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APPLICATION NUMBER:

21-925

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	21925
Submission Code	new NDA
Letter Date	June 28, 2005
Stamp Date	June 29, 2005
PDUFA Goal Date	July 29, 2006
Reviewer Name	Robert I Misbin MD
Review Completion Date	July 19, 2006
Established Name	Pioglitazone/Glimepiride
(Proposed) Trade Name	DUETACT
Therapeutic Class	Antihyperglycemia
Applicant	Takeda
Priority Designation	Standard
Dosing Regimen	one tablet daily
Indication	type 2 diabetes
Intended population	on pioglitazone and sulfonylurea

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This NDA is for fixed dose combinations (FDC) of pioglitazone plus glimepiride in doses of 30mg/2mg, 30mg/4mg [redacted]

Recommendations:

30 mg pioglitazone plus 2 mg glimepiride – APPROVABLE
30 mg pioglitazone plus 4 mg glimepiride – APPROVABLE

[redacted]

The following wording should be added to the label to reflect results of postmarketing studies with pioglitazone

In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were [redacted]/3656 ([redacted]) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six cases (0.16 %) on pioglitazone and two (0.05 %) on placebo

Assuming satisfactory changes are made in the label, the FDC of 30 mg pioglitazone plus 2 mg glimepiride, and 30 mg pioglitazone plus 4 mg glimepiride can be approved. These FDC tablets are bioequivalent to the individual components and may provide convenience for patients.

[redacted]

1.2 Summary of Clinical Findings

The NDA for pioglitazone (ACTOS) was approved in July 1999 (NDA 21073). The use of pioglitazone both as monotherapy and in combination with sulfonylureas was part of the original approval. The current submission (NDA 21925) is for a fixed dose combination (FDC) product containing pioglitazone plus the sulfonylurea, glimepiride. DMEDP previously agreed that clinical trials would not be necessary and that approval could be based on demonstration of bioequivalence of the FDC to its individual components. The indication would be patients who were already using pioglitazone plus a sulfonylurea, **and** patients who are using pioglitazone or a sulfonylurea where addition of the second component is judged to be needed to control hyperglycemia.

In the original NDA for Actos, the doses of pioglitazone in the monotherapy trials were 15, 30, and 45 mg. Only doses of 15 mg and 30 mg were used in the combination trials. For this reason, the 45 mg dose was recommended for monotherapy only. In December 2003, the Actos label was changed following submission of trials that compared 30 mg to 45 mg in combination with insulin, metformin, and sulfonylureas.

The doses of FDC in the current NDA are 30mg/2mg, 30mg/4mg [redacted]
DMEDP noted at filing of the NDA that a FDC containing 15 mg of pioglitazone would have been advantageous because the best starting dose for many patients may be 15 mg. Fixed dose combination products should typically include the full approved dose range of the individual components so that prescribing practices are not altered due to limited dosing options with the FDC. Lack of a FDC containing 15 mg might encourage use of higher doses of pioglitazone than may be necessary. It was also noted that the current label for ACTOS does not specify that 45 mg of pioglitazone should be used in combination with sulfonylureas. This is because it has not been shown that 45 mg of pioglitazone is more effective 30 mg when used in combination with sulfonylureas.

There are two major issues that must be considered regarding the approvability of this FDC of pioglitazone plus glimepiride. The first issue is whether the FDC is bioequivalent to its components. This issue is covered in the Biopharmacy review. Establishing bioequivalence between the FDC and the individual components is critical because clinical studies of efficacy and safety were not conducted with the FDC tablets. Reliance on efficacy/safety data from the coadministration studies reviewed under NDA 21073 requires bridging with a bioequivalence study. [redacted]

Efficacy of 30 vs 45 mg of pioglitazone:

Trial 341 was a 24-week double blind study of 30 mg vs 45 mg of pioglitazone in patients who had been on stable dose of a sulfonylurea for at least 30 days. The double blind period was preceded by two weeks of screening and by a one week placebo run-in. Study medication was 30

mg pioglitazone plus 15 mg of pioglitazone or matching placebo. This study was previously submitted and reviewed under NDA 21-073.

