H RHEE

IND # [redacted]

September 2, 1998

SEP - 3 1998

Sponsor: Takeda America Research & Development Center, Inc.
Princeton, New Jersey 08540
Scott L. Grossman, Ph. D., Regulatory Director (609)452-1113

Submission Date: 07/22/1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
AMENDMENT S#184

Drug: Pioglitazone HCl(AD-4844)

Pharmacological Class: Thiazolidinedione Derivative

Clinical dose: 30 mg per day

1. BACKGROUND: The sponsor wishes to provide additional information in response to this division's request (dated on 2/11/1998) on urine pH in pioglitazone-treated and control animal including human subjects .

2. COMMENTS:

On June 20, 1996 the sponsor submitted to this division the following table as an amendment(Serial Number 061). From their 2-year carcinogenicity studies the male rats had transitional cell tumors. The sponsor attributed the carcinoma in rats was due to high urine pH, which is not relevant to carcinogenic potential of pioglitazone in human because of differential acidic pH.

INCIDENCE OF THE FOCAL PROLIFERATIVE LESIONS IN THE URINARY BLADDER OF MALE RATS IN 2-YEAR CARCINOGENICITY STUDY(S#061)

Dose(mg/kg/d)	0	0	1	4	8	16	63
Sex	M / F	M / F	M / F	M / F	M / F	M / F	M / F
Hyperplasia							
a) Nodular	0 / 0	0 / 0	0 / 0	0 / 0	3 /-	1 / 0	0 / 0
b) Papillary	3 / 0	0 / 0	1 / 1	2 / 1	1 /-	1 / 0	1 / 1
Transitional cell tumors							
a) Benign	0 / 0	0 / 0	0 / 1	0 / 1	3 /-	2 / 1	2 / 1
b) Carcinoma	0 /-	0 /-	0 /-	2 /-	4 /-	5 /-	4 /-
Total Lesions	3 / 0	0 / 0	1 / 2	4 / 2	9 /-	9 / 1	7 / 1

3. RECOMMENDATIONS (Letter to the sponsor):

Please provide the following information for each rat that had a bladder tumor: urine pH, tumor type, presence or absence of bladder calculi.

/S/ [redacted]

Herman M. Rhee, Ph.D.

/S/ [redacted]

cc: Original IND, HFD-510
R. Steigerwalt/H. Rhee/J. Weber

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Sex	M / F	M / F	M / F	M / F	M / F	M / F	M / F
Hyperplasia							
a) Nodular	0 / 0	0 / 0	0 / 0	0 / 0	3 /-	1 / 0	0 / 0
b) Papillary	3 / 0	0 / 0	1 / 1	2 / 1	1 /-	1 / 0	1 / 1
Transitional cell tumors							

a) Benign	0 / 0	0 / 0	0 / 1	0 / 1	3 /-	2 / 1	2 / 1
b) Carcinoma	0 /-	0 /-	0 /-	2 /-	4 /-	5 /-	4 /-
Total Lesions	3 / 0	0 / 0	1 / 2	4 / 2	9 /-	9 / 1	7 / 1

3. RECOMMENDATIONS (Letter to the sponsor):

Please provide urine pH values of each control and treated rats including the information as to the presence of calculi in the rats that had bladder carcinoma.

/S/

Herman M. Rhee, Ph.D.

cc: Original IND, HFD-510
R. Steigerwalt/H. Rhee

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STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY

Date	APR 2 1999
NDA No.	21-073
IND No.	N/A
Applicant	Takeda America Research and Development Center, Inc.
Name of Drug	Actos™ (pioglitazone HCl)
Document Reviewed	• Rat Study: Vol. 1.048 • Mouse Study: Vol. 1.038
Statistical Reviewer	Ji-Yang (Ted) Guo, Div II/OEB, HFD-715
Pharmacologist	Herman Rhee, Ph.D., ODE 2, HFD-510

Summary

This review evaluates the sponsor's studies of Actos™ [AD-4833 (HCl)] for carcinogenic potential in rats and mice. Based on the survival-data analysis and the tests for dose-tumor positive linear trend, this reviewer informs the reviewing pharmacologist, Dr. Herman Rhee the carcinogenicity findings of Actos™. The following highlights summarize this reviewer's statistical conclusions:

- Actos™ is carcinogenic in **male** rats, causing
  - fibrosarcoma (code: 324) in skin, subcutis (code: 333)
  - carcinoma, transitionalc (code: 798) in urinarybladder (code: 78)
- The Actos™ is carcinogenic in **female** rats, causing

  lipoma (code: 508) in skin, subcutis (code: 333)
- The Actos™ is not carcinogenic in mice in either sex.

This reviewer concludes: Actos™ is carcinogenic in rats. The probability of erroneously concluding a significant test is 10% or less of the time.

