mg/dL)		Least Squares Mean Change from Baseline (mg/dL)	
Visit	30 mg QD Pioglitazone + Insulin (N=345)	45 mg QD Pioglitazone + Insulin (N=345)	30 mg QD Pioglitazone + Insulin (N=345)	45 mg QD Pioglitazone + Insulin (N=345)
Baseline				
N[a]	325	327	325	327
Mean/LS Mean	199.5	197.2	201.6	198.5
SE	3.97	3.82	4.09	4.07
Week 4				
N[b]	310	304	310	304
Mean/LS Mean Change	163.9	152.5	-33.0[c]	-45.0[c,d]
SE	4.07	3.68	3.83	3.77
Week 8				
N[b]	322	324	322	324
Mean/LS Mean Change	158.9	144.9	-39.8[c]	-53.2[c,d]
SE	3.92	3.66	3.75	3.72
Week 12				
N[b]	324	326	324	326
Mean/LS Mean Change	158.6	148.2	-40.4[c]	-51.9[c,d]
SE	3.72	3.65	3.66	3.64
Week 16				
N[b]	325	327	325	327
Mean/LS Mean Change	161.3	149.8	-36.0[c]	-49.4[c,d]
SE	3.93	3.73	3.84	3.82
Week 20				
N[b]	325	327	325	327
Mean/LS Mean Change	166.0	153.4	-30.5[c]	-44.1[c,d]
SE	3.91	3.92	3.97	3.95
Week 24 (Endpoint)				
N[b]	325	327	325	327
Mean/LS Mean Change	165.6	151.6	-31.9[c]	-45.8[c,d]
SE	3.88	3.98	4.05	4.03

(continued)

The mean insulin dose was about 69 units in both groups. Patients were required to maintain their insulin dose during the study except for reductions allowed for safety. At endpoint there were small but significant reductions in insulin dose in both arms. The reduction at 45 mg of 7.3units was greater than the reduction at 30 mg of 4.5 units. Mean body weight at baseline was 98.4 kg in the 30 mg arm and 96.3 kg in the 45 mg arm. At endpoint the increase in body weight was 3.5 kg in the 30 mg arm and 4.3 kg at 45 mg.

Lipids

Decreases in triglycerides and HDL cholesterol were greater at 45mg than at 30 mg but the differences between 30 and 45 mg were not statistically significant. However, the

reduction in free fatty acids was greater at 45 mg than at 30 mg. These results are shown in the following tables. For other lipid classes, there was no difference between 30 and 45 mg.

Table 11.4.1.3.1: Mean Values and Least Squares Mean Percent Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) — ITT Population

Visit	Mean Values (mg/dL)		Least Squares Mean % Change from Baseline	
	30 mg QD Pioglitazone + Insulin (N=345)	45 mg QD Pioglitazone + Insulin (N=345)	30 mg QD Pioglitazone + Insulin (N=345)	45 mg QD Pioglitazone + Insulin (N=345)
Baseline				
N[b]	305	290	305	290
Mean/LS Mean	204.6	179.9	203.7	180.2
SE	10.00	9.96	10.48	10.79
Week 12				
N[b]	293	276	293	276
Mean/LS Mean % Change	166.0	138.1	-8.5[c]	-12.2[c]
SE	6.65	5.41	2.25	2.41
Week 24 (Endpoint)				
N[b]	305	290	305	290
Mean/LS Mean % Change	171.7	153.9	-4.7	-5.9[c]
SE	6.99	7.49	2.79	2.93
Week 24 (Endpoint)				
LS Mean Difference[d]				-1.19
95% Confidence				

Table 11.4.1.5.1: Mean Values and Least Squares Mean Percent Change from Baseline in HDL-Cholesterol (mg/dL) by Visit (LOCF) — ITT Population

Visit	Mean Values (mg/dL)		Least Squares Mean % Change from Baseline	
	30 mg QD Pioglitazone + Insulin (N=345)	45 mg QD Pioglitazone + Insulin (N=345)	30 mg QD Pioglitazone + Insulin (N=345)	45 mg QD Pioglitazone + Insulin (N=345)
Baseline				
N[a]	305	290	305	290
Mean/LS Mean	40.5	42.2	40.9	42.2
SE	0.70	0.73	0.74	0.76
Week 12				
N[b]	293	275	293	275
Mean/LS Mean % Change	44.5	46.5	11.5[c]	13.3[c]
SE	0.74	0.77	1.16	1.25
Week 24 (Endpoint)				
N[b]	305	290	305	290
Mean/LS Mean % Change	43.8	46.5	9.7[c]	13.0[c]
SE	0.73	0.78	1.18	1.24
Week 24 (Endpoint)				
LS Mean Difference[d]				3.35
95% Confidence Interval				(0.00, 6.71)

Table 11.4.1.8.1:	Mean Values and Least Squares Mean Change from Baseline in FFA (mg/dL) by Visit (LOCF) — ITT Population			
	Mean Values (mg/dL)		Least Squares Mean Change from Baseline (mg/dL)	
Visit	30 mg QD Pioglitazone + Insulin (N=345)	45 mg QD Pioglitazone + Insulin (N=345)	30 mg QD Pioglitazone + Insulin (N=345)	45 mg QD Pioglitazone + Insulin (N=345)
Baseline				
N[a]	291	284	291	284
Mean/LS Mean	13.66	13.18	13.99	13.26
SE	0.405	0.415	0.436	0.445
Week 12				
N[b]	261	263	261	263
Mean/LS Mean Change	11.25	10.44	-2.17[c]	-2.91[c]
SE	0.395	0.392	0.396	0.398
Week 24 (Endpoint)				
N[b]	291	284	291	284
Mean/LS Mean Change	12.23	10.94	-0.94[c]	-2.13[c,d]
SE	0.401	0.389	0.387	0.394
Week 24 (Endpoint)				
LS Mean Difference[e]				-1.19
95% Confidence Interval				(-2.20, -0.17)

Trial 342 – Actos with metformin

This was a 24 week double blind study preceded by a two week screening period and one week placebo run-in. Patients were not allowed to adjust their dose of metformin during the study and continued their previous dose. This dose averaged 1700 mg for [redacted] and 1500 mg for [redacted] Antidiabetic medications other than metformin (54% of patients) were discontinued at screening.

Patients had a mean age of 53, 58% male, 65% white, 19% black, and 14% Hispanic, mean weight 95 kg, mean BMI 32.4

Efficacy:

As shown in the tables and figures that follow, HBA1c fell in both groups. The mean change at 45 mg was slightly greater than at 30 mg (-1.01 vs –0.8) but the difference did not quite achieve statistical significance. However, the reduction in FPG was statistically greater at 45 mg than at 30 mg.

HBA1c:

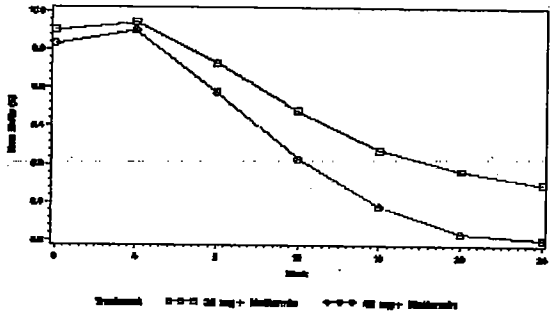
Table 11.4.1.1.1: Mean Values and Least Squares Mean Change From Baseline for HbA1c (%) by Visit (LOCF) — ITT Population

Visit	Mean Values (%)		Least Squares Mean Change from Baseline (%)	
	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)
Baseline				
N[a]	400	398	400	398
Mean/LS Mean	9.90	9.83	9.88	9.83
SE	0.077	0.077	0.079	0.079
Week 4				
N[b]	394	395	394	396
Mean/LS Mean Change	9.94	9.90	0.02	0.05
SE	0.090	0.091	0.047	0.046
Week 8				
N[c]	399	398	399	398
Mean/LS Mean Change	9.73	9.58	-0.19[a]	-0.28[a]
SE	0.099	0.099	0.068	0.67
Week 12				
N[d]	400	398	400	398
Mean/LS Mean Change	9.48	9.23	-0.43[a]	-0.60[a]
SE	0.104	0.106	0.080	0.089
Week 16				
N[e]	400	398	400	398
Mean/LS Mean Change	9.26	8.99	-0.52[a]	-0.85[a]
SE	0.104	0.109	0.087	0.089
Week 20				
N[f]	400	398	400	398
Mean/LS Mean Change	9.17	8.84	-0.73[a]	-0.97[a]
SE	0.105	0.112	0.092	0.091
Week 24 (Endpoint)				
N[g]	400	398	400	398
Mean/LS Mean Change	9.10	8.81	-0.80[a]	-1.01[a]
SE	0.106	0.114	0.094	0.093

Table 11.4.1.1.1: Mean Values and Least Squares Mean Change From Baseline for HbA_{1c} (%) by Visit (LOCF) — ITT Population				
	Mean Values (%)		Least Squares Mean Change from Baseline (%)	
Visit	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)
Week 24 (Endpoint)				
LS Mean Difference[d]				-0.21
95% Confidence Interval				(-0.47, 0.05)

[a] Significant change from baseline (p≤0.05), based on a paired t-test.
[b] N at baseline includes subjects who had a baseline value and at least one post-baseline value.
[c] N at a post-baseline visit includes subjects who had a baseline value and a value for that visit.
[d] Difference between the 45 mg QD pioglitazone group and 30 mg QD pioglitazone group in least

Figure 11.4.1.1.1: Mean HbA_{1c} (%) by Visit (LOCF) — ITT Population



Fasting Plasma Glucose:

Table 11.4.1.2.1: Mean Values and Least Squares Mean Change From Baseline in FPG (mg/dL) by Visit (LOCF) — ITT Population

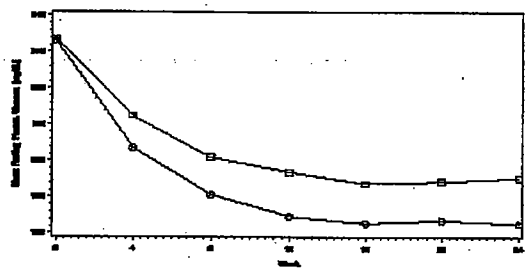
Visit	Mean Values (mg/dL)		Least Squares Mean Change from Baseline (mg/dL)	
	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)
Baseline				
N[a]	398	399	398	399
Mean/LS Mean	233.7	233.0	232.5	232.1
SE	3.48	3.43	3.45	3.44
Week 4				
N[a]	375	383	375	383
Mean/LS Mean Change	212.5	203.5	-22.2[b]	-30.7[b,c]
SE	3.58	3.58	2.36	2.27
Week 8				
N[a]	391	389	391	389
Mean/LS Mean Change	200.9	190.5	-32.2[b]	-42.1[b,c]
SE	3.53	3.45	2.48	2.42
Week 12				
N[a]	397	399	397	399
Mean/LS Mean Change	196.9	184.6	-37.1[b]	-48.6[b,c]
SE	3.53	3.47	2.68	2.65
Week 16				
N[a]	398	399	398	399
Mean/LS Mean Change	193.7	182.7	-39.3[b]	-49.3[b,c]
SE	3.51	3.55	2.78	2.76
Week 20				
N[a]	398	399	398	399
Mean/LS Mean Change	194.2	183.5	-39.3[b]	-49.4[b,c]
SE	3.54	3.58	2.84	2.81
Week 24 (Endpoint)				
N[a]	398	399	398	399
Mean/LS Mean Change	195.2	182.5	-38.2[b]	-50.7[b,c]
SE	3.57	3.57	2.91	2.88

(continued)

Table 11.4.1.2.1: Mean Values and Least Squares Mean Change From Baseline in FPG (mg/dL) by Visit (LOCF) — ITT Population				
	Mean Values (mg/dL)		Least Squares Mean Change from Baseline (mg/dL)	
Visit	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)
Week 24 (Endpoint)				
LS Mean Difference[e]				-12.47
95% Confidence Interval				(-20.51, -4.43)

[a] Significant change from baseline ($p \leq 0.05$), based on a paired t-test.
[b] Significantly different from 30 mg pioglitazone ($p \leq 0.05$).
[c] N at baseline includes subjects who had a baseline value and at least one post-baseline value.
[d] N at a post-baseline visit includes subjects who had a baseline value and a value for that visit.
[e] Difference between the 45 mg QD pioglitazone group and 30 mg QD pioglitazone group in least squares mean change from baseline.
Note: Model for baseline is based on a two-way ANOVA with effects for pooled center and treatment.
Note: Model for change from baseline is based on a two-way ANCOVA with effects for pooled center, treatment, and pooled-center-by-treatment interaction as factors, and baseline value as a covariate.
Data Source: End-of-Text Tables 10.1 and 10.2, and Data Listing 5.2

Figure 11.4.1.2.1: Mean FPG (mg/dL) by Visit (LOCF) — ITT Population



Efficacy subsets:

11.4.2.8.1 By Gender

The mean decreases from baseline in HbA_{1c} and FPG were larger for females than males in both treatment groups. HbA_{1c} decreased by 0.62% in males and 1.06% in females in the 30 mg QD pioglitazone group, and by 0.76% in males and 1.37% in females in the 45 mg QD pioglitazone group. FPG decreased by 34.1 mg/dL in males and 44.5 mg/dL in females in the 30 mg QD pioglitazone group, and by 45.7 mg/dL in males and 56.9 mg/dL in females in the 45 mg QD pioglitazone group.

Metformin dose

In subjects taking less than the median total daily dose of metformin at study entry, mean decrease from baseline to endpoint in HbA_{1c} was 1.02% in the 30 mg QD pioglitazone group and 1.22% in the 45 mg QD pioglitazone group. In subjects taking at least the median total daily dose of metformin at study entry, mean decrease from baseline to endpoint in HbA_{1c} was 0.61% in the 30 mg QD pioglitazone group and 0.84% in the 45 mg QD pioglitazone group.

Lipids:
The reduction in triglycerides was greater at 45 mg than at 30 mg. Otherwise there were no differences among the lipid classes.

Table 11.4.1.3.1: Mean Values and Least Squares Mean Percent Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) — ITT Population

Visit	Mean Values (mg/dL)		Least Squares Mean % Change from Baseline	
	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)	30 mg QD Pioglitazone + Metformin (N=411)	45 mg QD Pioglitazone + Metformin (N=416)
Baseline				
N[c]	371	363	371	363
Mean/LS Mean	238.9	243.2	233.4	244.9
SE	9.75	9.60	9.83	9.97
Week 12				
N[d]	361	357	361	357
Mean/LS Mean % Change	190.9	185.6	-8.0[a]	-13.5[a,b]
SE	8.13	8.11	1.87	1.91
Week 24 (Endpoint)				
N[d]	371	363	371	363
Mean/LS Mean % Change	198.8	184.9	-7.0[a]	-13.2[a,b]
SE	8.90	8.82	2.08	2.18
Week 24 (Endpoint)				
LS Mean Difference[e]				-6.20
95% Confidence Interval				(-11.97, -0.42)

[a] Significant change from baseline (p≤0.05), based on a paired t-test.
[b] Significantly different from 30 mg pioglitazone (p≤0.05).
[c] N at baseline includes subjects who had a baseline value and at least one post-baseline value.
[d] N at a post-baseline visit includes subjects who had a baseline value and a value for that visit.
[e] Difference between the 45 mg QD pioglitazone group and 30 mg QD pioglitazone group in least squares mean percent change from baseline.
Note: Model for baseline is based on a two-way ANOVA with effects for pooled center and treatment. Model for change from baseline is based on a two-way ANCOVA with effects for pooled center, [illegible]

Trail 341 - Actos with sulfonylureas (SFU's)

Table 11.4.1.1.1: Mean Values and Least Squares Mean Change From Baseline for HbA_{1c} (%) by Visit (LOCF) — ITT Population

Visit	Mean Values (%)		Least Squares Mean Change from Baseline (%)	
	30 mg QD Pioglitazone + Sulfonylurea (N=351)	45 mg QD Pioglitazone + Sulfonylurea (N=351)	30 mg QD Pioglitazone + Sulfonylurea (N=351)	45 mg QD Pioglitazone + Sulfonylurea (N=351)
Baseline				
N[b]	340	332	340	332
Mean/LS Mean	9.81	9.88	9.77	9.85
SE	0.079	0.080	0.062	0.063
Week 4				
N[b]	337	328	337	328
Mean/LS Mean Change	9.42	9.48	-0.38[c]	-0.38[d]
SE	0.084	0.089	0.046	0.046
Week 8				
N[b]	340	332	340	332
Mean/LS Mean Change	9.89	9.90	-0.92[c]	-0.97[d]
SE	0.088	0.092	0.057	0.056
Week 12				
N[b]	340	332	340	332
Mean/LS Mean Change	9.53	9.47	-1.25[c]	-1.38[d]
SE	0.092	0.098	0.076	0.077
Week 16				
N[b]	340	332	340	332
Mean/LS Mean Change	9.31	9.25	-1.47[c]	-1.59[d]
SE	0.094	0.098	0.063	0.063
Week 20				
N[b]	340	332	340	332
Mean/LS Mean Change	9.22	9.19	-1.56[c]	-1.64[d]
SE	0.094	0.099	0.064	0.064
Week 24 (Endpoint)				
N[b]	340	332	340	332
Mean/LS Mean Change	9.22	9.17	-1.55[c]	-1.67[d]
SE	0.095	0.100	0.065	0.065

Continued

This was a 24-week double blind tudy of ACTOS 30 vs 45 mg in patients who had been on stable dose of an SFU for at least 30 days. The two double blind period was preceded by two weeks of screening a one week placebo run-in. Study medication was 30 mg ACTOS plus 15 mg or placebo tablet. Actos was given without reference to time of day.

Demographics at baseline of ITT: 55 years old, 58% male, 67% white, 13% African American, 18% Hispanic, mean weight 95 kg, mean BMI 33. 49% of patients were taking the maximal daily-recommended dose of SFU.

Efficacy:

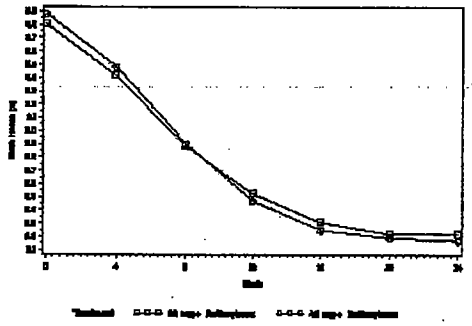
As shown in the table above and below, there was a tendency for greater reduction in HbA1c at 45 mg than at 30 mg but the difference was small and not statistically different.

Table 11.4.1.1.1: Mean Values and Least Squares Mean Change From Baseline for HbA_{1c} (%) by Visit (LOCF) — ITT Population

Visit	Mean Values (%)		Least Squares Mean Change from Baseline (%)	
	30 mg QD Pioglitazone + Sulfonylurea (N=351)	45 mg QD Pioglitazone + Sulfonylurea (N=351)	30 mg QD Pioglitazone + Sulfonylurea (N=351)	45 mg QD Pioglitazone + Sulfonylurea (N=351)
Week 24 (Endpoint)				
LS Mean Difference[c]				-0.12
95% Confidence Interval				(-0.36, 0.12)

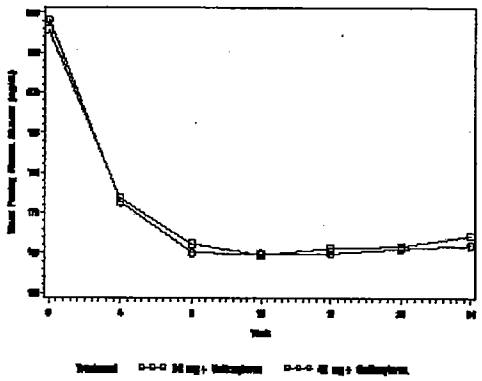
[a] N at baseline includes subjects who had a baseline value and at least one post-baseline value.
[b] N at a post-baseline visit includes subjects who had a baseline value and a value for that visit.
[c] Difference between the 45 mg QD pioglitazone group and the 30 mg QD pioglitazone group in least squares mean change from baseline.
[d] Significant change from baseline ($p \leq 0.05$), based on a paired t-test.
Note: Model for baseline is based on a two-way ANOVA with effects for pooled center and treatment.
Note: Model for change from baseline is based on a two-way ANCOVA with effects for pooled center, treatment, and pooled-center-by-treatment interaction as factors, and baseline value as a covariate.
Data Source: End-of-Text Tables 9.1 and 9.2, and Data Listing 8.1.