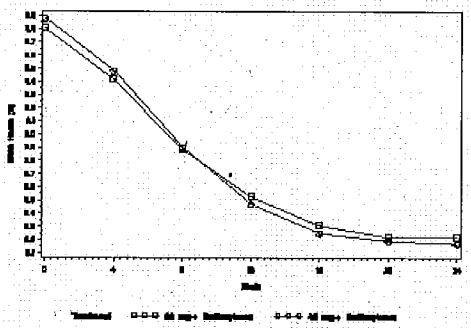
As shown in the tables and figure below, the difference in change in HbA1c between 45 mg and 30 mg was small and not statistically different.

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



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Baseline				
N[a]	340	332	340	332
Mean/LS Mean	9.81	9.88	9.77	9.85
SE	0.079	0.080	0.082	0.083
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	0.045
Week 8				
N[b]	340	332	340	332
Mean/LS Mean Change	8.69	8.90	-0.92[c]	-0.97[d]
SE	0.088	0.092	0.067	0.066
Week 12				
N[b]	340	332	340	332
Mean/LS Mean Change	8.53	8.47	-1.25[c]	-1.38[d]
SE	0.092	0.096	0.078	0.077
Week 16				
N[b]	340	332	340	332
Mean/LS Mean Change	8.31	8.25	-1.47[c]	-1.59[d]
SE	0.094	0.098	0.083	0.083
Week 20				
N[b]	340	332	340	332
Mean/LS Mean Change	8.22	8.19	-1.56[c]	-1.64[d]
SE	0.094	0.099	0.084	0.084
Week 24 (Endpoint)				
N[b]	340	332	340	332
Mean/LS Mean Change	8.22	8.17	-1.55[c]	-1.67[d]
SE	0.095	0.100	0.085	0.085

(continued)

Safety of 30 vs 45 mg of pioglitazone:

Safety data from trial 341 are shown in the table. The 45 mg dose appeared more likely to be associated with adverse events than the 30 mg. Lower leg edema was reported in 5.7% of patients on 30 mg and 12.3% on 45 mg. Cardiac disorders (all causes) were reported in 2.5% and 4.6% at 30 and 45 mg respectively. Decreases in hematocrit, greater than 20% from baseline, occurred in 0.3% of patients on 30 mg and 1.2% of patients on 45 mg. Mean body weight increased 4.3 kg at 30 mg and 5.5 kg at 45 mg.

Edema, lower leg	5.7%	12.3%
Cardiac disorders	2.5%	4.6%
> 20% fall in hematocrit	0.3%	1.2%
Withdrawal due to AE	6%	9.7%
Weight gain	4.3kg	5.5 kg

Adverse events leading to withdrawal were reported for 6% of patients on 30 mg and 9.7% of patients on 45 mg. Of the 350 patients in each arm, 3 patients on 30 mg and 6 patients on 45 mg withdrew due "cardiac disorders – all causes". These include one patient on 30 mg and three on 45 mg who withdraw because of congestive heart failure. There was no patient on 30 mg and two on 45 mg who withdraw because of edema. There were two myocardial infarctions at each dose. One of these (at 30 mg) was fatal.

Bladder cancer in patients taking pioglitazone

Bladder cancers were found in mice in preapproval studies of pioglitazone and in most, if not all, mixed PPAR agonists. In addition, Merck has found that both its PPAR agonist and pioglitazone promoted growth of bladder cancers in the presence of the tumor initiator BBN.

The following is a summary of new findings related to bladder cancer from phase 4 clinical trials lasting two years or longer. As discussed in the body of the review, PROactive is a trial of pioglitazone vs placebo on cardiovascular events in patients with type 2 diabetes. Study 506 was a comparison of pioglitazone vs glyburide on hepatic safety. In both trials, the initial dose of 15 mg pioglitazone was increased to 45 mg after two months.

PROactive

Bladder cancer	Placebo	Pioglitazone	Total
Yes	5*	14	19
No	2627	2591	5218
Total	2633	2605	5838

* does not include a patients whose bladder tumor was noted to be "benign histology".