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Introduction

This reviewer evaluates the studies of Actos™ (pioglitazone HCl, coded as AD-4833) for carcinogenic potential in rats and mice, conducted by Takeda America Research and Development Center, Inc. In this report, this reviewer presents to the reviewing pharmacologist, Dr. Herman Rhee his independent carcinogenicity analysis based on the sponsor's data. The computer output of major statistical calculations is included in the appendix.

Sponsor's Studies

The sponsor analyzed the carcinogenic potential of the Actos™ in male and female rats and mice. Table 1 summarizes the sponsor's studies (dated January 15, 1999):

Table 1. Description of Studies

Study Number	295-152	295-153
Species	Rat	Mouse
Strain	Crl: CD® BR	Crl: CD-1® (ICR) VAF/Plus™
Route of Administration	Oral gavage	Oral gavage
Dose Unit	Mg/kg/day	Mg/kg/day
Dose level	0, 0, 1, 4, 8, 16, and 63	0, 0, 3, 10, 30, and 100
Number of Animals/per treatment group	60	60
Length of Study	104 weeks	104 weeks
Study Duration	8/11/93-8/8/95	8/17/93-8/25/95

Please note that the female-rat study does not have the 8 mg/kg/day dose group. The zero-dose groups represent the control. The terminal sacrifice started on and after week 104.

Documents Reviewed

This reviewer did not formally received desk copies of the sponsor's report for review. However, a selected section of the NDA submission was photocopied from pages 17-21, section 5.1.2.3 Oncogenicity, vol. 1.038 & vol. 1.048. This reviewer finds the conclusions on carcinogenicity using these materials.

Data Analyzed

The sponsor submitted the data on a 3.5" diskette labeled FDA FORMAT DATA DISK STUDIES 295-152+153 12/16/98. The data were compressed into a self-extracting file, Mpidata.exe.

The following points list the uncompressed data files:

1. Rat Data (Study 295-152)
   - DATFL152.DAT
   - ORGAN152.DAT
   - TUMOR152.DAT

2. Mouse Data (Study 295-153)
   - DATFL153.DAT

- ORGAN153.DAT
- TUMOR153.DAT

MPI Research created the data files on 12/16/98, indicated in the README file.

Sponsor's Findings

In the rat study, the sponsor appeared to concern the lesions in urinary bladder in rats. In the section of Oncogenicity (section 5.1.2.3, pages 17-21), the sponsor described it's findings for lesions in urinary bladder in rats. This reviewer summarizes the sponsor's findings in Table 2.

Table 2. Number of Lesions in Urinary Bladder in Rats

Sex	Lesion	Incidence By Dose (mg/kg/day)						
		0	**0**	**1**	**4**	**8**	**16**	**63**
Male	Hyperplasia, epithelial, papillary	3	0	1	2	1	1	1
Female		0	0	1	1	[redacted]	0	1
Male	Hyperplasia, epithelial, simple	1	3	0	2	7	10	7
Female		1	1	2	5	[redacted]	3	11
Male	Hyperplasia, epithelial, nodular	0	0	0	0	4	1	0
Female		0	0	0	0	[redacted]	0	0
Male	Transitional cell tumor, benign	0	0	0	0	4	2	2
Female		0	0	1	1	[redacted]	1	0
Male	Carcinoma, transitional cell	0	0	0	2	3	5	4
Female		0	0	0	0	[redacted]	0	0

(Source: Sponsor's table on page 19, section 5.1.2.3)

The sponsor concluded, "These data support the hypothesis that the urinary bladder tumors observed in the male rats were due to the formation of calculi which subsequently induced hyperplasia."

In the mouse study, the sponsor concluded, "No increase in the incidence of tumors and no evidence of an orcogenic effect were observed at any dose."

Reviewer's Comment:

In the Oncogenicity section of the sponsor's report, the sponsor did not directly state whether the lesion in urinary bladder in rats was dose related. In the end, the sponsor concluded, "AD-4833 (HCl) was not considered to represent a carcinogenic risk to humans (page 21, section 5.1.2.3)." This reviewer concludes that the sponsor's viewpoint is equivocal.

Reviewer's Evaluation

Evaluation of Carcinogenicity Study on Male Rats

To evaluate the sponsor's carcinogenicity study on male rats, this reviewer analyzed the sponsor's data. The reviewer's evaluation comprises the following:

- survival-data analysis
- tumor-data analysis

The reviewer's conclusions are summarized at the end of this section.

Survival-Data Analysis

The survival-data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the higher the dose level is, the more deaths are likely to occur.