Figure 11.4.1.1.1: Mean HbA_{1c} (%) by Visit (LOCF) — ITT Population



There was virtually no difference with respect to fall in FPG as shown in the figure below:

Figure 11.4.1.2.1: Mean FPG (mg/dL) by Visit (LOCF) — ITT Population



There was also little difference between 30 and 45 mg with respect to response rate in HbA1c.

Table 11.4.1.1.2: HbA_{1c} Responder Rate at Endpoint (LOCF Analysis) — ITT Population

Parameter	30 mg QD Pioglitazone + Sulfonylurea (N=340)	45 mg QD Pioglitazone + Sulfonylurea (N=332)
Non-responders	77 (22.6%)	68 (20.5%)
Responders	263 (77.4%)	264 (79.5%)
HbA_{1c} ≤6.1%[a]	29 (8.5%)	30 (9.0%)
HbA_{1c} decreased from baseline by ≥0.5%	263 (77.4%)	264 (79.5%)

[a] HbA_{1c} ≤ the upper limit of normal for non-diabetics.
Note: Responder categories are not mutually exclusive.
N includes patients who had values at both baseline and endpoint.
Data Source: End-of-Text Table 9.3 and Listing 8.1.

Subset analysis did not disclose any important information. Analysis based on Age, race, gender, previous dose of SFU did not lead to any conclusion different from the groups as a whole.

Lipids

Triglycerides VLDL and FFA fell in both groups while total cholesterol, and LDL rose in both groups. The only significant difference was that the rise in HDL cholesterol was greater at 45 mg than at 30 mg.

Table 11.4.1.6.1: Mean Values and Least Squares Mean Percent Change from Baseline in HDL-Cholesterol (mg/dL) by Visit (LOCF) — ITT Population

Visit	Mean Values (mg/dL)		Least Squares Mean % Change from Baseline	
	30 mg QD Pioglitazone + Sulfonylurea (N=351)	45 mg QD Pioglitazone + Sulfonylurea (N=351)	30 mg QD Pioglitazone + Sulfonylurea (N=351)	45 mg QD Pioglitazone + Sulfonylurea (N=351)
Baseline				
N[a]	316	319	316	319
Mean/LS Mean	38.3	39.3	38.7	39.5
SE	0.56	0.62	0.61	0.61
Week 12				
N[a]	309	305	309	305
Mean/LS Mean % Change	43.0	44.7	13.7[d]	16.0[d]
SE	0.62	0.67	1.25	1.25
Week 24 (Endpoint)				
N[a]	316	319	316	319
Mean/LS Mean % Change	42.5	44.6	11.6[d]	15.2[d,e]
SE	0.59	0.67	1.18	1.17
Week 24 (Endpoint)				
LS Mean Difference[e]				3.29
95% Confidence Interval				(0.04, 6.65)

[a] N at baseline includes patients who had a baseline value and at least one post baseline value.

VII Review of Safety

Actos with insulin

Three deaths occurred during the treatment period, two at 30 mg and one at 45 mg. All three were related to preexisting CAD. CHF was reported as a SAE in 1/345 at 30 mg and 3/345 at 45 mg. CHF was cause of withdrawal 1/345 at 30 mg and 2/345 at 45 mg. Lower extremity edema was reported in 13.6% of patients on 30 mg and 13.9% on 45 mg.

Hypoglycemic events were reported in 44% of patients at 30 mg and 48% of patients at 45 mg, but these were usually mild in severity. Hypoglycemia reported as a SAE occurred in 3/345 patients at 30 mg and 0/345 at 45 mg. Body weight increased 4.14 kg on 30 mg and 4.94 on 45 mg.

Laboratory changes:

There were small declines in hematological parameters in both arms. This was slightly greater at 45 mg than at 30 mg.

Table 12.4.2.1.1: Mean at Baseline and Mean Change from Baseline to Endpoint (Week 24) for Hematology Results — ITT Population		
Variable	30 mg QD Pioglitazone + Insulin	45 mg QD Pioglitazone + Insulin
Hemoglobin (g/dL)		
N[a]	234	236
Mean[b]/Mean Change	14.05/-0.40	13.99/-0.55
SD	0.742	0.847
Hematocrit (%)		
N[a]	232	234
Mean[b]/Mean Change	42.84/-1.37	42.81/-1.77
SD	2.281	2.582
RBC ($x10^6$/µL)		
N[a]	232	234
Mean[b]/Mean Change	4.76/-0.17	4.77/-0.23
SD	0.252	0.294
MCV (fL)		
N[a]	232	234
Mean[b]/Mean Change	90.2/0.3	90.1/0.7
SD	2.64	2.55
MCH (pg)		
N[a]	232	234
Mean[b]/Mean Change	29.6/0.2	29.6/0.3
SD	0.93	0.99
MCHC (g/dL)		
N[a]	232	234
Mean[b]/Mean Change	32.9/0.1	32.8/0.0
SD	1.01	1.02
Platelets ($x10^3$/µL)		
N[a]	229	228
Mean[b]/Mean Change	253.2/-7.3	247.1/-5.8
SD	35.46	41.43
Reticulocytes (%)		
N[a]	235	236
Mean[b]/Mean Change	1.52/-0.10	1.44/-0.03
SD	0.530	0.536

Table 12.4.2.1.1: Mean at Baseline and Mean Change from Baseline to Endpoint (Week 24) for Hematology Results — ITT Population		
Variable	30 mg QD Pioglitazone + Insulin	45 mg QD Pioglitazone + Insulin
WBC ($x10^3$/µL)		
N[a]	234	236
Mean[b]/Mean Change	7.05/-0.36	6.97/-0.42
SD	1.488	1.609

[a] N includes subjects who had a baseline value and a Week 24 value.
[b] Mean at baseline for subjects who had a baseline value and a Week 24 value.

ALT/SGPT (IU/L)		
N[a]	238	240
Mean[b]/Mean Change	25.5/-3.4	27.0/-3.7
SD	10.31	12.63
AST/SGOT (IU/L)		
N[a]	239	240
Mean[b]/Mean Change	22.7/-1.5	23.7/-1.2
SD	8.18	9.25
LDH (IU/L)		
N[a]	237	238
Mean[b]/Mean Change	174.3/17.9	171.7/29.6
SD	29.99	31.26
CPK (IU/L)		
N[a]	239	240
Mean[b]/Mean Change	146.1/17.5	153.3/19.4
SD	79.00	98.57

Ten subjects (1.7% [4/238] in the 30 mg QD pioglitazone group and 2.5% [6/240] in the 45 mg QD pioglitazone group) had ALT values that shifted from normal range at baseline to above normal range at Week 24.

CPK values above the upper limit of normal at baseline were observed for 82 subjects (23.8%) in the 30 mg QD pioglitazone group and for 91 subjects (26.4%) in the 45 mg QD pioglitazone group (End-of-Text Table 33.33). At Week 24, elevated CPK values were observed for 65 subjects (27.2%) in the 30 mg QD pioglitazone group and for 73 subjects (30.4%) in the 45 mg QD pioglitazone group. CPK values shifted from normal range at baseline to above normal range at Week 24 for 55 subjects (11.7% [28/239] in the 30 mg QD pioglitazone group and 11.3% [27/240] in the 45 mg QD pioglitazone group; Table 12.4.2.2.1).

One patient (at 45 mg) had an ALT during the trial >3x ULN. This patient had an ALT of 115 at baseline, 122 at week 8 and 239 at week 24.

Actos with metformin

There were no deaths. Discontinuation due to an SAE was 7.8/7.7% at 30 and 45 mg. Cardiac SAE's were reported by 6/411(1.5%) at 30 mg at 3/416 (0.7%) at 45 mg. CHF? Lower limb edema was reported by 2.9% at 30 mg and 11.3% at 45 mg.

Weight increase was reported by 2.9% at 30 mg and 6.7% at 45 mg. Mean weight gain was 1.44 and 3.31 kg.

There were no reports of severe hypoglycemia in either groups. Only one report of hypoglycemia as an AE was confirmed by laboratory evaluation.

ALT elevation > 3X ULN during the trial was observed in 1 patient at 30 mg but this patient had a slightly elevated value at baseline. No patients discontinued because of a liver-related abnormality.

Otherwise, there were no notable changes in laboratory tests except for hemogram as shown below.

Table 12.4.2.1.1: Mean at Baseline and Mean Change from Baseline to Endpoint (Week 24) for Hematology Results ITT Population

Variable	30 mg QD Pioglitazone + Metformin	45 mg QD Pioglitazone + Metformin
Hemoglobin (g/dL)		
N[a]	269	274
Mean[b]/Mean Change	14.15/-0.55	14.26/-0.37
SD	0.702	0.761
Hematocrit (%) N[a]	270	273
Mean[b]/Mean Change	43.15/-1.64	43.44/-1.15
SD	2.220	2.489
RBC (x10^6/μL) N[a]	270	273
Mean[b]/Mean Change	4.85/-0.17	4.82/-0.22
SD	0.233	0.270
MCV (fL) N[a]	270	273
Mean[b]/Mean Change	89.8/0.6	89.8/0.8
SD	2.36	2.58
MCH (pg) N[a]	269	273
Mean[b]/Mean Change	29.6/0.2	29.5/0.2
SD	0.88	0.92
MCHC (gHb/dL) N[a]	269	273
Mean[b]/Mean Change	32.9/0.0	32.9/-0.1
SD	0.92	1.01
Platelets (x10^3/μL) N[a]	268	271
Mean[b]/Mean Change	254.6/-1.3	263.6/-6.3
SD	30.10	30.69
Reticulocytes (%) N[a]	270	274
Mean[b]/Mean Change	1.55/-0.05	1.48/-0.16
SD	0.462	0.476
WBC (x10^3/μL) N[a]	270	274
Mean[b]/Mean Change	6.69/-0.02	6.82/-0.30
SD	1.144	1.321

[a] N includes subjects who had a baseline value and a Week 24 value.
[b] Mean at baseline for subjects who had a baseline value and a Week 24 value.

Note – This table did not transfer appropriately.

The pertinent data are

Hemoglobin	-0.37g/dl	-0.55g/dl
Hematocrt	-1.15%	-1.64%

Actos with SFU's

There was one death due to a myocardial infarction on the 30-mg arm. 5.7% of patients in the 30-mg arm and 12.3% in the 45-mg arm reported lower leg edema. All cardiac disorders was reported in 2.5% and 4.6% at 30 and 45 mg respectively. Selected AE's leading to withdrawal are shown below:

System Organ Class/MedDRA Term	30 mg QD Pioglitazone + Sulfonylurea (N=351)	45 mg QD Pioglitazone + Sulfonylurea (N=351)
Subjects with AEs Leading to Study Discontinuation	21 (6.0%)	34 (9.7%)
Cardiac Disorders	3 (0.9%)	6 (1.7%)
Cardiac Failure Congestive	1 (0.3%)	3 (0.9%)
Myocardial Infarction	2 (0.6%)	2 (0.6%)
Gastrointestinal Disorders	4 (1.1%)	4 (1.1%)
Nausea	3 (0.9%)	1 (0.3%)
General Disorders and Administration Site Conditions	3 (0.9%)	7 (2.0%)
Edema Lower Limb	0 (0.0%)	2 (0.6%)

Reporting of hypoglycemia is shown in the table below:

Table 12.3.1.3.2.1: AEs of Hypoglycemia During the Double-Blind Treatment Period — ITT Population

	Number (%) of Events*							
	30 mg QD Pioglitazone + Sulfonylurea (N=351)				45 mg QD Pioglitazone + Sulfonylurea (N=351)			
System Organ Class/ MedDRA Term	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
AEs of Hypoglycemia	141 (88.0%)	19 (12.0%)	0 (0.0%)	160 (100.0%)	144 (84.0%)	23 (13.0%)	4 (2.0%)	171 (100.0%)
Clinical	138 (86.0%)	19 (12.0%)	0 (0.0%)	157 (100.0%)	141 (84.0%)	23 (14.0%)	4 (2.0%)	168 (100.0%)
Laboratory	3 (100.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)

* This table presents counts of AEs, not subjects.

Changes in hemogram are shown below

Table 12.4.2.1.1: Mean Change from Baseline to Endpoint (Week 24) for Hematology Results — ITT Population

Variable	30 mg QD Pioglitazone + Sulfonylurea	45 mg QD Pioglitazone + Sulfonylurea
Hemoglobin (g/dL)		
N*	262	247
Mean Change	-0.49	-0.68
SD	0.788	0.719
Hematocrit (%)		
N*	259	247
Mean Change	-1.49	-1.80
SD	2.531	2.366
RBC ($x10^6/\mu L$)		
N*	259	247
Mean Change	-0.19	-0.25
SD	0.278	0.262
MCV (fL)		

A greater than 20% fall in hematocrit occurred in 1 patient at 30 mg and 4 patients at 45 mg.

A rise in ALT> 3x ULN occurred in one patient on 30 mg at week 24 (EOS). One patient on 45 mg developed at CPK of 11,000. This fell to 4000 at week 24 and to <1000 at 2-week follow-up.

Mean body weight increased 4.26 kg at 30 mg and 5.55 kg at 45 mg.

Safety Update:

On March 20, 2003, FDA requested that Takeda submit a safety update of its ongoing trials and one completed phase 4 trial, with particular reference to hepatic safety, urinary tract tumors, and edema/CHF. By mutual agreement the cutoff date for Safety events was April 30, 2003.

This safety update was submitted on July 22, 2003. It comprises data from on-going trials and one completed trial.

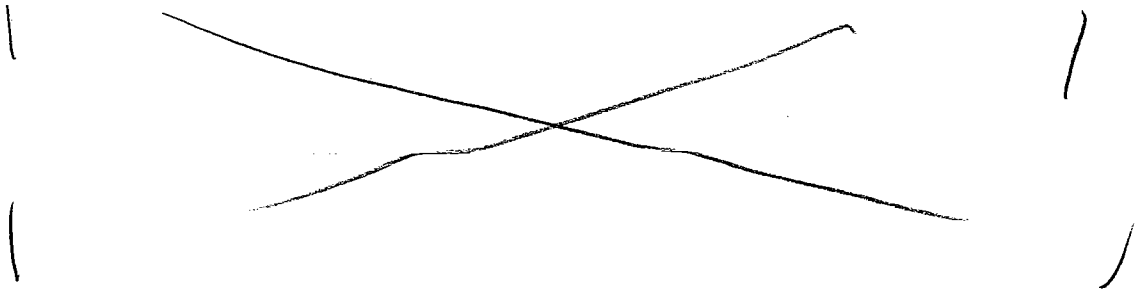
Completed trial:

Trial 520 - Double blind comparison of pioglitazone(15 mg titrated to 45 mg) to glyburide (2.5/5 mg titrated to 15 mg). in patients with type 2 diabetes and mild CHF (completed). There were 151 patients on pioglitazone with mean duration of 44.1 weeks. There were 149 patients on Glyburide with a mean duration of 45.9 weeks. Pertinent AE's reported in this study are as follows:

AE	Pioglitazone	Glyburide
Lower leg edema	16%	10%
Hypoglycemia	3%	11%
Weight gain	7%	3%
Dyspnea	6%	3%

No patient developed ALT>3x ULN. No cases of bladder tumors.

The on-going trials are::



The extent of drug exposure (blinded) in the on-going trials is given in the following table:

						Total
# patients	454	219	224	2003	611	3511
Mean duration, days	310	124	145	274	136	237
Patients years	385	74	89	1503	228	2279

8.4% of patients were had finds of edema and 1.2% of CHF.

In — there were two cases of bladder carcinoma and one benign bladder tumor on pioglitazone previously reported to FDA. In addition, one patient in — vas reported to have a benign bladder tumor. Blinded medication (PIO Vs placebo) has continued.

ALT values > 3 x ULN were experienced by 12/3511 (0.3%) of patients. Four of these patients were withdrawn. At the request of FDA, these patients were unblinded. Details were submitted by Takeda on August 13, 2003 and are described below:

— ALT 54 on screen ig rose to 144 on day 234. This patient was taking

— ALT 202, bilirubin=1.5 on day 323. This patient had been taking **Actos.**

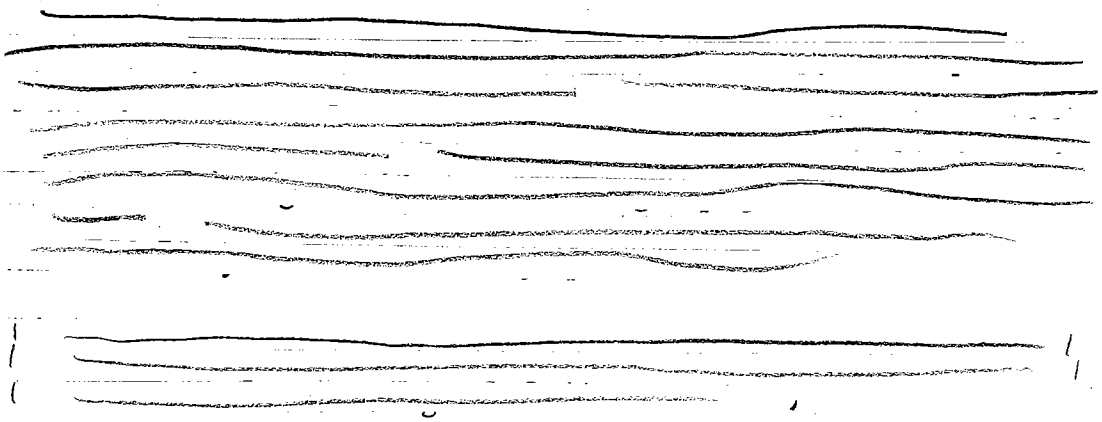
— ALT 445 on day 96 with bilirubin 1.0 Study drug was discontinued on day 98. ALT was normal on day 106, but was again elevated to ALT=266 on study day 134, 36 days after study drug was discontinued. ALT was again normal on study day 158. This patient had been taking **Actos.**

— ALT=284 bilirubin 4.0 on day 80. The patient was found to have **carcinoma** of the Ampulla of Vater and underwent a Whipple procedure. The patient had been randomized to **Actos**

ALT 235 on day 595. The patients continued on study drug and the ALT returned to normal. In view of a very elevated GGTP, this episode was thought to be due to cholelithiasis. **Still on blinded medication.**

In five patients the ALT elevation improved despite continued treatment. In three cases the ALT elevation was found to have been present at baseline.