Study 506

Bladder tumor	Placebo	Pioglitazone	Total
Yes	0	3	3
No	1046	1048	2094
Total	1046	1051	2097

Taking all cases, there were 17/3656 (0.47%) reports of bladder cancers in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. The one case of benign bladder tumor in a placebo patient in PROactive has been excluded. Of the three cases of bladder cancer in study 506, one was a recurrence. If we exclude this case, and restrict the analysis to new diagnoses, there are 16 cases on pioglitazone and 5 on placebo/glyburide. The odds ratio from the stratified analysis performed by FDA is 3.24 (95% CI limits:1.2, 9.9), p=0.02. Excluding diagnoses within one year of starting the test drug, there were two cases bladder cancer on placebo and six on pioglitazone. All of these were from PROactive.

2 INTRODUCTION AND BACKGROUND

ACTOS (NDA 21073) was approved in July 1999. The monotherapy trials in the original NDA had doses of 15, 30, and 45 mg, but the combination trials had doses of 15 mg and 30 mg. For this reason, the 45 mg dose was recommended for monotherapy only. In December 2003, the label was changed following submission of trials that compared 30 mg to 45 mg in combination with insulin, metformin, or sulfonylureas (SFU). As a result of this submission, the Actos label was revised to state that doses of 15 or 30 mg could be added to insulin, metformin or sulfonylureas in patients whose hyperglycemia is not adequately controlled on those agents alone. Increasing the dose to 45 mg is not specifically recommended, although the label states that the maximum dose is 45 mg.

The results of the trials submitted in December 2003 showed that 45 mg of Actos was more efficacious than 30 mg in insulin-treated patients, but was also associated with more congestive heart failure. In metformin-treated patients, the larger dose probably had somewhat more efficacy but was also associated with more edema. In SFU-treated patients, the larger dose did not improve efficacy but was associated with more edema. Results of this trial are shown in figures and tables that follow.

The current submission (NDA 21925) is for a fixed dose combination (FDC) product containing pioglitazone plus glimepiride. The doses are 30mg/2mg, 30mg/4mg [redacted] DMEDP previously agreed that clinical trials would not be necessary and that approval could be based on demonstration of bioequivalence.

DMEDP noted at filing of the NDA that a FDC containing 15 mg of pioglitazone would have been advantageous because the starting dose of pioglitazone is 15 mg. Lack of an FDC containing 15 mg might encourage use of more pioglitazone than may be necessary. It was also noted that the current label for ACTOS does not specify that 45 mg of pioglitazone should be used in combination with sulfonylureas. This is because it has not been shown that 45 mg of pioglitazone is more effective than 30 mg when used in combination with sulfonylureas.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

No comment

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Financial Disclosures:

The following financial disclosure information was submitted with the application. Form 0396 was signed by John Yates on June 3, 2005:

1 Form OMB no 0910-0396 in which the applicant certifies that Takeda has not entered into any financial arrangements with the clinical investigators named in the lists included in the NDA whereby the value of the compensation to the investigator could be affected by the outcome of the study.
2 The applicant certifies that none of the listed investigators disclosed a proprietary interest in the product or equity interest in Takeda.
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 form Takeda.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The original submission of this NDA contained — bioequivalence studies, — (30 mg/2mg, 30mg/4mg, — pioglitazone/glimepiride respectively). Results of these studies demonstrated that 30mg/2mg and 30mg/4 mg were bioequivalent to commercially available Actos and Amaryl tablets given concomitantly.

6 INTEGRATED REVIEW OF EFFICACY

Trial 341 - Clinical Trial of Pioglitazone plus sulfonylureas (SFU's)

This was a 24-week double blind study of 30 mg vs 45 mg of pioglitazone in patients who had been on stable dose of a SFU for at least 30 days. The double blind period was preceded by two weeks of screening and a one week placebo run-in. Study medication was 30 mg of pioglitazone plus 15 mg or placebo tablet.