Recent Update on Congestive Heart Failure:



Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during these clinical trials; therefore, ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular

Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. ACTOS is not recommended in these patients

Comments on Hepatic Safety Issues:

FDA has had several occasions to consider the potential of pioglitazone to damage the liver. For background, I shall begin this section with a review from May 2001. This is followed by a summary of new data from post-approval trials, spontaneous reports and published reports, and final recommendations:

Background:

(From review of May 15, 2001)

Troglitazone was approved January 29, 1997, but was withdrawn March 21, 2000 due to of 94 reports of liver failure including eleven transplants and at least 66 deaths (1). Pioglitazone were approved July 15, 1999. The initial labeling contained a recommendation for liver testing every two months because of fear that pioglitazone might damage the liver. A similar recommendation was made for rosiglitazone, approved in May 1999.

Data from the trials supporting approval of rosiglitazone and pioglitazone suggested that they were much less likely to damage the liver than was troglitazone. Of the 2510 patients in the original trials of troglitazone, there were five patients (0.2%) that had ALT levels over 30 times the upper limit of normal. No such severe ALT elevations occurred in the trials of rosiglitazone or pioglitazone despite a combined exposure of 8071 patients. ALT values over 8 times the upper limit of normal occurred in 0.9% of patients on troglitazone and 0.04% of patients on rosiglitazone or pioglitazone (2).

FDA has reviewed postmarking reports of liver injury for pioglitazone and rosiglitazone and compared results to reports of liver injury attributed to troglitazone. The data represent reports from initial treatment of the first one million patients or more for each drug.

Reports of irreversible liver failure for each of these drugs through January 2, 2001 are shown in the table in comparison to reports of irreversible liver failure after initial marketing of troglitazone received through June 5, 1998 (3). Despite a similar number of patients treated, reports of irreversible liver failure with rosiglitazone and pioglitazone are much less than with troglitazone. The table includes only reports of patients who died of liver failure or had liver transplants, and did not have conditions that I believed were more likely to have caused the liver injury than the thiazolidinedione. I have tried to use the same criteria in reporting cases with rosiglitazone and pioglitazone that I had used previously with troglitazone (3). One of the two rosiglitazone cases had a distant history of hepatitis B but the rise in ALT levels after rosiglitazone had the typical chronology of troglitazone-associated liver failure. I have not included a patient who developed liver failure 18 days after starting pioglitazone because the liver injury and death were probably the result of heart failure. I had previously excluded a case of troglitazone-associated hepatitis whose death was the result of acute heart failure (3).

INITIAL REPORTS OF IRREVERSIBLE LIVER FAILURE

	*Troglitazone**	*Rosiglitazone*	*Pioglitazone*
Months since approval	*16*	*19*	*17*
*Patients treated (millions)***	*1.2*	*1.7*	*1.2*
Drug attributed liver failure			
Transplants	*3*	*0*	*0*
Deaths	*21*	*2*	*0*

* *received through June 5, 1998 (3)*

FDA epidemeologist, Dr David Graham, has used a different definition for his tabulation of liver failure associated with troglitazone. He included patients who recovered from liver failure (1). Drs Zawadzki, and Graham, together with Lanh Green, have reported a comparison of liver failure (reversible plus irreversible) and hepatitis with rosiglitazone, pioglitazone, and troglitazone (4). As shown in the table below, it is clear that rosiglitazone and pioglitazone are much less likely to injure the liver than troglitazone. Also worth noting is the report of a patient, who recovered from troglitazone-associated hepatitis jaundice, and has been treated with rosiglitazone without reappearance of liver injury (5).

INITIAL REPORTS OF HEPATITIS AND ACUTE LIVER FAILURE

Drug	*Approval date*	*# prescriptions, millions**	*Hepatitis*	*Acute liver failure*
Troglitazone	*1/29/97*		*106*	*21*
Rosiglitazone	*5/25/99*		*69*	*3*
Pioglitazone	*7/15/99*		*36*	*3*

- *first 15 months of marketing,*
-

Whether rosiglitazone and pioglitazone can injure the liver at all is still uncertain. But it is important to bear in mind that unexplained hepatitis and liver failure occur in diabetic patients in the absence of a thiazolidinedione (6). Based on reports to date, there is no strong evidence that rosiglitazone or pioglitazone cause liver failure. At a very minimum, they appear to be much safer to the liver than troglitazone.

In this context it is time to reexamine the role of routine liver monitoring. Based on his review of the postmarking reports with troglitazone, David Graham concluded that routine liver monitoring was not effective in prevention liver failure, and that "by four months of therapy, fewer than 5% of patients were monitored in accordance with FDA recommendations" (1).

The incidence of ALT elevation > 3x ULN in patients on pioglitazone in the clinical trials was the same as in patients on placebo. The incidence of ALT elevation in the pioglitazone trials as a whole was the same in trials of other antidiabetic agents. Routine monitoring of 1000 patients taking pioglitazone would probably yield about 5 patients with ALT value of >3 x ULN. But most, if not all, of these elevations will be unrelated to pioglitazone. Over one million patients have been treated with pioglitazone over the last 18 months, but I have not seen even one report of a death or transplant that I could reasonable attribute to pioglitazone. Routine liver monitoring in patients on pioglitazone is unnecessary and counterproductive.

In summary, I recommend that we approve the labeling changes proposed in this supplement. I believe we should go a step further and remove the recommendation for routine liver monitoring.

Robert I Misbin MD
HFD 510
May 15, 2001

1 *Graham DJ. Final Report on Liver failure risk with troglitazone (Rezulin). Food and Drug Administration. March 28,2001*

2 *Misbin RI. Medical Officer's review of the new drug application for Actos. Food and Drug Administration, June 30, 1999*

3 *Misbin RI. Troglitazone-associated hepatic failure. Annals Intern Med 1999;130:330*

4 *Zawadski J, Green L, Graham D. Thiazolidinedione-associated hepatotoxicity (abst). Endocrine Society 2001 Annual Meeting(in press)*

5 *Lenhard MJ, Funk WB. Failure to develop hepatic injury from rosiglitazone in a patient with a history of troglitazone-induced hepatitis. Diabetes Care 2001, 24:168-169*

6 *Jick SS, Stender M, Meyers MW. Frequency of liver disease in type 2 diabetic patients treated with oral antidiabetic agents. Diabetes Care 1999;22:2067-71*

Summary of new information from post-approval trials:

Withdrawal due to serious liver injury was not observed during the three trials (45 mg vs 30mg) described in this sNDA. There were only two episodes of ALT >3x ULN to develop during the trials in a total exposure of over 2000 patients. There were no reports of jaundice

Findings in ongoing trials are summarized previously on pages 28-29. The incidence of ALT>3 ULN was 0.3%. There was no difference between Glyburide and Actos. Other than a patient who developed biliary cancer, there were no examples of serious or irreversible liver injury.

Post-marketing reports:

There are five published reports of liver injury attributed to Pioglitazone. **Cases 1 and 2** appear to have had cholestatic hepatitis. **Case 1** could fit the pattern of troglitazone-associated hepatitis if one assumes that the peak in ALT occurred 1- 2 weeks after Pioglitazone was started and before the first reported laboratory tests. That bilirubin peaked before ALT in **Case #2** was contrary to the pattern seen with troglitazone. **Case 3** appears to be a recurrence of autoimmune hepatitis. **Cases 4 and 5** had reversible hepatitis without jaundice.

Although not published, there are two additional reports that are of interest and are described below. **Case 6** is typical of the pattern of liver injury leading to failure that was seen with troglitazone. **Case 7** was poorly documented but may represent the first example of late onset hepatic injury.

Published Cases:

1 PintoAG Cummings, and Naga C: Severe but reversible cholestatic liver injury after pioglitazone therapy. Annals Int Med 137, 857 2002

This 52 yo female received Actos from [redacted] Actos was stopped because of clinical jaundice. Biopsy was read as chronic cholestasis and cholangitis. The patient has apparently fully recovered. No pretreatment laboratory evaluation was reported. Pertinent labs were:

ALT	131	120	84	58		
Bili			21.5	28.8	16	4

2 May LD, Lefkowitch JH, Kram MT, Rubin DE. Mixed Hepatocelluar-cholestatic liver injury after pioglitazone Ann Int Med 136,449, 2002.

This 49 year old male had been taking Actos for about six months in addition to Glyburide, metformin and other medications. Liver chemistries had been reported to be normal. The dose of Actos was initially 15 mg then increased to 30 mg and 45 mg. About one week after the dose increase to 45 mg the patients presented with jaundice. As shown in the fig in the article, the bilirubin peaked before the ALT level. Actos was discontinued and liver chemistries were normal three months later

3 Chase MP, Yarze JC, Pioglitazone-associated Fulminant Hepatic Failure. A J Gastro 97, 502, 2002.

This 78 year old was reported to have fulminant hepatitis two months after starting Actos. He was treated with prednisone and recovered.
peak ALT=2303, with bili 4.4
ALT=366 with peak bili=12.4

4 Nagasaka, S... amd S Ishibashi Diabetic medicine 19, 344-348 2002.. Piogltiazone induced hepatic injury in a patient previously treated with troglitazone with success.

This 62 year old female had previously been treated with troglitazone without evidence of liver problem. In , pioglitazone was started at 15 mg per day. Approximately one month later she had AST=605 and ALT=911. Bilirubin was reported to be normal. Pioglitazone was stopped and the patient recovered.

5 Akiko, K J Jap Soc Inter Med 2001 and J Gastroenterology 2003, 100(3)333-336

51 yo old female started ACTOS she developed facial edema.
labs showed ALT=583, AST=284 with normal bili. Actos stopped and normal labs on

Other cases of interest

6

7

Hepatic safety - Assessment and recommendation:

Despite exposure to three million patients, I am aware of only one adequately documented example **(case 6)** of a patient who developed a liver failure similar to the pattern seen with troglitazone. This patient had jaundice at the time of diagnosis; routine monitoring of ALT was not reported. Cases 1 and 2 presented with cholestatic jaundice. Even if one assumes that pioglitazone was the cause, monitoring of ALT played no role.

Data from several controlled trials have shown that the incidence of ALT elevation is the same with pioglitazone as with glyburide or placebo. The few cases of liver abnormalities that have been reported in patients taking pioglitazone could easily be accounted for the incidence of liver abnormalities that exists among patients with diabetes in general (Jick et al Diabetes Care 1999, 22:2067-2071.

There is no evidence that use of pioglitazone increases the risk of liver injury in patients with type 2 diabetes. Routine monitoring of ALT is pointless and should be eliminated. I support Takeda's proposal to replace monitoring every two months with "periodic monitoring".

Comments on Congestive Heart Failure:

The results of the three efficacy trials of 30 vs 45 mg in this application provide additional evidence of a dose-related increase in edema and congestive heart failure with piogltiazone.

Recent reports in the literature have also called attention to the development of congestive heart failure during treatment with thiazolidinediones (TZD). Delea and coworkers (Diabetes Care 2003,26:2983-89) used an insurance claims data base with information on 17 million patients annually to investigate insurance claims for congestive heart failure from 1/95 through 3/01 for patients on TZD's. They concluded that patients on TZD's were more likely to have CHF (hazard ratio=1.7, $p<.001$). The CHF risk at 40 months was 8.2% for patients on TZD's and 5.3% for controls.

While there is little doubt that TZD's cause fluid retention that can lead to CHF is some patients, the long term effects on cardiac function are unknown. As stated by Frank Kennedy in Mayo Clinic Proceedings 2003, 78: 1076-7

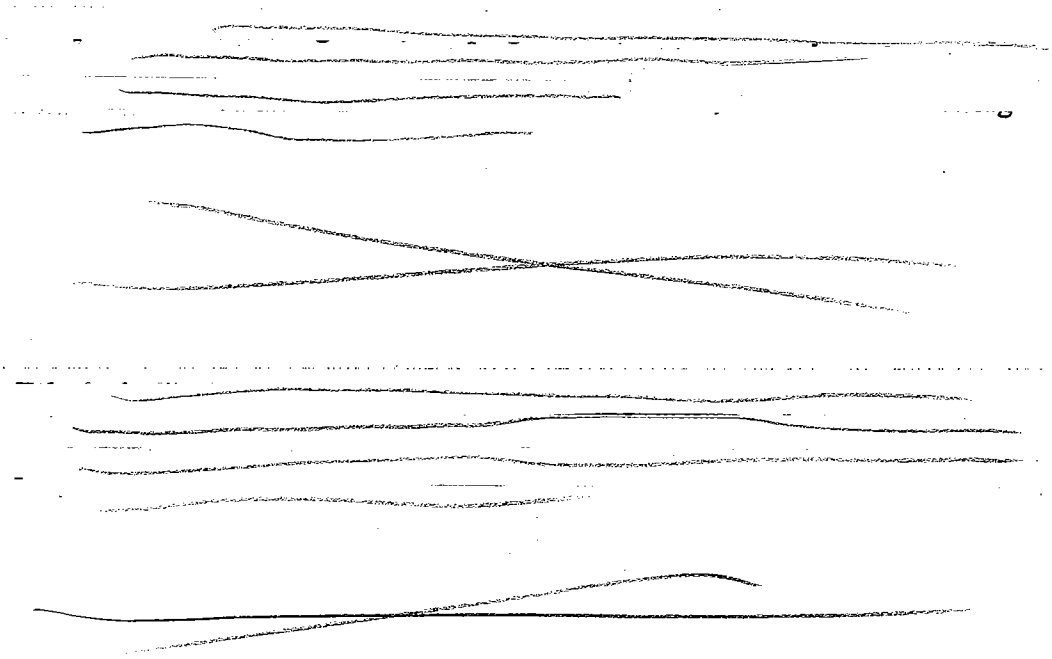
"...there is growing evidence to suggest that TZD's may have many positive effects on cardiac function"

In this regard it should be noted that congestive heart failure and pulmonary edema was reversible in all six cases reported by Kermani and Garg (Mayo Clin Proc 2003, 78: 1088-91), and in the cases reported by Tang et al.(J Am Coll Cardiol 2003, 41:1394-8).

Similarly, in patients with class 3-4 heart failure, troglitazone appeared to increase dyspnea, edema, and diuretic use, but total mortality, cardiac mortality and withdrawal due to non-fatal cardiac events may have been decreased (see appendix). These results suggest the possibility that fluid overload caused by TZD's may be offset by salutary effects on cardiac function.

Despite the hope that TZD's may have beneficial effects long-term, labeling should be dictated by the results of the clinical trials presently available.

Comments on Preclinical finding

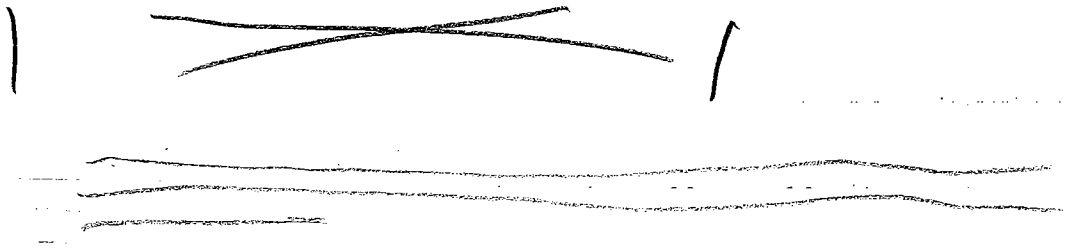


VIII Dosing and Administration Issues

Labeling:

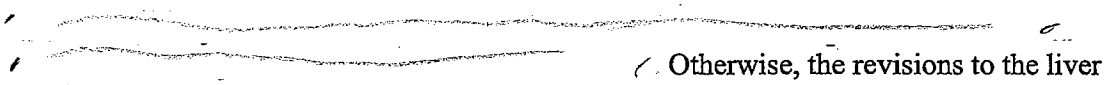
The efficacy data from the three new trials are accurately described in the proposed new label.

The current label describes the two insulin-treated patients at 15-mg ACTOS and two patients at 30 mg ACTOS that developed in CHF during the original 16-week trials. The revised label would go to read:

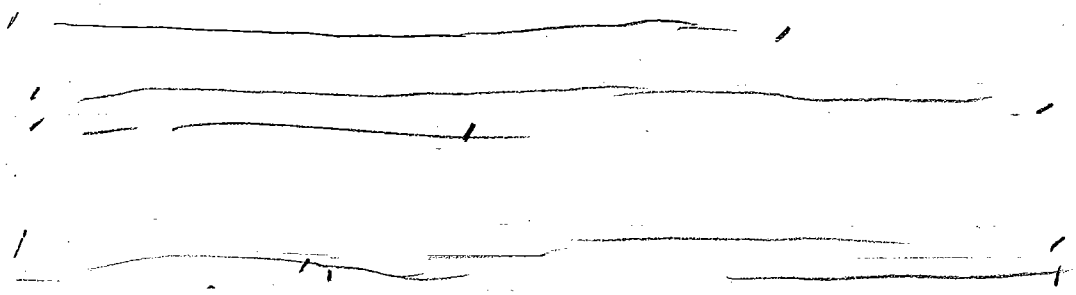


In a 24 week dose-controlled study in which ACTOS was coadministered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event

Also, the development of edema in patients treated with Actos **appears** to be dose related



Otherwise, the revisions to the liver section are acceptable.*



The fall in hemoglobin and hematocrit with ACTOS appears to be dose related.

The Dosage and Administration section is changed as shown below under " Comments on labeling..."

The 45-mg dose is not recommended for combination therapy. However, the revised wording about the maximum recommended dose does not make a distinction between monotherapy and combination therapy. The statement about lack of data in excess of 30 mg in placebo-controlled trials of combination therapy is still true. But deletion of this statement is appropriate because it implies that no safety data is available at all above 30 mg in combination therapy. This was the situation when the label was originally written but is no longer the case.

When taken as a whole, I think the revised label is appropriate, [redacted]. The 45-mg dose is not actually recommended for combination therapy. But the label contains the data from which clinical decisions can be made.

IX Use in Special Populations: NA

X Conclusions and Recommendations

The results of the new trials show that 45 mg of Actos is more efficacious than 30 mg in insulin-treated patients, but may to be associated with more congestive heart failure. The higher dose may therefore be appropriate in some patients depending on individual circumstances. In metformin-treated patients, the larger dose probably had somewhat more efficacy but was also associated with more edema. Congestive heart failure was not reported in metformin-treated patients, perhaps because patients likely to develop CHF are not generally be treated with metformin because of the fear of lactic acidosis. In SFU-treated patients, the larger dose did not improve efficacy but was associated with more edema and CHF.

The Sponsor has not recommended the 45 mg dose for combination therapy in the dosage and Administration section. Instead, the Sponsor has apparently chosen (wisely in my judgment) just to present the data from the three new trials so that physicians and patients can decide for themselves if the higher dose is appropriate. The revised wording about the maximum recommended dose (45 mg) no longer makes the distinction between monotherapy and combination therapy.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ACTOS.

Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose

The dose of ACTOS should not exceed 45 mg once daily in monotherapy or in combination with sulfonylurea, metformin, or insulin. ~~since doses higher than 45 mg once daily have not been studied in placebo-controlled clinical studies. No placebo-controlled clinical studies of more than 30 mg once daily have been conducted in combination therapy.~~

Three safety issues should be updated as described under "labeling". The sections dealing with congestive heart failure/edema need to be updated to reflect new findings from the trials in this sNDA (30 mg vs 45 mg) and

The Sponsor's proposal for periodic measurement of ALT levels is acceptable

Robert I Misbin MD
November 26, 2003
(Submitted in draft to team leader, 11/12/03)

Comments on Labeling to be sent to Takeda:

The proposed ACTOS label submitted Nov 7 2003 is acceptable EXCEPT as follows:

The previous label describes the two insulin-treated patients at 15-mg ACTOS and two patients at 30 mg ACTOS that developed in CHF during the original 16-week trials. The proposed label would go on to read:

In a 24 week dose-controlled study in which ACTOS was coadministered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event

Also, the new wording in the section on edema should be revised:

Should read:

edema was reported more frequently in patients treated with Actos than in placebo-treated patients and appears to be dose related

The description of anemia under "Adverse Events" should state:

The fall in hemoglobin and hematocrit with ACTOS appears to be dose related.

Under Hepatic effects:

Appendix – Troglitazone Heart Failure Study

What follows is a description of a phase 4 trial of troglitazone in patients with class 3 and 4 congestive heart failure that appeared in my August 2, 2002 review of the use of rosiglitazone in combination with Glucovance. It must be stressed that the numbers are very small. Furthermore the patients in this trial were brought to "dry weight" with diuretic prior to randomization. Therefore, these results may not be applicable to a more general population:

A postmarketing study on the effect of 600 mg troglitazone (TRZ) on the echocardiogram parameters, left ventricular mass index (LVMI) and stroke volume index (SVI), in patients with class 3 and 4 heart failure was reported March 12, 2002. The patients had poor glycemic control on pharmacological therapy. Most patients were taking sulfonylureas; about half were taking insulin.

The study was double-blind, placebo controlled and was preceded by a four week run-in during which an attempt was made to bring the patients to "dry weight" by optimizing diuretic therapy. Although planned for 24 week, the study was terminated in March 2000. 77 patients (40 placebo and 37 TRZ) were randomized but only 39 patients (20 placebo and 19 on TRZ) completed the 24 weeks. There were seven deaths, 5 in the placebo-treated group (heart arrest, peritonitis, myocardial infarction, heart arrest, urosepsis) and 2 in TRZ-treated patients (myocardial infarction, retroperitoneal hemorrhage with renal failure). Of the four cardiac deaths, three were on placebo and one on troglitazone. Excluding the deaths, there were five placebo patients who withdrew for reasons related to cardiac/CHF status (two with new myocardial infarcts, and three said to have worsening CHF) and four troglitazone-patients (one with a pleural effusion and three said to have worsening CHF).

There was little change in measurements related to CHF and small differences between the two groups between baseline and final visit. 17% had worsening of pulmonary rales on TRZ and none on placebo. Diuretic therapy remained unchanged in 28 placebo-treated patients and 25 TRZ-treated patients. The dose of diuretics increased in 5 placebo-treated patients and 9 TRZ-treated patients. Three in each group reduced their doses of diuretics. Mean (SE) left ventricular ejection fraction was 40.5(2.5)% in placebo patients and 32.4(2.7)% in TRZ-treated patients. The change from baseline to last observation was –0.9 (2.5)% for placebo patients and 2(1.9)% for TRZ patients.

Of the patients who completed 24 week, 16% of patients on TRZ had worsening ankle edema compared to 5% on placebo. 26% of patients on troglitazone had improvement in ankle edema compared to 41% on placebo. Change from baseline to 24 weeks for the primary echocardiographic parameters are shown in the table.

	LVMI	*SVI*
Baseline mean	*123.2 gr/m2*	*29.2 mL/m2*
TRZ: adjusted mean change from baseline (n)	*-12.9 (19)*	*-0.1 (16)*
Placebo: adjusted mean change from baseline (n)	*-11.3 (20)*	*0.4 (19)*
Treatment effect	*-1.6*	*-0.5*
90% confidence interval	*-10.5, 7.3*	*-5.1, 4.1*

An ANCOVA based on general linear model incorporating the effects of treatment, center, and baseline (as covariant) was used

Change from baseline to 24 weeks for metabolic parameters are as follows. Mean HbA1c was 7.8 and 8.4% for patients on placebo and TRZ respectively. The change at 24 weeks was +0.2 for placebo patients and –1.2 for TRZ-treated patients. Mean FPG was 161 mg/dl and 189 mg/dl for patients on placebo and TRZ respectively. The change at 24 weeks was +13 mg/dl for placebo patients and –51 mg/dl for TRZ-treated patients. Patients on placebo had a mean weight loss of 2.7kg compared to a mean weight gain of 3.2kg in patients of TRZ (p=0.045). Mean triglycerides at baseline were 288 mg/dl and 361 mg/dl for patients on placebo and TRZ respectively. The change at 24 weeks was -50 mg/dl for placebo patients and –94 mg/dl for TRZ-treated patients. Because of the wide range in baseline values and responses, this difference in the fall in triglycerides was not statistically significant.

Given the small number of patients in this study, one must be cautious about drawing firm conclusions. It appears that TRZ caused fluid retention in a few patients, as manifested by worsening of ankle edema, pulmonary rales, and increased use of diuretics. But the frequency and magnitude of these changes were surprisingly small when one considers the baseline characteristics. Echocardiographic parameters showed little change. There were fewer deaths on TRZ than on placebo (2 vs 5), fewer cardiac deaths (1 vs 3), and fewer withdrawals because of cardiac events in patients who did not die (4 vs 5). Glycemic control was unquestionably improved by TRZ.

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

/s/

Robert Misbin
11/26/03 04:16:22 PM
MEDICAL OFFICER
45 mg Actos+ heart failure+liver monitoring

David Orloff
11/26/03 04:17:50 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-073/S-020

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-073/SE8-020
Submission Date	January 24, 2003
Brand Name	ACTOS®
Generic Name	Pioglitazone HCl
Reviewers	S.W. Johnny Lau and Jaya Vaidyanathan
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM Division	Metabolic and Endocrine (HFD-510)
Sponsor	Takeda Pharmaceuticals North America, Inc.
Relevant IND	33,729
Submission Type; Code	Labeling supplement; S
Formulation; Strength(s)	Oral tablet; 15, 30, and 45 mg (as base)
Indication	Adjunct to diet and exercise to improve glycemic control in type 2 diabetic patients

1 Executive Summary

The sponsor markets pioglitazone HCl (ACTOS®), a thiazolidinedione, as an adjunct to diet and exercise to improve glycemic control in type 2 diabetic patients. The sponsor submitted NDA 21-073/SE8-020 to support labeling changes to the safety profile, Drug-Drug Interactions, and Dosage and Administration sections of the July 2002 version of the labeling.

For the Drug-Drug Interactions statement changes, the sponsor submitted 2 studies between pioglitazone and reproductive steroids.

Study 01-00-TL-OPI-513 evaluated the pharmacokinetic effect of 45 mg pioglitazone daily on OC (1 mg norethindrone plus 0.035 mg ethinyl estradiol) daily. Coadministration of 45 mg pioglitazone once daily and 1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily for 21 days resulted in an 11% and 11-14% decrease in ethinyl estradiol $AUC_{(0\text{-}24h)}$ and C_{max}, respectively. There were no significant changes in norethindrone $AUC_{(0\text{-}24h)}$ and C_{max}.

1.1. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE2) has reviewed the Human Pharmacokinetics and Bioavailability section for NDA 21-073/SE8-020 and finds it acceptable. However, the sponsor should receive these labeling comments "Oral Contraceptives:

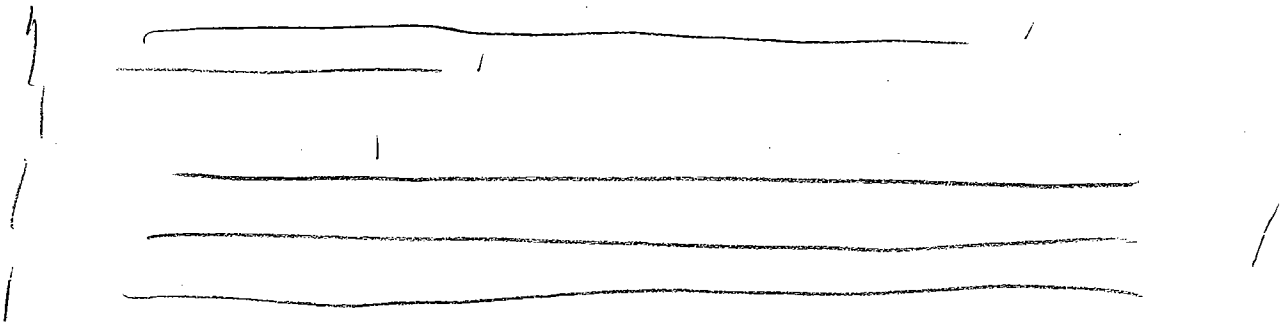
S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPE2

FT signed by Hae-Young Ahn, Ph.D., Team Leader 11/ /03

2 Table of Contents

3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted 2 studies to evaluate the drug-drug interaction potential between pioglitazone and reproductive steroids for labeling changes.



Study 01-00-TL-OPI-513 evaluated the pharmacokinetic effect of 45 mg pioglitazone daily on OC (Ortho-Novum 1/35, 1 mg norethindrone plus 0.035 mg ethinyl estradiol) daily. Thirty five healthy women received Ortho-Novum 1/35 for 2 cycles, 1 cycle (21 days) with 45 mg pioglitazone and another cycle with placebo or vice versa. A washout of 7 days separated the 2 cycles. Coadministration of 45 mg pioglitazone once daily and 1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily for 21 days resulted in an 11% and 11-14% decrease in ethinyl estradiol $AUC_{(0\text{-}24h)}$ and C_{max}, respectively. There were no significant changes in norethindrone $AUC_{(0\text{-}24h)}$ and C_{max}.

4 Question-Based Review

4.1 Background

The current ACTOS® labeling has these statements "Oral Contraceptives: Administration of another thiazolidinedione with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. The pharmacokinetics of coadministration of ACTOS and oral contraceptives have not been evaluated in patients receiving ACTOS and an oral contraceptive. Therefore, additional caution regarding contraception should be exercised in patients receiving ACTOS and an oral contraceptive." in the Precaution section. The sponsor submitted 2 clinical pharmacology studies concerning the interactions between pioglitazone and reproductive steroids. The sponsor proposed changes to the Drug-Drug Interactions statement with Oral Contraceptives in the labeling.

4.2 General Clinical Pharmacology

Pioglitazone clinical pharmacology information is available in:

- product labeling
- *Drugs* 60:333-43 (2000)

4.3 Bioanalytical

Are the bioanalytical methods for pioglitazone, its M-III and M-IV metabolites, ethinyl estradiol, and norethindrone used in Study 01-00-TL-OPI-513 properly validated?

Yes.

Validation for the bioanalytical methods of pioglitazone and its metabolites in human plasma samples:

	pioglitazone	M-III	M-IV
Method	HPLC-UV	HPLC-UV	HPLC-UV
LLOQ, ng/mL			
Linearity, ng/mL	25 - 2500	25 - 2500	25 - 2500
Precision (RSD%)			
75 ng/mL	12.0	5.8	11.6
375 ng/mL	3.9	6.4	4.8
2000 ng/mL	3.9	6.6	4.8
Accuracy (DMT%)			
75 ng/mL	4.7	4.5	4.9
375 ng/mL	-1.9	-4.8	-2.4
2000 ng/mL	0.5	-1.5	0.5

HPLC = high pressure liquid chromatography; UV = ultraviolet detection; LLOQ = lower limit of quantitation; RSD = relative standard deviation; DMT = deviation of mean from theoretical

Validation for the bioanalytical methods of ethinyl estradiol and norethindrone in human plasma samples:

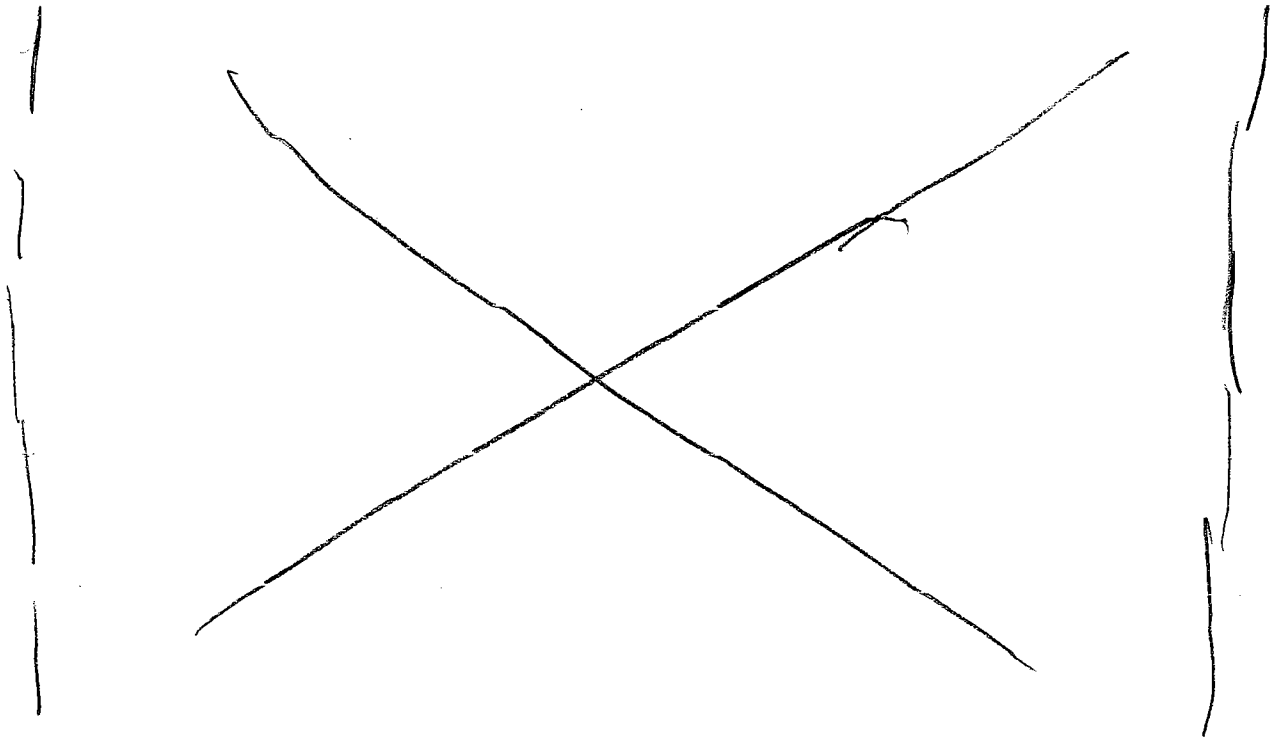
	ethinyl estradiol		norethindrone
Method	GC-MS	Method	GC-MS
LLOQ, pg/mL		LLOQ, ng/mL	
Linearity, pg/mL	2 - 1000	Linearity, ng/mL	0.05 - 25
Precision (RSD%)		Precision (RSD%)	
6 pg/mL	9.04	0.15 ng/mL	7.06
40 pg/ml	8.26	1 ng/mL	9.14
400 pg/mL	9.64	10 ng/mL	7.89
Accuracy (DMT%)		Accuracy (DMT%)	
6 pg/mL	3.8	0.15 ng/mL	-1.13
40 pg/ml	2.53	1 ng/mL	-1
400 pg/mL	0.914	10 ng/mL	1.62

GC = gas chromatography; MS = mass spectrometry detection; LLOQ = lower limit of quantitation; RSD = relative standard deviation; DMT = deviation of mean from theoretical

Validation of the bioanalytical methods for pioglitazone, M-III, M-IV, ethinyl estradiol, and norethindrone are acceptable. However, the interday precision values for 75 ng/mL pioglitazone and M-IV (12 and 11.6%, respectively) were nearing the limit of acceptance.

4.4 Extrinsic Factor

Did the sponsor adequately assess the interaction potential between OC and pioglitazone?
Yes.



The sponsor conducted another study as follow:
Study 01-00-TL-OPI-513 evaluated the PK effect of daily 45 mg oral pioglitazone on daily OC (Ortho-Novum 1/35, 1 mg norethindrone plus 0.035 mg ethinyl estradiol) for 2 cycles. Thirty five healthy women already receiving any OC received Ortho-Novum 1/35 for 1 cycle (screening period). These randomized participants received either Ortho-Novum 1/35 plus 45 (30 + 15) mg pioglitazone daily (treatment A) or Ortho-Novum 1/35 plus placebo daily (treatment B) for 21 days followed with a 7-day washout. Participants then crossed over their previous treatment for another 21 days (Period 2). All doses were administered at the study site. Plasma samples were collected for determination of predose concentrations of pioglitazone, ethinyl estradiol, and norethindrone on Days 1, 18 - 21, 29, and 46 - 48. On Days 21 and 49, serial PK-plasma samples were collected for ethinyl estradiol and norethindrone determination over 24 hours postdose (with the exception of predose assessments for pioglitazone). See Attachment 2 for study synopsis. The sponsor selected the 45 mg pioglitazone dose since this is the maximum recommended dose. The sponsor chose Ortho-Novum 1/35 because it was studied with troglitazone, another thiazolidinedione (*J Clin Pharmacol* **39**:410-7 (1999)).

Study 01-00-TL-OPI-513's results follow:
Predose plasma concentrations for pioglitazone, ethinyl estradiol, and norethindrone showed that all of them achieved steady state on Day 18 (without regard to coadministration with pioglitazone or placebo for ethinyl estradiol and norethindrone steady state determination). See Attachment 3 for details.

Figure 11.2a Mean ± Standard Error Ethinyl Estradiol Plasma Concentrations

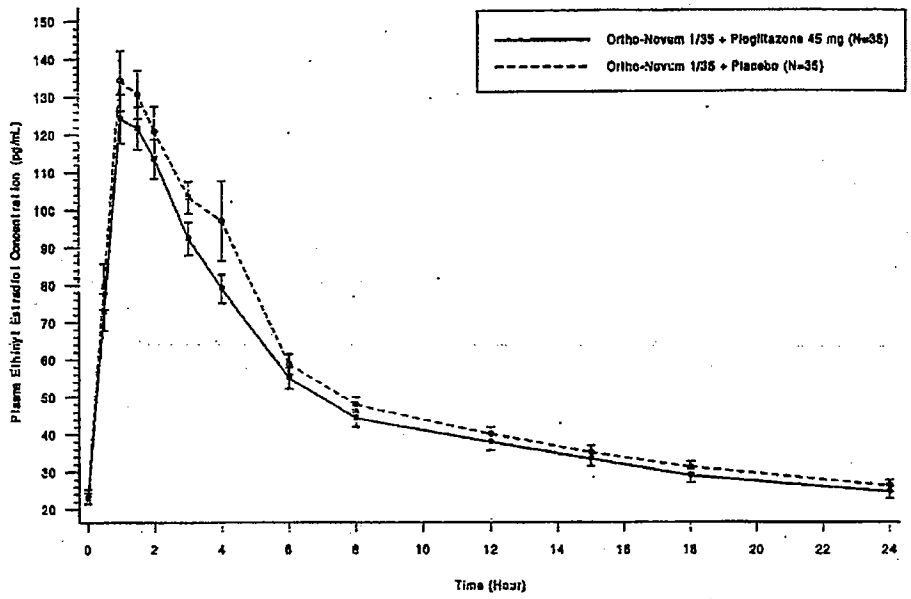


Table 11.2a Summary Statistics and ANOVA Results of the Ethinyl Estradiol Pharmacokinetic Parameters by Treatment

Parameter	Least Squares (LS) Means: Ortho-Novum 1/35 + Pioglitazone HCl	Least Squares (LS) Means: Ortho-Novum 1/35 + Placebo	Ratio of LS Means (%)	90% Confidence Interval on Ratio (%)
$AUC_{(0\text{-}24)}$ (hour·pg/mL)	1077.7	1208.9	89.1	82.7 - 96.1
C_{max} (pg/mL) (including Subject 1036)	122.5	141.6	86.5	78.2 - 95.7
C_{max} (pg/mL) (excluding Subject 1036)	122.6	137.0	89.5	82.3 - 97.4
C_{min} (pg/mL)	20.7	21.8	95.2	88.1 - 102.9

Participant 1036 had unexplainably high [redacted] for treatment A, whereas other 34 participants' C_{max} ranged from 70.4 – 240 pg/mL. Participant 1036's 2 and 6 h concentrations were [redacted] respectively. Comparisons of treatments A to B showed that ethinyl estradiol $AUC_{(0\text{-}24h)}$, C_{max}, and C_{min} were decreased 11%, 11 - 14%, and 5%, respectively.