Demographics at baseline in the intent-to-treat (ITT): 55 years of age, 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.

As shown in the tables and figure below, the difference in change in HbA1c between 45 mg and 30 mg 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 (%)	
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Baseline				
N[a]	340	332	340	332
Mean/LS Mean	9.81	9.88	9.77	9.85
SE	0.079	0.080	0.082	0.083
Week 4				
N[b]	337	328	337	328
Mean/LS Mean Change	9.42	9.48	-0.38[d]	-0.38[d]
SE	0.084	0.089	0.046	0.045
Week 8				
N[b]	340	332	340	332
Mean/LS Mean Change	8.89	8.90	-0.92[d]	-0.97[d]
SE	0.088	0.092	0.067	0.066
Week 12				
N[b]	340	332	340	332
Mean/LS Mean Change	8.53	8.47	-1.25[d]	-1.38[d]
SE	0.092	0.096	0.078	0.077
Week 16				
N[b]	340	332	340	332
Mean/LS Mean Change	8.31	8.25	-1.47[d]	-1.59[d]
SE	0.094	0.098	0.083	0.083
Week 20				
N[b]	340	332	340	332
Mean/LS Mean Change	8.22	8.19	-1.56[d]	-1.64[d]
SE	0.094	0.099	0.084	0.084
Week 24 (Endpoint)				
N[b]	340	332	340	332
Mean/LS Mean Change	8.22	8.17	-1.55[d]	-1.67[d]
SE	0.095	0.100	0.085	0.085

(continued)

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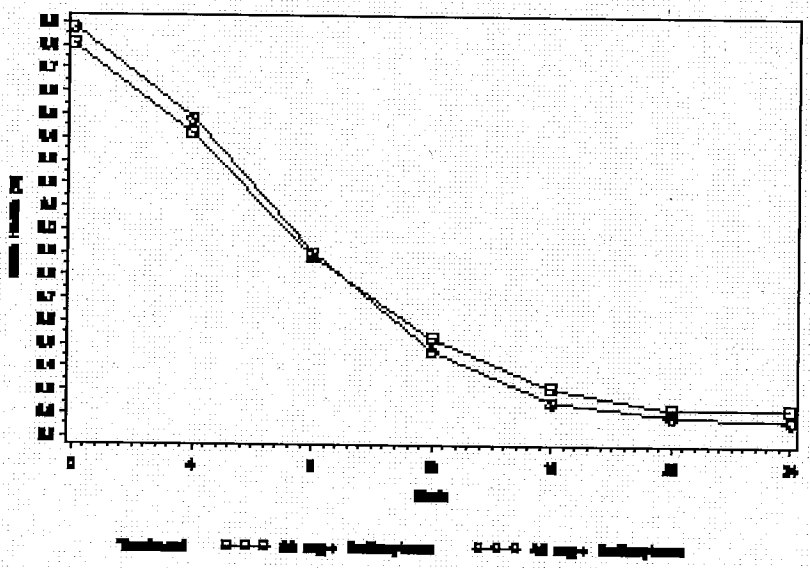
Week 24 (Endpoint)				
LS Mean Difference[c]				-0.12
95% Confidence Interval				(-0.36, 0.12)

[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



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

As shown in the following table, there was little, if any, difference between 30 and 45 mg with respect to the proportion of patients who respond to pioglitazone with reduction 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%*	29 (8.5%)	30 (9.0%)
HbA_{1c} decreased from baseline by ≥0.6%	263 (77.4%)	264 (79.5%)

*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.

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7 INTEGRATED REVIEW OF SAFETY

Trial 341 - Clinical Trial of Pioglitazone (30 mg vs 45 mg) plus sulfonylureas:

Lower leg edema was reported in 5.7% of patients on 30 mg and 12.3% on 45 mg. Cardiac disorders (all causes) were reported in 2.5% and 4.6% at 30 and 45 mg respectively. Decreases in hematocrit, greater than 20% from baseline, occurred in 0.3% of patients on 30 mg and 1.2% of patients on 45 mg. Mean body weight increased 4.3 kg at 30 mg and 5.5 kg at 45 mg.