Figure 11.2b Mean ± Standard Error Norethindrone Plasma Concentrations

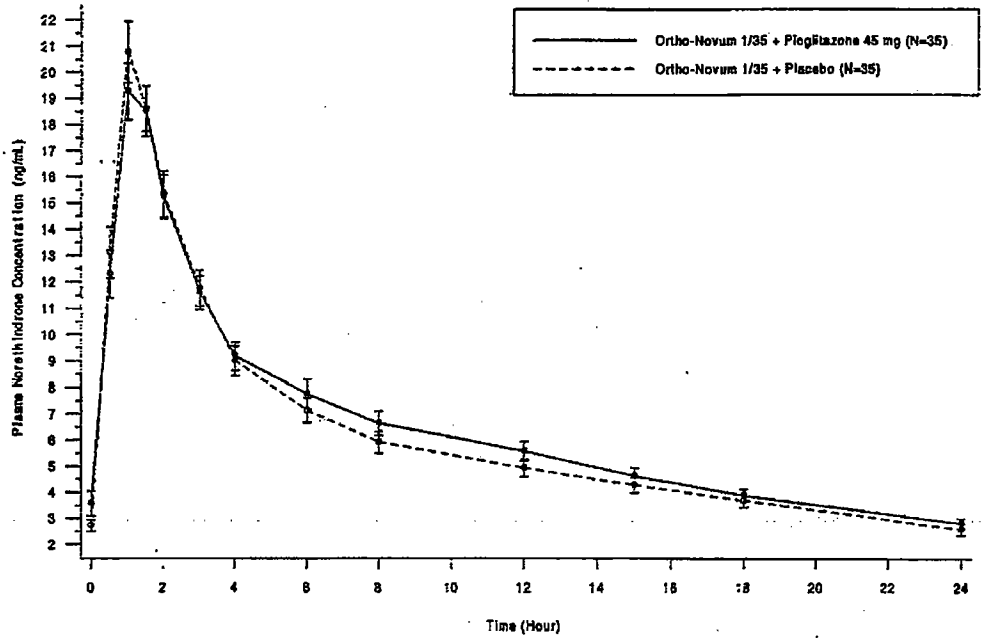


Table 11.2b Summary Statistics and ANOVA Results of the Norethindrone Pharmacokinetic Parameters by Treatment

Parameter	Least Squares (LS) Means		Ratio of LS Means (%)	90% Confidence Interval on Ratio (%)
	Ortho-Novum 1/35 + Pioglitazone HCl	Ortho-Novum 1/35 + Placebo		
$AUC_{(0\text{-}24)}$ (hour·ng/mL)	144.0	140.1	102.8	92.5 - 114.2
C_{max} (ng/mL)	19.0	20.4	93.2	83.9 - 103.5
C_{min} (ng/mL)	2.44	2.13	114.7	104.5 – 125.9

Comparisons of treatments A to B showed that norethindrone $AUC_{(0\text{-}24h)}$, C_{max}, and C_{min} were increased 3%, decreased 7%, and increased 15%, respectively.

5 Labeling Comments

CLINICAL PHARMACOLOGY

Drug-Drug Interactions

The sponsor should change to this statement "Oral Contraceptives:

proposed "Oral Contraceptives:

4 Page(s) Withheld

X § 5 (b)(4) Trade Secret / Confidential

_____ § 5 (b)(4) Draft Labeling

_____ § 5 (b)(5) Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-*21-073 S000

2. SYNOPSIS

Name of Company: Takeda Pharmaceuticals North America, Inc.	**Individual Study Table Referring to part of the Dossier** Volume:	**(For National Authority Use Only)**
Name of Finished Product: ACTOS®		
Name of Active Ingredient: Pioglitazone HCl	Page:	
Title of Study: A Double-Blind, Crossover, Placebo-Controlled Study of the Effects of Pioglitazone HCl on the Pharmacokinetics of Ethinyl Estradiol and Norethindrone (Ortho-Novum) in Healthy Female Volunteers		
Investigators: [redacted]		
Study Centers: [redacted]		
Publication (reference): None		
Study Period (years): 15 July 2001 — 9 December 2001	**Phase of Development:** Phase I	
Objectives: The objective of this study was to evaluate the effects of pioglitazone HCl on the pharmacokinetics of ethinyl estradiol and norethindrone (Ortho-Novum 1/35 [norethindrone 1.0 mg; ethinyl estradiol 0.035 mg]).		
Methodology: The pharmacokinetic effect of 45 mg pioglitazone HCl (ACTOS®) on the oral contraceptive Ortho-Novum 1/35 when administered concurrently once every morning (for 2 cycles) was evaluated in a single-center, randomized, double-blind, placebo-controlled, crossover pharmacokinetic (PK) study. Subjects were given Ortho-Novum 1/35 to be taken for 1 cycle during the screening period (prior to which subjects were required to have taken at least 1 cycle of any oral contraceptive). Following the screening period, subjects were randomly administered 1 of 2 treatments (Ortho-Novum 1/35 plus pioglitazone HCl 45 mg [Treatment A] or Ortho-Novum 1/35 plus placebo [Treatment B]) for 21 days (Period 1) followed by a 7-day washout. Subjects then crossed over from their previous treatment for another 21 days (Period 2). All doses were administered at the study site. Subjects were admitted to the study site for screening (pregnancy test, alcohol/drug screen, PAP test, ECG) and/or safety (vital signs, adverse events [AEs], clinical laboratory tests, physical examinations) assessments from Days −1 through 1, Days 20 through 22, Days 28 through 29, and Days 48 through 50. Plasma samples were taken for determinations of predose levels of pioglitazone HCl, ethinyl estradiol, and norethindrone on Days 1, 18 through 21, 29, and 46 through 48. Following dosing on Days 21 and 49, subjects underwent serial blood sampling for PK analysis (for ethinyl estradiol and norethindrone only, with the exception of predose assessments for pioglitazone HCl) at protocol-specified times between 0 and 24 hours postdose. On Days 22 and 50, in addition to the 18- and 24-hour postdose PK sampling, vital sign assessments and liver function tests were performed. Upon readmission to the study facility on Day 48, a brief physical examination was performed. Adverse events and concomitant medications were assessed daily throughout the study period.		
Number of Subjects (Planned and Analyzed): Planned: 36 (18 in each treatment sequence). Analyzed: 35 in PK analyses; 35 in safety analyses.		

Name of Company: Takeda Pharmaceuticals North America, Inc.	**Individual Study Table Referring to part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: ACTOS®	Volume:	
Name of Active Ingredient: Pioglitazone HCl	Page:	

Diagnosis and Main Criteria for Inclusion: The study included females in good health who were 20 to 42 years of age, who were within –10% and +30% of their ideal body weight, had normal clinical laboratory results, a negative hepatitis panel, negative HIV screen, and negative urine screen for drugs of abuse including alcohol. In addition, subjects were to have taken at least 1 cycle of any oral contraceptive followed by 1 cycle of Ortho-Novum 1/35 prior to randomization and were to use barrier contraceptive methods during the study.

Test Product, Dose and Mode of Administration, Batch Number: Single orally administered 15 mg pioglitazone HCl tablet (lot number 01043) and 30 mg pioglitazone HCl tablet (lot number 01073) administered together for a total dose of 45 mg, plus 1 tablet of Ortho-Novum 1/35 (lot number 29N211), administered once every morning for 21 days per cycle.

Duration of Treatment: Two treatment periods of 21 days, separated by a washout period of 7 days.

Reference Therapy, Dose and Mode of Administration, Batch Number: Two orally administered placebo tablets (lot number 01013) taken concurrently with 1 tablet of Ortho-Novum 1/35 (lot number 29N211) administered once every morning for 21 days per cycle.

Criteria for Evaluation:
Pharmacokinetics: The PK variables were calculated for ethinyl estradiol and norethindrone and included the area under the plasma concentration-time curve from dosing until 24 hours ($AUC_{(0-24)}$), maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}), and fluctuation index (FI).
Safety: Safety was based on the incidence of AEs, changes over time in laboratory values (including liver function tests), vital signs, electrocardiograms (ECGs), and physical examinations.

Statistical Methods:
Demographic and Baseline Characteristics: Descriptive statistics and frequencies were used to summarize demographic variables (race, age, height, and weight) by treatment sequence.
Pharmacokinetic Measures: For plasma concentrations, descriptive statistics were tabulated by time point and by treatment. For ethinyl estradiol and norethindrone, descriptive statistics were tabulated by treatment for pharmacokinetic parameters. An analysis of variance (ANOVA) was performed on $AUC_{(0-24)}$, C_{max}, C_{min}, T_{max}, and FI. The values for $AUC_{(0-24)}$, C_{max}, and C_{min} were natural log transformed prior to analysis, and the confidence intervals (CIs) of least square (LS) means ratio for $AUC_{(0-24)}$, C_{max}, and C_{min} were obtained by taking the antilog of 90% CIs for treatment difference between LS means for Ortho-Novum 1/35 plus pioglitazone HCl 45 mg and Ortho-Novum 1/35 plus placebo on the log scale.
The following model was used to assess drug-drug interaction:

The following model was used to assess steady state of ethinyl estradiol and norethindrone:

The following model was used to assess unchanged pioglitazone HCl, its major metabolites M-III and M-IV, and total pioglitazone:

Safety: Adverse events were summarized by system organ class and preferred term within each system organ class based on the Medical Dictionary for Regulatory Affairs (MedDRA). Data for laboratory values and vital signs were summarized using descriptive statistics. Shift tables of laboratory data were

Name of Company: Takeda Pharmaceuticals North America, Inc.	Individual Study Table Referring to part of the Dossier Volume:	(For National Authority Use Only)
Name of Finished Product: ACTOS®		
Name of Active Ingredient: Pioglitazone HCl	Page:	

also provided.

Subject Disposition:
A total of 40 subjects were enrolled in the study. Five subjects were discontinued prior to receiving any study drug and, therefore, were excluded from the safety and PK analyses. All of the remaining 35 subjects (18 subjects in treatment sequence AB and 17 subjects in treatment sequence BA) completed the study and were included in the PK analyses.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Pioglitazone HCl: For subjects who received pioglitazone HCl and Ortho-Novum 1/35, steady state concentrations of unchanged pioglitazone, M-III, M-IV, and total pioglitazone were attained by Day 18.

Ethinyl Estradiol: Steady state ethinyl estradiol concentrations were attained by Day 18 for subjects who received Ortho-Novum 1/35 plus pioglitazone HCl and for subjects who received Ortho-Novum 1/35 alone. Following daily dosing for 21 days, statistically significant differences between treatments were observed for the LS mean ethinyl estradiol $AUC_{(0\text{-}24)}$ and C_{max}. The LS mean $AUC_{(0\text{-}24)}$ and C_{max} following treatment with Ortho-Novum 1/35 plus pioglitazone HCl were 10.9% and 13.5% lower, respectively, compared to treatment with Ortho-Novum 1/35 alone ($AUC_{(0\text{-}24)}$, 1077.7 vs. 1208.9 pg/mL; C_{max}, 122.5 vs. 141.6 pg/mL). Similar results were obtained when Subject 1036 was excluded from the analysis of C_{max}. There were no statistical differences observed between treatment groups for the LS mean C_{min}, T_{max}, or FI. Based on the analysis that included Subject 1036, the 90% CI of the ratio for ethinyl estradiol LS mean $AUC_{(0\text{-}24)}$ for subjects who received Ortho-Novum 1/35 plus pioglitazone HCl to subjects who received Ortho-Novum 1/35 alone was within 80% to 125%, but was not within this range for LS mean C_{max}. However, when Subject 1036 was excluded, the 90% CI of the treatment ratio for LS mean C_{max} was within the 80% to 125% range. These results indicate that there is a lack of drug interaction between pioglitazone HCl and ethinyl estradiol.

Parameter	Least Squares (LS) Means: Ortho-Novum 1/35 + Pioglitazone HCl	Least Squares (LS) Means: Ortho-Novum 1/35 + Placebo	Ratio of LS Means (%)	90% Confidence Interval on Ratio (%)
$AUC_{(0\text{-}24)}$ (hour·pg/mL)	1077.7	1208.9	89.1	82.7 - 96.1
C_{max} (pg/mL) (including Subject 1036)	122.5	141.6	86.5	78.2 - 95.7
C_{max} (pg/mL) (excluding Subject 1036)	122.6	137.0	89.5	82.3 - 97.4
C_{min} (pg/mL)	20.7	21.8	95.2	88.1 - 102.9

For subjects who received Ortho-Novum 1/35 plus pioglitazone HCl, the ethinyl estradiol LS mean T_{max} and FI were 1.3 hours and 2.3, respectively. The corresponding values for subjects who received Ortho-Novum 1/35 alone were 1.5 hours and 2.4, respectively.

Norethindrone: Steady state norethindrone concentrations were attained by Day 18 for subjects who received pioglitazone HCl and Ortho-Novum 1/35 and for subjects who received Ortho-Novum 1/35 alone. Following daily dosing for 21 days, statistically significant differences between treatments were observed for the LS mean norethindrone C_{min} (2.4 ng/mL following treatment with Ortho-Novum 1/35

Name of Company: Takeda Pharmaceuticals North America, Inc.	Individual Study Table Referring to part of the Dossier	(For National Authority Use Only)
Name of Finished Product: ACTOS®	Volume:	
Name of Active Ingredient: Pioglitazone HCl	Page:	

plus pioglitazone HCl vs. 2.1 ng/mL following treatment with Ortho-Novum 1/35 alone) and FI (2.8 vs. 3.2). There were no statistical differences observed between treatment groups for the LS mean $AUC_{(0-24)}$, C_{max}, or T_{max}. The 90% CI of the ratio for norethindrone LS mean $AUC_{(0-24)}$ and C_{max} for subjects who received Ortho-Novum 1/35 plus pioglitazone HCl to subjects who received Ortho-Novum 1/35 alone were within the 80% to 125% range, indicating that there is a lack of drug interaction between pioglitazone HCl and norethindrone.

Parameter	Least Squares (LS) Means: Ortho-Novum 1/35 + Pioglitazone HCl	Least Squares (LS) Means: Ortho-Novum 1/35 + Placebo	Ratio of LS Means (%)	90% Confidence Interval on Ratio (%)
$AUC_{(0-24)}$ (hour·ng/mL)	144.0	140.1	102.8	92.5 - 114.2
C_{max} (ng/mL)	19.0	20.4	93.2	83.9 - 103.5
C_{min} (ng/mL)	2.44	2.13	114.7	104.5 – 125.9

For subjects who received pioglitazone HCl and Ortho-Novum 1/35, the norethindrone LS mean T_{max} and FI were 1.2 hours and 2.8, respectively. The corresponding values for subjects who received Ortho-Novum 1/35 alone were 1.2 hours and 3.2, respectively.

Safety Results:

- There were no deaths or other serious AEs experienced in this study, and no subject (who received study drug) was discontinued due to an AE.
- The overall incidence of AEs was similar in subjects during treatment with Ortho-Novum 1/35 plus pioglitazone HCl as compared with Ortho-Novum 1/35 alone.
- Adverse events experienced by subjects in this study most frequently affected the nervous and gastrointestinal body systems; the most frequently experienced events in both treatment groups included headache, abdominal pain, nausea, pharyngolaryngeal pain, and nasal congestion. Overall, there were no apparent differences between treatments with regard to AE severity and relationship to study drug.

CONCLUSIONS:

In conclusion, results from the present study indicate that concomitant administration of pioglitazone HCl at a maximal therapeutic dosage (45 mg/day) did not significantly alter the peak (C_{max}) or total ($AUC_{(0-24)}$) exposure of ethinyl estradiol and norethindrone (Ortho-Novum 1/35).

The above conclusions are based on the following findings:

- There is a lack of drug interaction of pioglitazone HCl upon ethinyl estradiol.
- There is a lack of drug interaction of pioglitazone HCl upon norethindrone.
- The safety profile of pioglitazone HCl when coadministered with ethinyl estradiol and norethindrone was comparable to administration of ethinyl estradiol and norethindrone alone.

Date of Report: 2 July 2002

Attachment 3

Table 14.6.3
Steady State Tests for Unchanged Pioglitazone Trough Concentration in Plasma (Days 18 Through 21)

Study Day	Statistics	Treatment A	P-value Day	Pairwise P-value Day 18	Day 19	Day 20	Day 21
Overall	N	140					
	Mean (S.D.)	124.1 (62.93)					
	LS Mean	115.4	0.475				
	Median	116.0					
	Min - Max	[redacted]					
Day 18	N	35					
	Mean (S.D.)	120.4 (59.05)					
	LS Mean	117.7			0.215	0.929	0.958
	Median	116.0					
	Min - Max	[redacted]					
Day 19	N	35					
	Mean (S.D.)	112.1 (64.01)					
	LS Mean	107.6				0.180	0.191
	Median	109.0					
	Min - Max	[redacted]					
Day 20	N	35					
	Mean (S.D.)	130.2 (70.45)					
	LS Mean	118.4					0.970
	Median	103.0					
	Min - Max	[redacted]					
Day 21	N	35					
	Mean (S.D.)	133.7 (57.83)					
	LS Mean	118.1					
	Median	137.0					
	Min - Max	[redacted]					

Treatment: A = Ortho-Novum 1/35 + Pioglitazone 45 mg
Model used for the steady state test: log(concentration) = intercept + study day

Table 14.6.1
Steady State Tests for Ethinyl Estradiol Trough Concentration in Plasma (Days 18 Through 21)

Study Day	Statistics	Treatment A	Treatment B	P-value Day	P-value Treatment	Pairwise P-value
Overall	N	139	138			
	Mean (S.D.)	23.2 (9.30)	26.6 (17.41)			
	LS Mean	21.8	23.8	0.282	0.001 **	
	Median	23.5	24.0			
	Min - Max	[redacted]				
Day 18	N	35	35			
	Mean (S.D.)	23.3 (8.68)	24.3 (9.43)			
	LS Mean	21.7	23.7			
	Median	24.5	[redacted]			
	Min - Max	[redacted]				
Day 19	N	35	35			
	Mean (S.D.)	23.1 (9.76)	27.8 (15.52)			
	LS Mean	22.2	24.3			
	Median	21.7	25.0			
	Min - Max	[redacted]				
Day 20	N	35	35			
	Mean (S.D.)	23.3 (10.18)	30.6 (27.70)			
	LS Mean	22.3	24.4			
	Median	23.6	24.0			
	Min - Max	[redacted]				
Day 21	N	34	33			
	Mean (S.D.)	22.9 (8.88)	23.5 (9.85)			
	LS Mean	20.9	22.8			
	Median	23.6	23.6			
	Min - Max	[redacted]				
Pairwise 18 vs 19						0.577
Pairwise 18 vs 20						0.464
Pairwise 18 vs 21						0.297
Pairwise 19 vs 20						0.861
Pairwise 19 vs 21						0.110
Pairwise 20 vs 21						0.076

Treatment: A = Ortho-Novum 1/35 + Pioglitazone 45 mg
B = Ortho-Novum 1/35 + Placebo
Final model used for the steady state test: log(concentration) = intercept + study day + treatment
**: P-value less than 0.01

Table 14.6.2
Steady State Tests for Norethindrone Trough Concentration in Plasma (Days 18 Through 21)