	Pioglitazone 30 mg	Pioglitazone 45 mg
Edema, lower leg	5.7%	12.3%
Cardiac disorders	2.5%	4.6%
> 20% fall in hematocrit	0.3%	1.2%
Withdrawal due to AE	6%	9.7%
Weight gain	4.3kg	5.5 kg

Adverse events leading to withdrawal were reported for 6% of patients on 30 mg and 9.7% of patients on 45 mg. Of the 350 patients in each arm, 3 patients on 30 mg and 6 patients on 45 mg withdrawal due "cardiac disorders – all causes". There was one patient on 30 mg and three on 45 mg to withdraw because of congestive heart failure. There was no patient on 30 mg and two on 45 mg to withdraw because of edema. There were two myocardial infractions at each dose. One of these (at 30 mg) was fatal.

Bladder Cancer

This section pertains to **all** products that contain pioglitazone.

Bladder tumors had been found in mice in preapproval studies of pioglitazone. Because there were no similar findings with troglitazone or rosiglitazone, FDA initially accepted the explanation offered by Takeda that the tumors were due to the presence of bladder calculi in the pioglitazone studies. It later became clear that most, if not all, mixed PPAR* agonists were associated with bladder tumors in animal toxicology studies. In addition, Merck had found that both its PPAR agonist [redacted] and pioglitazone promoted the growth of bladder tumors in the presence of the tumor initiator, BBN (butyl-nitrosbutyl nitrosamine). These issues were discussed with Takeda in a telecon of July 31, 2002.

Based on these findings, the Carcinogenicity Assessment Committee of FDA recommended on Dec 17, 2002 that the following wording be placed into the ACTOS label:

[redacted]

Takeda declined to go along with this recommendation. In an attempt to come up with "physician-friendly" language that would be acceptable to Takeda, the following proposal for wording was faxed to Takeda on November 24, 2004:

Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR alpha/gamma activity

Initially, Takeda declined to go along with this wording. However, in a submission dated April 9, 2004, they proposed the following:

Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR alpha/gamma activity; however ACTOS is a selective agonist for PPAR gamma.

The phrase "ACTOS is a selective agonist for PPAR gamma" was already in the label, so no new claims were being made.[1]

[redacted]

[1] It is worth noting that pioglitazone decreases mean LDL and triglyceride levels and increases HDL. These properties are suggestive of PPAR **alpha** activity and are not found with rosiglitazone. From studies done by Takeda with COS-1 cells, pioglitazone was less **gamma** selective than rosiglitazone. Urinary tract tumors were also not found in animals treated with rosiglitazone. For these reasons, I believe that the alpha/gamma selectivity statement should be removed from the section dealing with bladder tumors

Results from phase 4 Clinical trials lasting > 2 years

PROactive:

PROactive was a trial of pioglitazone vs placebo on risk of fatal and non-fatal cardiovascular events in patients with type 2 diabetes who were believed to be at high risk of cardiovascular events. Patients randomized to pioglitazone (n= 2605) were given 15 mg for the first month, 30 mg for the second month and 45 mg thereafter. Patients randomized to the other arm (n= 2633) received matching placebo. The trial continued until the last patient randomized had been followed for 30 months and at least 760 patients had had one or more endpoint (cardiovascular) events. The two treatment arms were well-matched as shown by selected baseline characteristics in the following table. The groups were also well-matched with respect to background antidiabetic therapy. Approximately 10% were taking metformin alone, 20% sulfonylurea (SFU) alone, 25% Metformin plus SFU, 30% insulin with oral agents, 12% other combinations, and 4% diet only. There were also no notable differences with respect to concomitant medications.

	PIOGLITAZONE (n=2605)	PLACEBO (n=2633)
Male	1735 (67%)	1728 (66%)
White	2564 (98%)	2600 (99%)
Age in years, mean	61.9	61.6
Current smoker	340 (13%)	381 (14%)
Past smoker	1199 (46%)	1159 (44%)
HbA1c, median	7.8%	7.9%

As expected, patients given pioglitazone showed statistically greater reductions in HbA1c, triglyceride, and LDL/HDL than patients randomized to placebo. Changes in cardiovascular endpoints will be the subject of a later review.