Study Day	Statistics	Treatment A	Treatment B	----- P-value ----- Day	Treatment	Pairwise P-value
Overall	N	140	139			
	Mean (S.D.)	3.2 (1.84)	2.9 (1.81)			
	LS Mean	2.7	2.4	0.186	0.004 **	
	Median	3.2	2.8			
	Min - Max					
Day 18	N	35	35			
	Mean (S.D.)	3.0 (1.30)	2.7 (1.23)			
	LS Mean	2.5	2.3			
	Median	3.2	2.8			
	Min - Max					
Day 19	N	35	35			
	Mean (S.D.)	3.1 (1.26)	3.2 (2.87)			
	LS Mean	2.8	2.5			
	Median	3.1	2.9			
	Min - Max					
Day 20	N	35	35			
	Mean (S.D.)	3.1 (1.47)	2.8 (1.28)			
	LS Mean	2.7	2.4			
	Median	3.1	2.8			
	Min - Max					
Day 21	N	35	34			
	Mean (S.D.)	3.6 (2.87)	2.7 (1.33)			
	LS Mean	2.8	2.5			
	Median	3.3	2.7			
	Min - Max					
Pairwise 18 vs 19						0.040 *
Pairwise 18 vs 20						0.295
Pairwise 18 vs 21						0.100
Pairwise 19 vs 20						0.307
Pairwise 19 vs 21						0.678
Pairwise 20 vs 21						0.545

Treatment: A = Ortho-Novum 1/35 + Pioglitazone 45 mg
B = Ortho-Novum 1/35 + Placebo
Final model used for the steady state test: log(concentration) = intercept + study day + treatment
*, **: P-value less than 0.05 or 0.01 respectively

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S.W. Johnny Lau
10/27/03 11:59:45 AM
BIOPHARMACEUTICS

Hae-Young Ahn
10/28/03 10:37:25 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-073/S-020

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-073 SE1-020
Name of drug:	Actos (pioglitazone HCl) Tablets 15, 30 and 45 mg
Applicant:	Takeda Pharm North America, Inc. (TPNA)
Indication:	Type 2 Diabetes
Documents reviewed:	\\Cdsesub1 \N21073\S_020\2003-01-24
Project manager:	Jena Weber (HFD-510)
Clinical reviewer:	Robert Misbin, M.D. (HFD-510)
Dates:	Received 01/24/03; user fee (10 months) 11/27/03
Statistical reviewer:	Lee-Ping Pian, Ph.D. (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Biometrics division director:	Edward Nevius, Ph.D. (HFD-715)

Keywords: NDA review, clinical studies

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS

The three pioglitazone add on trials with metformin, sulfonylurea, or insulin as background therapy were designed to show superiority of the 45 mg QD regimen to the 30 mg QD regimen in HbA_{1c} change from baseline. The effectiveness of pioglitazone 30 mg was comparable to that observed in the add on studies in the original NDA. The current insulin trial showed a statistically significant difference between 45 mg and 30 mg pioglitazone in mean HbA_{1c} reduction. The metformin and sulfonylurea trials showed greater reductions in mean HbA_{1c} in the 45 mg pioglitazone-treated patients than the 30 mg pioglitazone-treated patients without statistical significance. [redacted] Therefore, it is concluded that 45 mg pioglitazone QD is efficacious in HbA_{1c} reduction when added to metformin, sulfonylurea or insulin.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Actos was approved for treatment of type 2 diabetes based on the results of 3 monotherapy and 3 combination therapy studies in which pioglitazone was initiated at 15 mg QD or 30 mg QD. In the monotherapy studies, dose adjustments to a maximal daily dose of 45 mg QD were allowed.

This submission included three 24-week pioglitazone combination therapy trials to evaluate the efficacy and safety of pioglitazone 45 mg QD compared to that of pioglitazone 30 mg QD when added to a sulfonylurea, metformin, or insulin regimen.

The purpose of this sNDA is to update the dosing / [redacted] , and safety sections of the current Package Insert to reflect the new data.

Table 1 Design summary of the add on studies of pioglitazone

Study	# of Centers	Dose	Sample size	HbA_{1c} change	Type of Study & Control	Design primary efficacy	Duration of Treatment
PNFP-341 (Sulfonyluria)	79 US	30 mg	340	-1.55	multicenter, randomized, double-blind of a combination of SU + actose	superiority HbA_{1c} change from baseline	24 weels
		45 mg	332	-1.67			
PNFP-342 (metformin)	86 US	30 mg	400	-0.80	multicenter, randomized, double-blind of a combination of Metformin + actose	superiority HbA_{1c} change from baseline	24 weels
		45 mg	398	-1.01			
PNFP-343 (Insulin)	98 US	30 mg	328	-1.17	multicenter, randomized, double-blind of a combination of insulin + actose	superiority HbA_{1c} change from baseline	24 weels
		45 mg	328	-1.46			

2.2 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.2.1 SPONSOR'S RESULTS AND CONCLUSIONS

The primary efficacy variable was the change from baseline in HbA_{1c} at Week 24. The primary efficacy analysis population was the intent-to-treat population with last observation carried forward for the missing values. Model for change from baseline is based on a 2-way ANCOVA with effects for pooled center, treatment, and pooled-center-by-treatment interaction as factors, and baseline value as a covariate.

The sponsor concluded that the results of the 3 studies indicate that pioglitazone 30 mg QD or 45 mg QD added to sulfonylurea, metformin, or insulin regimen improves glycemic control as measured by glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG) levels. Additionally, no new safety issues were identified in the 24-week studies.

Table 2 HbA_{1c} change from baseline (%) at Week 24, ITT – SU add on

	30 mg QD Pio+SU	45 mg QD Pio+SU
N	351	351
Baseline LSMean	9.77 (0.082)	9.85 (0.083)
Mean Endpoint	8.22 (0.095)	8.17 (0.100)
LS Change (SE)	-1.55 (0.085)	-1.67 (0.085)
LSM Difference (95% 2-sided C.I.)	-0.12 (-0.36, 0.12)	

Table 3 HbA_{1c} change from baseline (%) at Week 24, ITT – Metformin add on

	30 mg QD Pio+Metformin	45 mg QD Pio+Metformin
N	411	416
Baseline LSMean	9.88 (0.079)	9.81 (0.079)
Mean Endpoint	9.10 (0.105)	8.81 (0.114)
LS Change (SE)	-0.80 (0.094)	-1.01 (0.093)
LSM Difference (95% 2-sided C.I.)	-0.21 (-0.47, 0.05)	

Table 4 HbA_{1c} change from baseline (%) at Week 24, ITT – Insulin add on

	30 mg QD Pio+Insulin	45 mg QD Pio+Insulin
N	345	345
Baseline LSMean	9.86 (0.084)	9.68 (0.085)
Mean Endpoint	8.65 (0.095)	8.23 (0.092)
LS Change (SE)	-1.17 (0.080)	-1.46 (0.081)
LSM Difference (95% 2-sided C.I.)	-0.29 (-0.51, -0.07)*	

*Significantly different from 30 mg QD pioglitazone group ($p \leq 0.05$).

2.2.2 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.2.2.1 Study PNFP 341 – Sulfonylurea add on

Patient Disposition

A total of 1631 patients were screened. Of this number, 919 patients were enrolled in the placebo lead-in phase. A total of 868 patients were randomized and 737 (85%) completed the study. Table 5 is the sponsor's table which displays reasons for discontinuation.

Table 5 Reasons for Discontinuation during Double-Blind Phase – Sulfonylurea add on

	30 mg QD Pioglitazone + Sulfonylurea	45 mg QD Pioglitazone + Sulfonylurea
All Randomized Patients	351 (100.0%)	351 (100.0%)
Randomized, Not Treated	0 (0.0%)	0 (0.0%)
Completed Double-Blind Treatment Period	267 (76.1%)	254 (72.4%)
Discontinued from Double-Blind Treatment Period	84 (23.9%)	97 (27.6%)
Insufficient Therapeutic Effect	12 (3.4%)	14 (4.0%)
Symptomatic Hyperglycemia	2 (0.6%)	2 (0.6%)
Asymptomatic Hyperglycemia (Lab AE)	1 (0.3%)	2 (0.6%)
Symptomatic Hypoglycemia	0 (0.0%)	2 (0.6%)
All Other Clinical AEs	17 (4.8%)	27 (7.7%)
Other Lab AEs	2 (0.6%)	2 (0.6%)
Non-Compliance	6 (1.7%)	7 (2.0%)
Lost to Follow-Up	7 (2.0%)	14 (4.0%)
Withdrew Consent	22 (6.3%)	17 (4.8%)
Protocol Violation	11 (3.1%)	7 (2.0%)
Other	4 (1.1%)	3 (0.9%)
ITT Patients	351 (100.0%)	351 (100.0%)
Evaluable Patients	257 (73.2%)	258 (73.5%)

Twenty-seven percent patients withdrew from the study. The major reason for discontinuation was adverse events.

Primary Efficacy Analysis –HbA_{1c} change from baseline at Week 24

Table 6 HbA1c (%) least square mean change from baseline to week 24 (endpoint) (LOCF) — ITT Population

	30 mg QD Pioglitazone +Sulfonylurea (N=340)	45 mg QD Pioglitazone +Sulfonylurea (N=332)
Baseline LSM (SE)	9.81 (0.079)	9.88 (0.080)
Endpoint LSM (SE)	8.22 (0.095)	8.27 (0.100)
LSM Change (SE)	-1.55 (0.085)	-1.67 (0.085)
LSM Difference (95% C.I.)		-0.12 (-0.36, 0.12)
p-value *		0.36

* model based on a 2-way ANCOVA with effects for pooled center, treatment, and baseline value as a covariate

The 45 mg dose was not statistically different from the 35 mg dose when added on to sulfonylurea. However, the mean HbA_{1c} reduction was greater in the 45 mg treated patients than the 30 mg treated patients.

2.2.2.2 Study PNFP-34 - Metformin add on

Of the 883 patients who entered the single-blind period and received placebo, 827 were randomized and received double-blind medication, Of the 827 patients who were randomized to double-blind treatment, a total of 561 patients completed the study and 266 patients discontinued. Table 7 displays patients disposition.

The mean age of the patients was 53.8 years. A total of 536 (64.8%) of the patients were Caucasian; slightly more than half (57.9%) of the patients were male. Slightly more than half (54%) of the patients had reported other antidiabetic medications in combination with their metformin before enrolling in the study. Median metformin dosage at baseline was 1700 mg/day and 1500 mg/day for extended release. Metformin dosage was similar in the two treatment groups.

Table 7 Patient Disposition – Metformin

	30 mg QD Pioglitazone + Metformin	45 mg QD Pioglitazone + Metformin
All Randomized Subjects	411	416
Randomized, Not Treated	0	0
Completed Double-Blind Treatment Period	280 (68.1%)	281 (67.5%)
Discontinued from Double-Blind Treatment Period	131 (31.9%)	135 (32.5%)
Insufficient Therapeutic Effect	50 (12.2%)	48 (11.5%)
Symptomatic Hyperglycemia	8 (1.9%)	5 (1.2%)
Asymptomatic Hyperglycemia (Lab AE)	7 (1.7%)	6 (1.4%)
Symptomatic Hypoglycemia	0 (0%)	1 (0.2%)
Renal Disease and Renal Dysfunction	2 (0.5%)	2 (0.5%)
All Other Clinical AEs	8 (1.9%)	18 (4.3%)
Other Lab AEs	3 (0.7%)	1 (0.2%)
Noncompliance	10 (2.4%)	9 (2.2%)
Lost to Follow-Up	5 (1.2%)	7 (1.7%)
Withdrew Consent	18 (4.4%)	25 (6.0%)
Protocol Violation	15 (3.6%)	8 (1.9%)
Other	5 (1.2%)	5 (1.2%)
ITT Subjects	411 (100%)	416 (100%)
Evaluable Subjects	311 (75.7%)	324 (77.9%)

More than 30% of patients did not complete the double-blind portion of the treatment period. More than 10% of patients did not complete due to insufficient therapeutic effect followed by approximately 7% of patients due to adverse events.

Primary Efficacy Analysis – HbA_{1c} Change from baseline

Table 8 displays the LSM HbA_{1c} change from baseline for the ITT population.

Table 8 HbA1c (%) least square mean change from baseline to week 24 (Endpoint) (LOCF) — ITT

	30 mg QD Pioglitazone + Metformin (N=400)	45 mg QD Pioglitazone + Metformin (N=398)
Baseline LSM (SE)	9.90 (0.077)	9.83 (0.077)
Endpoint LSM (SE)	9.10 (0.105)	8.81 (0.114)
LSM Change[a] (SE)	-0.80 (0.094)	-1.01 (0.093)
LSM Difference (95% C.I.)		-0.21(-0.47, 0.05)
p-value *		0.08

* model based on a 2-way ANCOVA with effects for pooled center, treatment, and baseline value as a covariate

2.2.2.3 Study PNFP-343 - Insulin add on

Of the 745 patients entered the single-blind period and received placebo, 690 were randomized to the double-blind treatment. A total of 486 patients completed the study and 204 patients discontinued. Table 9 displays patient disposition during the double-blind phase.

Table 9 Patient disposition – Insulin + pioglitazone

	30 mg QD Pioglitazone + Insulin	45 mg QD Pioglitazone + Insulin
All Randomized Subjects	345 (100.0%)	345 (100.0%)
Randomized, Not Treated	1 (0.3%)	0 (0.0%)
Completed Double-Blind Treatment Period	244 (70.7%)	242 (70.1%)
Discontinued from Double-Blind Treatment Period	101 (29.3%)	103 (29.9%)
Insufficient Therapeutic Effect	13 (3.8%)	10 (2.9%)
Symptomatic Hyperglycemia	2 (0.6%)	0 (0.0%)
Asymptomatic Hyperglycemia (Lab AE)	2 (0.6%)	0 (0.0%)
Symptomatic Hypoglycemia	1 (0.3%)	6 (1.7%)
All Other Clinical AEs	16 (4.6%)	25 (7.2%)
Other Lab AEs	4 (1.2%)	2 (0.6%)
Noncompliance	7 (2.0%)	6 (1.7%)
Lost to Follow-Up	10 (2.9%)	13 (3.8%)
Withdrew Consent	20 (5.8%)	16 (4.6%)
Protocol Violation	17 (4.9%)	19 (5.5%)
Other	9 (2.6%)	6 (1.7%)
ITT Subjects	345 (100.0%)	345 (100.0%)
Evaluable Subjects	166 (48.1%)	149 (43.2%)

The mean age of the patients was 56.5 years. The majority (63.3%) of the patients were Caucasian, 24.3% were Black, 9.6% were Hispanic. The majority of patients (54.6%) were male. Most (72.9%) of the patients had not reported other antidiabetic medications in combination with their insulin before enrolling in the study. Median insulin dosage at baseline was 60.0 units/day. Insulin dosage was similar in the two treatment groups.

The treatment-by-baseline HbA_{1c} was significant (p=0.03). Figure 1 displays the regression of HbA_{1c} change from baseline by baseline HbA_{1c}. The graph showed that greater separation of the 2 regression lines as baseline HbA_{1c} increases. The greatest reduction of HbA_{1c} occurred in patients baseline HbA_{1c} >14. When patients with baseline HbA_{1c} >14% were excluded from the analysis the treatment-by-baseline interaction was no longer significant (p=0.2) (Fig. 2).

Figure 1 HbA_{1c} change from baseline by baseline HbA_{1c} - ITT

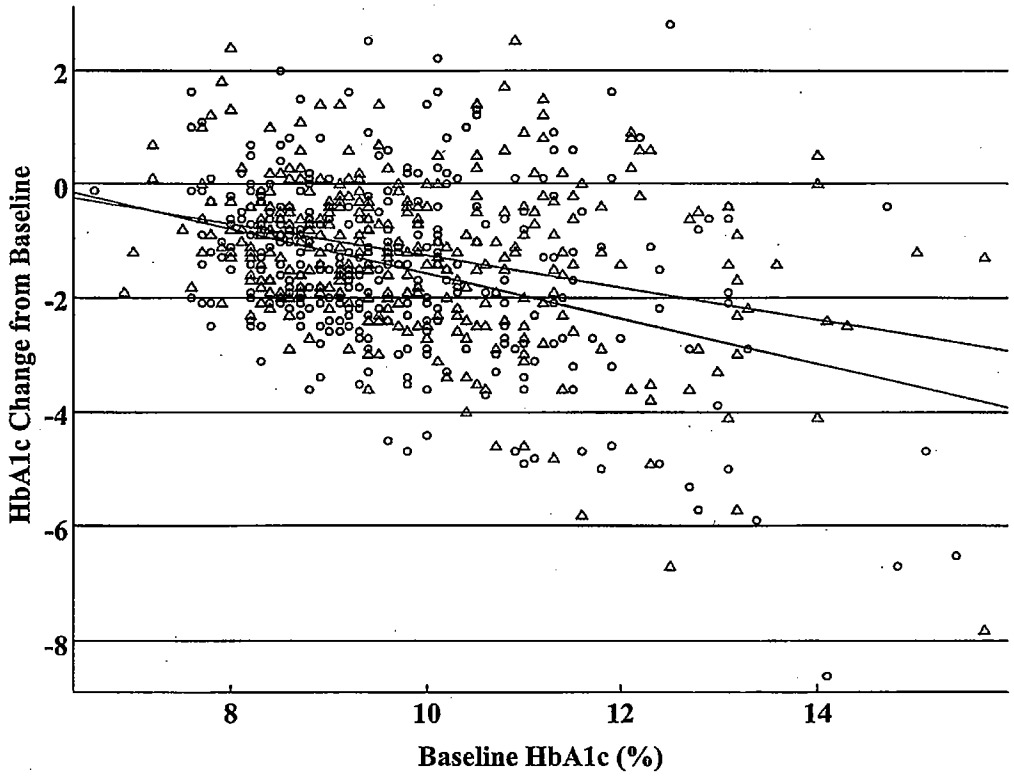
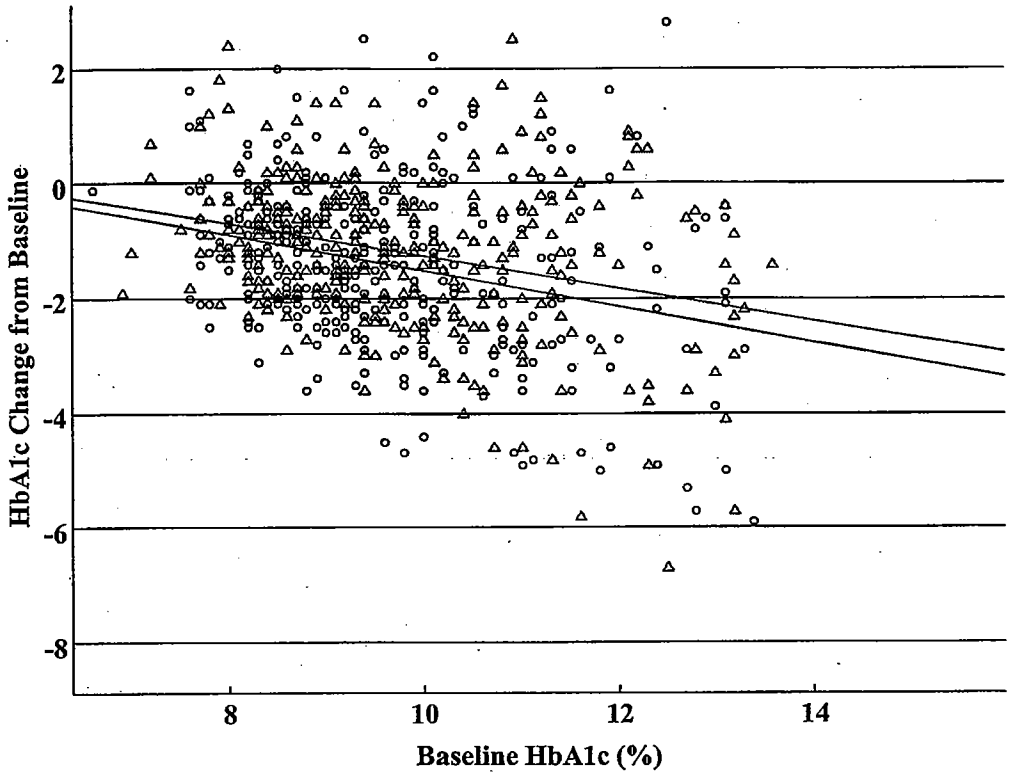


Figure 2 HbA_{1c} change from baseline by HbA_{1c} baseline<14%



Treatment:
Pioglitazone 30 mg + Insulin
Pioglitazone 45 mg + Insulin

Table 10 displays HbA_{1c} change from baseline in patients whose baseline HbA_{1c} was less than or equal to 14%. Results remained statistically significant when patients with baseline HbA_{1c} >14% were removed from the analysis

Table 10 HbA1c (%) least square mean change from baseline to week 24 (Endpoint) for baseline HbA_{1c} ≤14%

	30 mg QD Pioglitazone + Insulin (N=320)	45 mg QD Pioglitazone + Insulin (N=323)
Baseline LSM (SE)	9.75 (0.080)	9.64 (0.080)
Endpoint LSM (SE)	8.59 (0.098)	8.24 (0.098)
LSM Change[a] (SE)	-1.16 (0.081)	-1.41 (0.080)
LSM Difference (95% C.I.)		-0.25(-0.47, -0.02)
p-value *		0.03

* model based on a 2-way ANCOVA with effects for pooled center, treatment, treatment-by-center interaction, and baseline value as a covariate

2.3 CONCLUSIONS AND RECOMMENDATION

The 3, 24-week pioglitazone add on trials with sulfonylurea, metformin or insulin as background therapy showed HbA_{1c} changes from a baseline of approximately 9.8% of -1.55%, -0.80%, and -1.17%, respectively, for the 30 mg pioglitazone groups and -1.67%, -1.01%, and -1.46%, respectively for the 45 pioglitazone groups. The HbA_{1c} changes from baseline in the 30 mg pioglitazone groups were comparable to the HbA_{1c} changes from baseline in the 30 mg groups in the 3 add on trials of 16 weeks in the original NDA submission (-1.22%, -0.64% and -1.26%, respectively). Compared to the 30 mg dose groups, the 45 mg pioglitazone dose groups showed consistently greater HbA_{1c} reductions.