Serious malignant neoplasms were reported in 97/2605 (3.7%) of patients on pioglitazone and 98/2633 (3.7%) on placebo. Possible apparent imbalances were observed for bladder (14 vs 5), breast (3 vs 11), and kidney (3 vs 7).

In view of the preclinical findings, the apparent imbalance in bladder tumors is of particular interest.

There were 14 cases of bladder cancers reported in patients on pioglitazone compared to 5 cases of bladder cancer in patients on placebo. There was also one benign bladder tumor in a patient on placebo. Reporting of the cancer occurred within one year of randomization in 8 patients on pioglitazone and 3 patients on placebo. Reporting of the cancer occurred beyond one year of randomization in 6 patients on pioglitazone and 2 patients on placebo. In the report of the trial, the authors stated: "Taking into account the timeframe of these cases and the potential

confounding factors, it is improbable that the imbalance (in bladder tumors) is related to pioglitazone treatment." No mention was made of the finding of bladder tumors in laboratory animals treated with pioglitazone. (Dormandy JA, Charbonnet B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study. (Lancet 366, 1279-1289, 2005). In

Study 506: Hepatic Safety Study

This three year trial was performed as a phase 4 commitment to evaluate the hepatic safety of pioglitazone vs glyburide. Eligible patients had HbA1c > 7% while taking an oral hypoglycemic agent other than a thiazolidinedione. After a washout period, patients were randomized to pioglitazone or glyburide. The initial dose of pioglitazone was 15 mg. This was titrated to 30 mg and then to 45 mg. The initial dose of glyburide was 5 mg. This was titrated to 10 mg and then 15 mg. Matching placebos were used for blinding. Titration was done every three months based on HbA1c > 7.5%. After maximal doses of study medications, rescue therapy with metformin (up to 2g /d) and finally insulin were allowed.

The two treatment arms were well matched as shown by selected baseline characteristics in the following table. There were also no notable differences with respect to baseline medications.

	PIOGLITAZONE (n=1051)	GLYBURIDE (n=1046)
Male	601 (57%)	581 (56%)
White	628 (60%)	650 (62%)
Age in years, mean	54.5	54.8
HbA1c	9.5	9.5

Study medications:

The last titrated dose of study medication is shown in the following table. With both treatments, approximately 55% of patients were titrated to the maximum dose.

	PIOGLITAZONE (n=1051)	GLYBURIDE (n=1046)
Gly 5 mg or Pio 15 mg	18.8%	20.5%
Gly 10 mg or Pio 30mg	26.6%	23.5%
Gly 15 or Pio 45	54.5%	56%

At baseline, 660 patients randomized to pioglitazone were using metformin. The mean dose was 780 mg. At baseline, 676 patients randomized to glyburide were using metformin. The mean dose was 770 mg. At week 156, 259 patients randomized to pioglitazone were using metformin. The mean dose was 906 mg. At week 156, 253 patients randomized to glyburide were using

metformin. The mean dose was 991 mg. At week 156, 39 patients randomized to pioglitazone were using insulin. The mean dose was 37 units. At week 156, 58 patients randomized to glyburide were using insulin. The mean dose was 25 units

Reports of cancer as an serious adverse event occurred in 1.2% of patients (13/1051) on pioglitazone and 1.3% of patients (14/ 1046) on glyburide. There were 3 cases of colon cancer in each arm. With respect to bladder tumors, there were two new case of bladder cancer, and one recurrence of bladder cancer. All three were in patients taking pioglitazone:

Patient A00116 had been on 30 mg pioglitazone for 334 when she developed hematuria. The diagnosis of bladder cancer was made three weeks later.

Patient A001127 had a history of bladder cancer, and experienced a recurrence six months after starting 45 mg pioglitazone.

Patient A00876 had a two year history of hematuria. The diagnosis of bladder cancer was made six weeks after starting 30 mg pioglitazone.

Post-marketing reports:

Through January 31, 2006, there have been 12 spontaneous reports of bladder cancer in patients taking pioglitazone. These reports must be interpreted in light of a total exposure of greater than 6 million patient years.

Kaiser Permanente Northern California (KPNC) Diabetes Registry:

The Sponsor has submitted an interim analysis on a cohort of 207,239 patients age 40 or older with type 2 diabetes who enrolled in KPNC between Jan 1, 1997 and Dec 31, 2002. 806 patients were excluded because they had a diagnosis of bladder cancer upon entry or within six months of entry. 6.782 patients were also excluded because of lapses in membership.

The remaining 193,127 eligible men and women with type 2 diabetes were followed. The primary outcome was incident diagnosis of bladder cancer. The following is from an interim analysis of data through Dec 31, 2003. Cox proportional hazard models were used for all calculations of the relative risk of bladder cancer with pioglitazone.

The hazard ratio for risk of bladder cancer in diabetes patients taking pioglitazone was 1.2 (95% cf 0.8 – 1.9). Increased risk was only observed for the 12-24 months stratum and the 7-18 gram cumulative dose stratum.

Medication	Hazard Ratio	95% CF
Pioglitazone	1.2	0.8-1.9
Other TZD	1.2	0.7-2.0
Metformin	1.1	0.9-1.4
Insulin	1.1	0.8-1.5
Sulfonylurea	1.0	0.8-1.4
Other oral agents	1.2	0.5-2.7
Pioglitazone		
<12 months	0.9	0.5-1.8
12 to 24 months	2.3	1.2-4.1
> 24 months	1.6	0.7-3.6
Cumulative dose, mg		
< 7000	0.8	0.4-1.6
7001-18000	2.3	1.3-4.0
> 18000	1.7	0.8-3.9

Summary of New Bladder Cancer Findings:

The following is a summary of new findings related to bladder cancer from clinical trials lasting longer than two years

PROactive

Bladder cancer	Placebo	Pioglitazone	Total
Yes	5*	14	20
No	2627	2591	5218
Total	2633	2605	5238

* does not include a patients whose bladder tumor was noted to be "benign histology".

Study 506

Bladder tumor	Placebo	Pioglitazone	Total
Yes	0	3	3
No	1046	1048	2094
Total	1046	1051	2097

Taking all cases, there were 17/3656 (0.47%) reports of bladder cancers in patients taking ACTOS compared to 5/3679 (0.14%) in patients not taking ACTOS.

The one case of benign bladder tumor in a placebo patient in PROactive has been excluded. Of the three cases of bladder cancer in study 506, one was a recurrence. If we exclude this case, and restrict the analysis to new diagnoses, there are 16 cases on pioglitazone and 5 on placebo/glyburide. The odds ratio from the stratified analysis is 3.24 (95% CI limits:1.2, 9.9), p=0.02. Excluding diagnoses within one year of starting the test drug, there were two cases bladder cancer on placebo and six on pioglitazone. All of these were from PROactive.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

DUETACT is to be used in patients who are taking pioglitazone and a sulfonylurea or in patients who are taking pioglitazone **or** a sulfonylurea where the judgment has been made that the second drug should be added to control hyperglycemia

8.2 Pediatrics

Neither pioglitazone nor glimepiride are recommended for pediatric patients.

9 OVERALL ASSESSMENT

9.1 CONCLUSIONS:

This NDA is for fixed-dose combinations (FDC) of pioglitazone plus glimepiride in doses of 30mg/2mg, 30mg/4mg [redacted] Assuming satisfactory changes are made in the label, the FDC of 30 mg pioglitazone plus 2 mg glimepiride and 30 mg pioglitazone plus 4 mg glimepiride should be approved. This product may provide convenience for patients who are already taking pioglitazone plus a sulfonylurea as individual dosages.