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/s/

Lee-Ping Pian
10/21/03 03:50:57 PM
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Todd Sahlroot
10/22/03 08:05:06 AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-073/S-020

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Item 13. Patent Information

21 CFR 314.50(h) Patent Information
ACTOS (Pioglitazone HCl-AD-4833) Tablets

The following ten patents were issued for AD-4833. The drug product name for this chemical entity will be ACTOS (pioglitazone HCl) tablets.

21 CFR 314.53 (c) (i); (ii); (iii); (iv)

US Patent Number	Expiration Date	Type of Patent	Patent Owner	US Representative
4,444,779	July 27, 1999	Drug, Drug Product	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
4,687,777	January 17, 2006	Drug, Drug Product	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
5,965,584	June 19, 2016	Drug Product Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,160,383	June 19, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,150,384	June 19, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,166,042	June 19, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,166,043	June 19, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,172,090	June 19, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,211,205	June 19, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,271,243	June 19, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,303,640	August 9, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.
6,329, 404	June 19, 2016	Method of Use	Takeda Chemical Industries, Ltd.	Takeda Pharmaceuticals North America, Inc.

EXCLUSIVITY SUMMARY FOR NDA 21-073 SUPPL #020

Trade Name: Actos Generic Name: pioglitazone HCl tablets

Applicant Name: Takeda North America, Inc. HFD-510

Approval Date If Known: November 26, 2003

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /✔/ NO /___/

If yes, what type? Specify 505(b); SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✔/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✔/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✔/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✔/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✔/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 21-073 pioglitazone HCl

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✔/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✔/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is

not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✔/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✔/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✔/

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✔/

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 341 and Study 342

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✔/
Investigation #2	YES /___/	NO /✔/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✔/
Investigation #2	YES /___/	NO /✔/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in

#2(c), less any that are not "new"):

Study 341
Study 342

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND 33,729 YES /✔/ NO /___/ Explain: _____

Investigation #2 !
!
IND 33,729 YES /✔/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 N/A

_____ _____

Investigation #2 N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✔/

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/s/

David Orloff
7/12/04 05:00:37 PM

Item 16
Debarment Certification

A Debarment Certification as specified by the Generic Drug Enforcement Act of 1992 is provided.

Certification of Compliance with the Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, Takeda Pharmaceuticals North America, Inc certifies that we or the US affiliate Takeda America Research and Development Center, Inc. did not use in any capacity the services of any person debarred under subsections (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act in connection with this supplemental new drug application.

Alfonso Perez, M.D.
Senior Director, Clinical Research

11/29/07
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

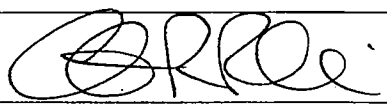
Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	PNFP-341	PNFP-342
	PNFP-343	01-00-TL-OPI-513
	PNFP-032	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Curtis Rhine	Vice President, Finance and Controller
FIRM / ORGANIZATION: Takeda Pharmaceuticals North America, Inc.	
SIGNATURE 	DATE 11/11/02

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_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-073
5020

Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510

PROJECT MANAGER LABELING REVIEW

Application Number: 21-073/S-20

Name of Drug: Actos® (pioglitazone HCl) Tablets, 15 mg, 30 mg and 45 mg.

Sponsor: Takeda Pharmaceuticals North America, Inc.

Material Reviewed: Draft package insert.

Submission Date: January 24, 2003.

Receipt Date: January 27, 2003.

Background and Summary: Actos tablets are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. It is indicated both as monotherapy, and in combination with a sulfonylurea, metformin or insulin when diet and exercise plus the single agent do not result in adequate glycemic control.

Proposed Indication: This prior approval supplement provides for documentation to support multiple labeling changes to the **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions** subsection, **Pharmacodynamics and Clinical Effects** subsection, **Clinical Studies – Combination Therapy** subsection, (to include revisions of Actos in combination with metformin, a sulfonylurea, or insulin), **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE and ADMINISTRATION** sections, of the package insert.

Review: The proposed draft package insert (PI) label was compared to the currently approved label (S-021, identifier 5012100-6, revised April 2003). Changes to the PI as recommended in the clinical, statistical, and biopharm reviews have been implemented. The Project Management staff concurs with these revisions.

Conclusion: Issue approval (AP) letter and request FPL.

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/s/

Jena Weber
11/28/03 12:38:31 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	Tuesday October 28, 2003
TIME:	1:00 am
LOCATION:	14B-39
APPLICATION:	NDA 21-073/S-020 Actos (pioglitazone HCl) Takeda IND 33,729
TYPE OF MEETING:	Type A
MEETING CHAIR:	David Orloff, M.D., Division Director, Metabolic and Endocrine Drug Products (DMEDP)
MEETING RECORDER:	Jena Weber, Project Manager

FDA ATTENDEES, TITLES, Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510:

David Orloff, M.D.	Division Director
Robert Misbin, M.D.	Clinical Reviewer
Todd Sahlroot, Ph.D.	Team Leader - Biometrics
Jena Weber, BS	Project Manager

Takeda North America, Inc. ATTENDEES AND TITLES:

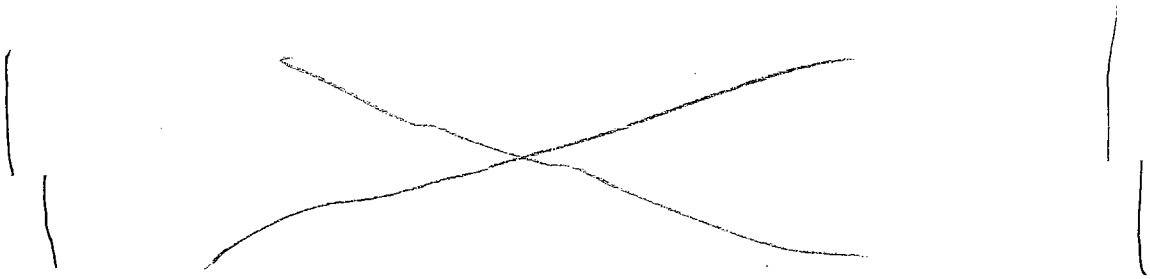
Monidira Bhattacharya, M.D.	Associate Director Product Safety
Claire Thom, PharmD.	VP, Research & Development
Mary Jo Pritza, PharmD	Manager, Regulatory Affairs
Alfonzo Perez, M.D.	VP Clinical Development

Indications and Usage: Actos is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type diabetes. It may be used in monotherapy, or for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Purpose of meeting: To obtain Agency concurrence and clarification on issues pertaining to Actos and the labeling for this product, [redacted]

Background: Supplement 020 was submitted on January 24, 2003, and provided for documentation to support multiple labeling changes to the **CLINICAL PHARMACOLOGY** section, (**Clinical Studies** subsection to include revisions of Actos in combination with metformin, a sulfonylurea, or insulin), **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE and ADMINISTRATION** sections, of the package insert.

Discussion: [redacted]



- Recommended changes to the labeling regarding patients with NYHA Class III and IV cardiac status have been made.

DMEDP requested (on November 14, 2003), that the following labeling changes be implemented to the package insert:

New sentence in the "**Actos plus Sulfonylurea**" section:

- The mean reductions from baseline at Week 24 in HbA1c were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

ew sentence in the "**ACTOS plus Metformin Studies**" section:

- The mean reductions from baseline at Week 24 in HbA1c were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

ew sentence in the "**ACTOS plus Insulin Studies**" section:

- The mean reductions from baseline at Week 24 in HbA1c were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL.

Also, please remove the word ——— from the next sentence which begins "Improved glycemic control was accompanied by...."

Under the **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions** subsection, please revise this paragraph to read: Oral Contraceptives:

- Additional comments regarding the clinical sections of the PI will be forwarded to Takeda.

Division of Metabolic and Endocrine Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-073/S-020

Name of Drug: Actos (pioglitazone HCl) Tablets, 15 mg, 30 mg & 45 mg.

Sponsor: Takeda

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination

Submission Date: January 24, 2003

Receipt Date: January 27, 2003

Filing Date: March 14, 2003

User-fee Goal Date: November 27, 2003.

Proposed Indication: This supplement provides for documentation to support multiple labeling changes to the **CLINICAL PHARMACOLOGY (Clinical Studies** subsection to include revisions of Actos in combination with metformin, a sulfonylurea, or insulin), **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE and ADMINISTRATION** sections, of the package insert.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	✔		Vol. 1.1
2. Form FDA 356h (original signature)	✔		Vol. 1.1
a. Establishment information (facilities ready for inspection?)			NN
b. Reference to DMF(s) & Other Applications		✔	NN

3. User Fee FDA Form 3397 4. Patent information & certification	✔		Vol. 1.1
5. Debarment certification (Note: Must have a definitive statement)	✔		Vol. 1
6. Field Copy Certification		✔	
7. Financial Disclosure	✔		Vol. 1.1
8. Comprehensive Index	✔		Vol. 1.1
9. Pagination	✔		Vol. 1.1
10. Summary Volume	✔		Vol. 1
11. Review Volumes	✔		
12. Labeling (PI, container, & carton labels)			Vol. 1.1
a. unannotated PI	✔		Vol. 1
b. annotated PI	✔		Vol. 1.1
c. immediate container			N/A
d. carton			N/A
e. patient package insert (PPI)			N/A
f. foreign labeling (English translation)		✔	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	✔		Electronic
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	✔		Electronic

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS

			(If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	✔		Vol. 1
2. Foreign Marketing History		✔	
3. Summary of Each Technical Section	✔		
a. Chemistry, Manufacturing, & Controls (CMC)		✔	NN
b. Nonclinical Pharmacology/Toxicology		✔	NN
c. Human Pharmacokinetic & Bioavailability	✔		Electronic
d. Microbiology			N/A
e. Clinical Data & Results of Statistical Analysis	✔		Electronic
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies			
5. Summary of Safety	✔		Vol. 1
6. Summary of Efficacy	✔		Vol. 1

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	✔		Electronic
2. Controlled Clinical Studies	✔		Electronic
a. Table of all studies	✔		
b. Synopsis, protocol, related	✔		Electronic

publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)			
c. Optional overall summary & evaluation of data from controlled clinical studies	✔		Electronic
3. Integrated Summary of Efficacy (ISE)		✔	
4. Integrated Summary of Safety (ISS)		✔	
5. Drug Abuse & Overdosage Information		✔	N/A
6. Integrated Summary of Benefits & Risks of the Drug	✔		Vol. 1
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		✔	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		✔	
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		✔	N/A
a. Proposed unannotated labeling in MS WORD	✔		1.1
b. Stability data in SAS data set format (only if paper submission)		✔	

c. Efficacy data in SAS data set format (only if paper submission)		✔	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)	✔		
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)			N/A
3. Exclusivity Statement (optional)		✔	

Y=Yes (Present), N=No (Absent)

Conclusions

Jena Weber
Regulatory Project Manager

ADMINISTRATIVE REVIEW

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/s/

Jena Weber
11/28/03 12:26:29 PM
CSO

Labeling:

The proposed ACTOS label submitted November 7, 2003, is acceptable except for the following:

Under the **WARNINGS** section, **Cardiac Failure and Other Cardiac Effects** subsection, the previous label describes two insulin-treated patients at 15-mg ACTOS, and two patients at 30 mg ACTOS that developed in CHF during the original 16-week trials.

- In a 24-week dose-controlled study in which ACTOS was coadministered with insulin, 0.3% of patients (1/345) on 30 mg, and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event.

The new wording under the **PRECAUTIONS** section, **Edema** subsection should be revised to read:

- . . . edema was reported more frequently in patients treated with Actos than in placebo-treated patients and appears to be dose related.
- Under the **PRECAUTIONS** section, **Hepatic Effects** subsection, the terms '

Otherwise, the revisions to the liver section are acceptable.

The description of anemia under the **ADVERSE EVENTS** section should be revised to read:

- The fall in hemoglobin and hematocrit with ACTOS appears to be dose related.

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/s/

Jena Weber
11/25/03 01:50:41 PM

2 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-073
S020

DUPLICATE

AMENDMENT TO A PENDING APPLICATION

November 26, 2003

RECEIVED
NOV 28 2003
FDR/CDER

David Orloff, M.D., Director
Division of Metabolic & Endocrine Drug Product (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SE8020(C)
SUPPL NEW CORRESP

RE: NDA 21-073/s-020
ACTOS® (pioglitazone HCL)

Dear Dr. Orloff:

Please refer to Takeda Pharmaceuticals North America, Inc. (TPNA) initial supplemental application to NDA 21-073 dated January 24, 2003 and subsequent submissions dated April 24 (fax), May 13, July 22, August 14, Nov 7, 2003; to the Agency's acknowledgement letter to supplement 020 dated March 20, 2003; and to telephone communications dated May 29, Aug 4, October 28, and November 4 between TPNA and the Agency in regard to this supplement. Please also refer to the Agency's fax communications dated November 14 and 24, 2003, where recommendations to labeling supplement 020 were provided to TPNA.

Pursuant to teleconferences held between TPNA and the Agency on November 25 and 26, 2003, the above referenced labeling changes were agreed upon with the following exceptions:

- The request for new wording [redacted]
- Agreement was obtained to include the language recommended by the Agency under the Clinical Pharmacology section, Drug-Drug interaction subsection regarding Oral Contraceptives. Additionally, TPNA and the Agency agreed to the addition of the statement, "In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown." to follow the proposed language.

Provided herein is final annotated and clean copy draft labeling reflecting all above referenced changes. These documents have also been e-mailed directly to the Agency for review.

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.
475 Half Day Road Lincolnshire, Illinois 60069 Phone: 847-383-3000

Please do not hesitate to contact the undersigned for any additional questions or concerns.

Sincerely,

Mary Jo Pritza MPH, PharmD
Regulatory Affairs Manager
Takeda Pharmaceuticals North America, Inc.
P/847-383-3739
F/847-383-3427

cc: Jena Weber (email)

22 Page(s) Withheld

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

_X_ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-21-073
5020

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: November 14, 2003

To: Mary Jo Pritza Regulatory Affairs Manager	**From:** Jena Weber Project Manager
Company: Takeda Pharmaceuticals North America, Inc.	Division of Metabolic and Endocrine Drug Products, HFD-510
Fax number: 847-383-3427	**Fax number:** 301-443-9282
Phone number: 847- 383-3000	**Phone number:** 301-827-6422

Subject: Reference NDA 21-073/S-020; labeling revisions as per biometrics and biopharm.

Total no. of pages including cover: 2

Comments: Please revise the package insert as follows:

New sentence in the "**ACTOS plus Sulfonylurea Studies**" section:

- The mean reductions from baseline at Week 24 in HbA1c were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

New sentence in the "**ACTOS plus Metformin Studies**" section:

- The mean reductions from baseline at Week 24 in HbA1c were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

New sentence in the "**ACTOS plus Insulin Studies**" section:

- The mean reductions from baseline at Week 24 in HbA1c were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL.

Also, please remove the word / — / from the next sentence which begins "Improved glycemic control was accompanied by...."

Under the **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions** subsection, please revise this paragraph to read: Oral Contraceptives: /

Document to be mailed: ☐ YES ☑ NO

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/s/

Jena Weber
11/14/03 02:29:43 PM

Weber, Jena M

From: Holovac, Mary Ann
Sent: Thursday, January 08, 2004 9:12 AM
To: Weber, Jena M
Cc: Stewart, Kendra
Subject: Actos (Pioglitazone) NDA 21093 S020

Hi Jena,

In order to make an exclusivity determination for NDA 21073 S020, I will need to have part III of the summary completed. Question 2 of the summary inaccurately directs you not to complete the form... Please complete part III of the summary so that we may make an accurate exclusivity determination for this approval.

Mary Ann

Mary Ann Holovac, R.Ph.
301-827-0492
301-827-5911 (fax)
Office of Generic Drugs
Division of Labeling and Program Support
holovacm@cder.fda.gov

Weber, Jena M

From: mjpritza@tpna.com

Sent: Thursday, December 11, 2003 1:12 PM

To: weberj@cder.fda.gov

Subject: label edit

Jena- Under Clinical studies section, combo therapy, ACTOS plus insulin, 2nd paragraph, could the Agency please delete the sentence underlined below which reads exactly like the sentence before? If you can make this happen I'd appreciate it, total oversight in our review. Many thanks- Mary Jo

(on the copy of the label you mailed to us this error appears on a page that the page number didn't print, but should've been page 14..if that helps at all)

In the second study, 690 patients receiving a median of 60.0 units per day of insulin received either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current insulin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively.

Weber, Jena M

From: Weber, Jena M
Sent: Friday, November 28, 2003 11:02 AM
To: CDER-APPROVALS
Subject: NDA 21-073/S-020

From the Division of Metabolic and Endocrine Drug Products, HFD-510
NDA 21-073
S-020
Drug: Actos (pioglitazone HCl) Tablets
Sponsor: Takeda
Indication: As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Actos is indicated for monotherapy, and in combination with a sulfonylurea, metformin or insulin.