9.2 Recommendation on Regulatory Action

30 mg pioglitazone plus 2 mg glimepiride – APPROVABLE
30 mg pioglitazone plus 4 mg glimepiride – APPROVABLE

The following wording should be added to the label to reflect results of post-marketing studies with pioglitazone

In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were /3656 ( ) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six cases (0.16%) on pioglitazone and two (0.05%) on placebo

9.4 Labeling Review

Doses of 15 or 30 mg of pioglitazone are approved for initial treatment in patients taking sulfonylureas. Although 30 mg is somewhat more effective in treating hyperglycemia, it is also more likely to cause edema. Labeling of DUETACT should not encourage the use of 30 mg of pioglitazone when 15 mg would be preferable (see 9.5 "Comments to Applicant")

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The following text comes from the *Carcinogenicity* section of the current ACTOS label:

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. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR α/γ activity; however pioglitazone is a selective agonist for PPARγ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving pioglitazone 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 pioglitazone (0.72%) and patients treated with placebo (0.88%).

This should be amended to read:

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 pioglitazone in clinical trials up to one year in duration, no new cases of bladder tumors were identified In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were —/3656 (—— reports of bladder cancer in patients taking pioglitazone compared

to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six cases on pioglitazone and two on placebo

9.5 Comments to Applicant

Doses of 15 **and** 30 mg of pioglitazone are approved for initial treatment in patients taking sulfonylureas. Labeling of DUETACT should not encourage the use of 30 mg in preference to 15 mg. The following changes should be made to the proposed label:

Line 909: [redacted]

Line 1002: Add a statement to indicate that treatment with pioglitazone should be initiated at 15 or 30 mg

Line 1012: Delete the sentence "[redacted] Restate the sentence in a way that does not dismiss the option of using 15 mg

Line 1019: "Starting dose for patients currently on pioglitazone monotherapy" should be [redacted]

Line 1033: [redacted]

The following text comes from the *Carcinogenicity* section of the current ACTOS label:

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. Urinary tract

tumors have been reported in rodents taking experimental drugs with dual PPAR α/γ activity; however pioglitazone is a selective agonist for PPARγ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving pioglitazone 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 pioglitazone (0.72%) and patients treated with placebo (0.88%).

This should be amended to read:

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 pioglitazone in clinical trials up to one year in duration, no new cases of bladder tumors were identified. In two 3 year studies in which pioglitazone was compared to placebo or glyburide, there were 7/3656 [redacted] reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six cases (0.16%) on pioglitazone and two (0.05%) on placebo

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/s/

Robert Misbin
7/20/2006 03:53:48 PM
MEDICAL OFFICER

Duetact

Mary Parks
7/20/2006 05:26:35 PM
MEDICAL OFFICER

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MEDICAL OFFICER REVIEW

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

APPLICATION #:	**IND 21925**	**APPLICATION TYPE:**	**NDA.....**
SPONSOR:	**Takeda**	**PROPRIETARY NAME:**	**..**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**Pioglitazone/Glimepirid**
		ROUTE:	**Oral.....**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	**August 22, 2005..**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
July 7, 2005		NDA	Filing memo

This NDA is for a fixed dose combination product containing pioglitazone plus glimepiride: 30mg/2mg, 30mg/4mg.

The NDA can be filed

Signed: **Medical Reviewer: Robert I Misbin MD** **Date: August 22, 2005**

This NDA is for a fixed dose combination product containing pioglitazone plus glimepiride. It is to be labeled for patients who are already taking pioglitazone plus a sulfonylurea or for patients inadequate controlled on sulfonylurea monotherapy in whom pioglitazone will be added. The Sponsor intends to market [redacted] dosage strengths of pioglitazone/glimepiride: 30mg/2mg, 30 mg/4mg, [redacted]

The NDA filed. The following comments should be conveyed to the Sponsor:

The starting dose of ACTOS is 15 mg in patients whose hyperglycemia is inadequately controlled on sulfonylureas. It would be desirable to market a formulation of [redacted] that contained 15 mg of pioglitazone.

[redacted]

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/s/

Robert Misbin
8/23/2005 02:38:05 PM
MEDICAL OFFICER

filing memo

David Orloff
8/24/2005 05:20:24 PM
MEDICAL OFFICER

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