Supplement 020 provided for documentation to support multiple labeling changes to the CLINICAL PHARMACOLOGY section, (Clinical Studies subsection to include revisions of Actos in combination with metformin, a sulfonylurea, or insulin), WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE and ADMINISTRATION sections, of the package insert.

Dosage form: Tablets, 15 mg, 30 mg & 45 mg.
Rx only
Standard review; oral hypoglycemic agent.

Thanks,
Jena

Weber, Jena M

From: Sahlroot, Jon T
Sent: Wednesday, November 12, 2003 11:32 AM
To: Weber, Jena M
Cc: Pian, Lee Ping; Misbin, Robert I; Lau, S. W. Johnny
Subject: pio label changes

Jena,

Here is the new sentence in the "**ACTOS plus Sulfonylurea Studies"** section:

The mean reductions from baseline at Week 24 in HbA1c were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

Here is the new sentence in the "**ACTOS plus Metformin Studies"** section:

The mean reductions from baseline at Week 24 in HbA1c were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

Here is the new sentence in the "**ACTOS plus Insulin Studies"** section:

The mean reductions from baseline at Week 24 in HbA1c were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL.

Also, remove the word '———' from the next sentence which begins "Improved glycemic control was accompanied by...."

Todd

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.

DUPLICATE

AMENDMENT TO A PENDING APPLICATION

RECEIVED
NOV 1 0 2003
FDR/CDER

November 7, 2003

SE8 020 BL
NDA SUPPL AMENDMENT

David Orloff , M.D., Director
Division of Metabolic & Endocrine Drug Product (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-073/s-020
ACTOS® (pioglitazone HCL)

Dear Dr. Orloff:

Please refer to Takeda Pharmaceuticals North America, Inc's. (TPNA) Supplemental New Drug Application (s-020) dated January 24, 2003 and amendments to this pending supplement dated July 22, 2003 and November 3, 2003. TPNA also makes reference to the meeting minutes from the October 28, 2003, teleconference held between the Division and TPNA, where recommended changes to the labeling language regarding patients with NYHA Class III and IV cardiac status were made. Subsequent to the November 3, 2003 submission, the Agency contacted TPNA requesting that the revised labeling be resubmitted to include additional changes to ensure consistency in language when describing the clinical experience of ACTOS in the NYHA Class III and IV population. During the same discussion the Agency proposed that TPNA also include modified language regarding the frequency of hepatic monitoring in the draft labeling, which was previously submitted by TPNA on July 22, 2003. The July 22, 2003 submission . These preceding changes as well as the language proposed by the Agency are provided in the enclosed labeling submission.

Per the Agency's request, TPNA hereby resubmits final annotated and clean labeling incorporating changes proposed by the Agency on November 4, 2003, as well as all changes previously submitted to NDA 21-073/s-020.

Should you need any additional information, please feel free to contact me directly.

Sincerely,

Mary Jo Pritza MPH, PharmD
Regulatory Affairs Manager
Takeda Pharmaceuticals North America, Inc.
P/847-383-3739
F/847-383-3427

29 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-073
5020

DUPLICATE

AMENDMENT TO A PENDING APPLICATION

RECEIVED
NOV - 4 2003
FDR/CDER

November 3, 2003

David Orloff , M.D., Director
Division of Metabolic & Endocrine Drug Product (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SE8 020 BL
NDA SUPPL AMENDMENT

RE: NDA 21-073/s-020
ACTOS® (pioglitazone HCL)

Dear Dr. Orloff:

Pursuant to the Agency's request made during a teleconference held on October 28, 2003, Takeda Pharmaceuticals North America, Inc. (TPNA) submits a revision to the ACTOS labeling language regarding patients with NYHA Class III and IV cardiac status. Per 21 CFR 314.60, TPNA submits final annotated labeling as an amendment to pending supplement 020 to include the Agency's proposed change.

Addition of the word "*these*" to the following sentence under "WARNINGS, Cardiac Failure and Other Cardiac Effects" was made.

> "Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during *these* clinical trials; therefore ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular)."

Also included for Agency review are meeting minutes from the October 28, 2003 teleconference as documented by TPNA. Please notify TPNA of any significant differences in understanding between the Agency and TPNA regarding discussion points and meeting outcomes.

Should you need any additional information, please feel free to contact me directly.

Sincerely,

Mary Jo Pritza MPH, PharmD
Regulatory Affairs Manager
Takeda Pharmaceuticals North America, Inc.
P/847-383-3739
F/847-383-3427

DUPLICATE

RESPONSE TO FDA REQUEST FOR INFORMATION

SE4 020 BM
NDA SUPPL AMENDMENT

RECEIVED
AUG 15 2003
FDR/CDER

David Orloff , M.D., Director
Division of Metabolic & Endocrine Drug Product (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-073/s-020
ACTOS® (pioglitazone HCL)

Dear Dr. Orloff:

Pursuant to the Agency's request made during a teleconference held August 4, 2003, Takeda Pharmaceuticals North America, Inc. (TPNA) provides the following submission to support the ACTOS® 120-day Safety update report dated July 22, 2003:

- **Attachment 1:**
  - [redacted]
  - [redacted] of
  - [redacted] case review sheets.
- **Attachment 2:** An updated summary of post marketing cases of liver failure as reported through the MedWatch reporting system and from the literature beginning in January 2002 until August 10, 2003. A brief clinical summary is provided for each case followed by the MedWatch reporting form, and ACTOS Liver Safety Board case assessment form. Each literature case is accompanied by a copy of the publication.

In addition to the archival copies, a desk copy of this submission has been provided to Dr. Misbin as requested.

Should you need any additional information, please feel free to contact me directly.

Sincerely,

for

Mary Jo Pritza MPH, PharmD
Regulatory Affairs Manager
Takeda Pharmaceuticals North America, Inc.
P/847-383-3739
F/847-383-3427

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.

ORIGINAL

RESPONSE TO FDA REQUEST FOR INFORMATION

SE8020 (BZ)
NDA SUPPL AMENDMENT

July 22, 2003

Robert Misbin , M.D., Medical Officer
Division of Metabolic & Endocrine Drug Product (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
JUL 23 2003
FDR/CDER

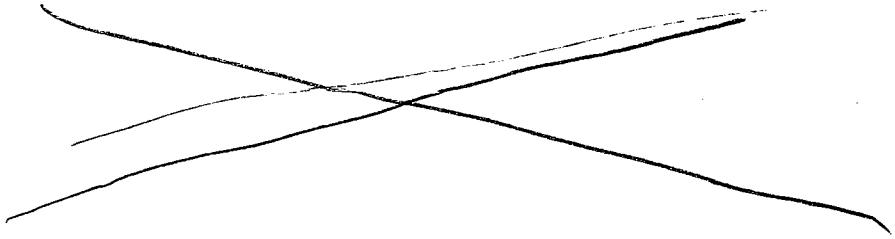
RE: NDA 21-073/s-020
ACTOS® (pioglitazone HCL)

Dear Dr. Misbin:

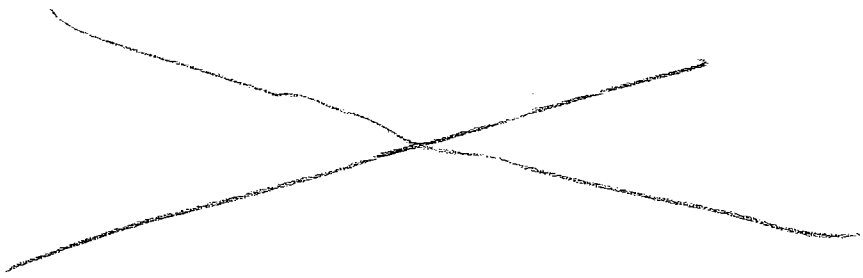
Please refer to the Agency's correspondence dated 20 March 2003, to Takeda Pharmaceuticals North America, Inc. (TPNA) requesting a 120-Day update on safety information for ACTOS® (pioglitazone HCL). Through this letter, the Agency requested TPNA collect safety data from the on-going Phase IV studies with a focus on liver safety, increases in ALT and CPK levels, events of CHF and edema, and cases of bladder tumors. TPNA responded in a letter dated 24 April 2003 by proposing studies that would be included in the data collection and suggested the timing of the submission. Please also refer to the minutes from the 25 April 2003 teleconference between TPNA and the Agency which reflects the agreement to the preceding and to additional submission information, including a summary of post-marketing reports for liver abnormalities (Interim Findings from the ACTOS Liver Safety Committee), and a copy of the most recent [redacted]. It was also agreed that 30 April 2003 would be the data cut-off date for this safety report. Lastly, TPNA acknowledges, as part of the same teleconference, the Agency's request that TPNA provide proposed language to reduce the frequency of the current hepatic monitoring in the ACTOS product labeling .

Enclosed for your review are the following:

- **Attachment 1**: Summary of safety data from 5 on-going and one completed Phase IV study, including end of text tables and listings.



475 Half Day Road, Suite 500 Lincolnshire, Illinois 60069 Phone: 847-383-3000



- **Completed Study 01-00-TL-OPI-520** entitled: "A Randomized, Double-Blind, Comparator-Controlled Study of Pioglitazone HCl Vs Glyburide in the Treatment of Subjects with Type 2 (Non-Insulin Dependent) Diabetes Mellitus and Mild Cardiac Disease (NYHA I)."

- **APPENDIX A: End-of-Text Tables and Listings**
- **APPENDIX B: Narratives of Deaths**

- **Attachment 2**: A copy of the interim report from the ACTOS Liver Safety Committee that provides an evaluation of spontaneous reports of liver abnormalities from post-marketing surveillance programs worldwide, and of serious adverse events from clinical trials conducted since FDA approval of ACTOS.

- **Attachment 3**: An assessment of liver abnormalities by, [redacted] from the ongoing Liver Safety [redacted]

- **Attachment 4**: [redacted]

Hepatic Monitoring

The labeling modification to the PRECAUTIONS, Hepatic Effects section of the ACTOS product labeling, as requested by FDA, is presented below and is supported by the enclosed attachments, including liver safety evaluations by the DSMB and Liver Safety Committee, and the attached summary report with tables and listings. This modification is also supported within this submission by data from studies 520 and the [redacted]. The data collected since the approval of ACTOS indicate that the occurrence of severe liver disease with this compound is very low. The suggested modification is as follows:

- Serum ALT levels should be evaluated prior to the initiation of therapy with ACTOS in all patients, ~~every two months for the first year of therapy,~~ and periodically thereafter *per the clinical judgment of the health care professional* (italics added).

This modification would also replace the current statement that appears in the PRECAUTIONS, Laboratory Tests and Information for Patients sections of the label to qualify the periodic monitoring of liver enzymes.

TPNA would also like the Agency to consider [redacted]

TPNA believes the proposed labeling changes will provide clinicians with a more accurate, relevant product label in regard to safety as related to hepatic effects and monitoring requirements.

Should you need any additional information, please feel free to contact me directly.

Sincerely,

Mary Jo Pritza MPH, PharmD
Regulatory Affairs Manager
Takeda Pharmaceuticals North America, Inc.
P/847-383-3739
F/847-383-3427

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 33,729

Takeda Pharmaceuticals North America, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Dr. Pritza:

We received your October 10, 2003, correspondence on October 14, 2003, requesting a meeting to discuss [redacted].

The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.

Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].

Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm.

You requested a type A meeting. The teleconference is scheduled for:

Date: Tuesday October 28, 2003
Time: 1:00 pm
Tentative CDER participants:

David Orloff, M.D.	Division Director, Metabolic & Endocrine Drug Products
Robert Misbin, M.D.	Medical Officer
Todd Sahlroot, Ph.D.	Team Leader – Biometrics
Lee-Ping Pian, Ph.D.	Biometrics Reviewer
Jena Weber, BS	Project Manager

We note that the background information for this teleconference was provided in your meeting request letter.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Jena Weber
10/24/03 12:59:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING ISSUES IDENTIFIED

NDA 21-073/S-020

Takeda Pharmaceuticals North America, Inc.
Attention: Janet L. Haskins
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Ms. Haskins:

Please refer to your January 24, 2003, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos® (pioglitazone HCl) Tablets, 15 mg, 30 mg and 45 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed on March 28, 2003, under section 505(b) of the Act in accordance with 21 CFR 314.101(a).

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Please submit a 120-Day safety update when appropriate. These safety data should include data from ongoing phase 4 trials focusing on liver safety, documenting increases in ALT and CPK levels, CHF and events of edema, and cases of bladder tumors.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Jena Weber
3/20/03 08:25:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-073/S-020

Takeda Pharmaceuticals North America, Inc.
Attention: Janet L. Haskins
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Ms. Haskins:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Actos (pioglitazone HCl) Tablets, 15 mg, 30 mg & 45 mg
NDA Number:	21-073
Supplement number:	S-020
Review Priority Classification:	Standard
Date of supplement:	January 24, 2003
Date of receipt:	January 27, 2003

This supplement provides for documentation to support multiple labeling changes to the **CLINICAL PHARMACOLOGY (Clinical Studies** subsection to include revisions of Actos in combination with metformin, a sulfonylurea, or insulin), **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE and ADMINISTRATION** sections, of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 28, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **November 27, 2003.**

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Jena Weber
1/29/03 08:16:30 AM

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.

January 24, 2003

David Orloff, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-073
ACTOS® (pioglitazone HCl) Tablets, 15, 30 and 45 mg

Dear Dr. Orloff:

Pursuant to CFR §314.70 Takeda Pharmaceuticals North America, Inc. (TPNA) submits the following information to the above referenced NDA.

Included in this submission is documentation to support labeling modification to the safety profile, Drug-Drug Interactions and Dosage and Administration sections of the July 2002 version of the ACTOS package insert.

Please note that this submission is compiled in accordance with the Guidance for Industry *Providing Regulatory Submission in Electronic Format – NDAs.* All applicable sections of the sNDA are provided in electronic format. A paper archive copy is included for all items with the exception of Item 12 Case Report Forms and the SAS transport files. This submission is being provided on one DLT tape with an approximate size of 1.63 GB. The tape format is MFT (Microsoft Tape Format). This submission is virus free. A certification of virus scan is included.

Should you have any comments, or questions, please feel free to contact me.

Sincerely,

Janet L. Haskins
Manager, Regulatory Affairs
Takeda Pharmaceuticals North America, Inc.
847-383-3243 (Telephone)
847-383-3427 (Fax)

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.

January 21, 2003

Food and Drug Administration (360909)
Mellon Client Service Center RM 670
500 Ross Street
Pittsburgh, PA 15262-0001

NDA 21-073
ACTOS® (pioglitazone HCl) Tablets, 15, 30 and 45 mg
USER Fee ID Number

Dear Sir:

Takeda Pharmaceuticals North America, Inc. (TPNA) submits User Fees for a sNDA with clinical data. The User Fee Identification Number assigned to this sNDA is

Should you have any questions, or require additional information, please do not hesitate to contact the undersigned.

Sincerely,

Janet L. Haskins
Manager, Regulatory Affairs
Takeda Pharmaceuticals North America, Inc.
P/847-383-3243
F/847-383-3427

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Takeda Pharmaceuticals North America, Inc.
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

2. TELEPHONE NUMBER *(Include Area Code)*

(847) 383-3243

3. PRODUCT NAME

ACTOS (pioglitazone hydrochloride)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021073

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Manager, Regulatory Affairs	January 21, 2003

Takeda

Takeda Pharmaceuticals North America, Inc. & Subsidiaries
475 Half Day Rd. Suite 500
Lincolnshire, IL 60069
(847) 383-3000

Bank One, NA-07.10
Newark, New Jersey
Payable through FCC National Bank
Wilmington, Delaware

62-28
311
0000039468
09 37284

ONE HUNDRED FIFTY-SIX THOUSAND SIX HUNDRED SIXTY USD and 00/100 **********

Pay to the order of
Food and Drug Administration
PO Box 360909
Pittsburgh PA 15251-6909

Date
11/21/2002

Check Amount
****156,660.00 USD

User fee ID#:
NDA No. 21-073

Authorized Signature
Void after 90 days

⑈0000039468⑈ ⑆031100283⑆ 09 37284⑈

Takeda

Takeda Pharmaceuticals North America, Inc. & Subsidiaries
475 Half Day Rd. Suite 500
Lincolnshire, IL 60069

Date
11/21/2002

0000039468

Invoice Date	Invoice Number	Gross Payment Amount	Discount	Net Payment Amount
11/18/2002	12872	156,660.00	0.00	156,660.00
Totals		156,660.00	0.00	156,660.00

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA 21-073 Supplement -020 SE8

Trade Name: Actos
Generic Name: pioglitazone HCl
Strengths: 15 mg, 30 mg & 45 mg Tablets

Applicant: Takeda

Date of Application: January 24, 2003
Date of Receipt: January 27, 2003
Date clock started after UN: N/A
Date of Filing Meeting: March 14, 2003
Filing Date: March 28, 2003
Action Goal Date (optional): User Fee Goal Date: November 27, 2003

Indication requested: **Proposed Indication:** This supplement provides for documentation to support multiple labeling changes to the **CLINICAL PHARMACOLOGY (Clinical Studies** subsection to include revisions of Actos in combination with metformin, a sulfonylurea, or insulin), **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE and ADMINISTRATION** sections, of the package insert.

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA _____
(b)(1) Supplement ✔ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S
Resubmission after a withdrawal? No Resubmission after a refuse to file? No
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid: Yes
Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID # 1
Clinical data? YES

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application? NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A

Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES

- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If an electronic NDA, does it follow the Guidance? YES
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

- If in Common Technical Document format, does it follow the guidance? N/A

- Is it an electronic CTD? NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

- Patent information included with authorized signature? YES

- Exclusivity requested? NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure information included with authorized signature? YES
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in DFS? YES
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? YES

- List referenced IND numbers: 33,729

- End-of-Phase 2 Meeting(s)? NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? NO
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? NO

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? N/A

- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? NO
  If no, did applicant submit a complete environmental assessment? NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? NO

- Establishment Evaluation Request (EER) submitted to DMPQ? NO

- If parenteral product, consulted to Microbiology Team (HFD-805)? N/A

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
  ____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
    - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
    - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
    - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
    - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
    - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES NO
    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES NO
    - EITHER
      The number of the applicant's IND under which the studies essential to approval were conducted.

      YES, IND # _____ NO

      OR
      A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application? NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: Friday March 14, 2003.

BACKGROUND:
(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Drs. Misbin, S.Johnson, Sahlroot, Pian, and Ms. Weber

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	David Orloff
Secondary Medical:	Robert Misbin
Statistical:	Todd Sahlroot and Lee-Ping Pian
Pharmacology:	NN
Statistical Pharmacology:	NN
Chemist:	NN
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Steven Johnson
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	NN
Regulatory Project Manager:	Jena Weber
Other Consults:	NN

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY N/A

STATISTICS	FILE
BIOPHARMACEUTICS	FILE
• Biopharm. inspection needed:	NO
PHARMACOLOGY	N/A
• GLP inspection needed:	N/A
CHEMISTRY	N/A
• Establishment(s) ready for inspection?	NN
• Microbiology	N/A

ELECTRONIC SUBMISSION: YES
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES: No filing issues identified.

_____ The application is unsuitable for filing. Explain why:

✔ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

ACTION ITEMS:

No filing issues conveyed to applicant by Day 74.

All reviews will be completed by October 30, 2003. Company should submit a 120-Day safety update before we take an action. These safety data should include data from ongoing phase 4 trials focusing on liver safety, including increases in ALT and CPK levels, CHF and edema events, and cases of bladder tumors.

JMWeber 3/17/03
Regulatory Project Manager, HFD-510

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

/s/

Jena Weber
11/28/03 12:31:25 PM
CSO