Table 3 shows the number of male rats by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," "MEDHI," "HIGH," and "MAXI" represent 0, 0, 1, 4, 8, 16, and 63 mg/kg/day, respectively. The time interval "104-105" represents the terminal-sacrifice week. Please note that the number of rats died in 78 weeks of study is higher in the MAXI group than in other groups.

Table 3. Number of Male Rats by Treatment and Age Group

Number of Animals
Species: Rat
Sex: Male

	Treatment Group							
	CTRL1	CTRL2	LOW	MED	MEDHI	HIGH	MAXI	Total
	Count	Count	Count	Count	Count	Count	Count	Count
Time Interval								
0-52	4	7	4	3	6	9	13	46
53-78	9	8	2	12	9	14	19	73
79-91	4	8	8	12	13	4	12	61
92-103	10	13	10	10	9	11	11	74
104-105	33	24	36	23	23	22	5	166
Total	60	60	60	60	60	60	60	420

Source: D:\ACTOS\rats.txt

Table 4 describes, for the male rats, the number of deaths, the number at risk, and the cumulate percentages of deaths by treatment and age group.

Table 4. Cumulative Percentages of Deaths in Male Rats

Analysis of Mortality
Species: Rat
Sex: Male

	Dose														
	CTRL1			CTRL2			LOW			MED			MEDHI		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Time(-wks)															
0-52	4	60	6.7	7	60	11.7	4	60	6.7	3	60	5.0	6	60	10.0
53-78	9	56	21.7	8	53	25.0	2	56	10.0	12	57	25.0	9	54	25.0
79-91	4	47	28.3	8	45	38.3	8	54	23.3	12	45	45.0	13	45	46.7
92-103	10	43	45.0	13	37	60.0	10	46	40.0	10	33	61.7	9	32	61.7
104-105	33	60	55.0	24	60	40.0	36	60	60.0	23	60	38.3	23	60	38.3

(CONTINUED)

Species: Rat
Sex: Male

	Dose					
	HIGH			MAXI		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Time(-wks)						
0-52	9	60	15.0	13	60	21.7
53-78	14	51	38.3	19	47	53.3
79-91	4	37	45.0	12	28	73.3
92-103	11	33	63.3	11	16	91.7
104-105	22	60	36.7	5	60	8.3

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Figure 1 helps visualize the cumulative percentages of deaths over time by treatment. The HIGH and MAXI groups clearly shows dose-related mortalities compared with the two control groups.

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Figure 1. Line Graph of Cumulative Percentages of Deaths in Male Rats

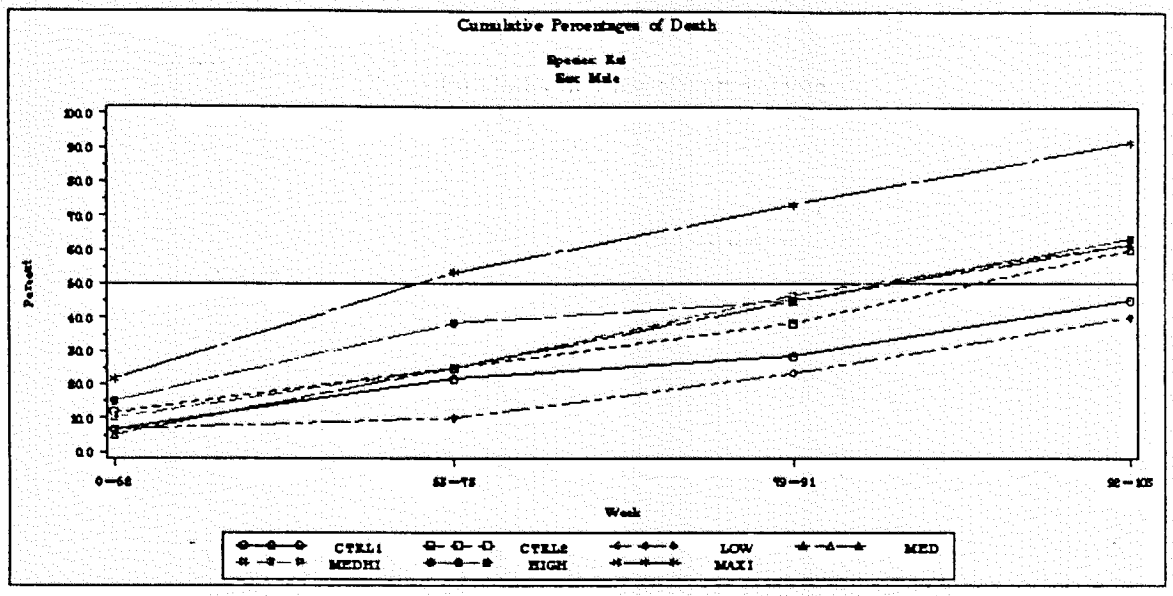
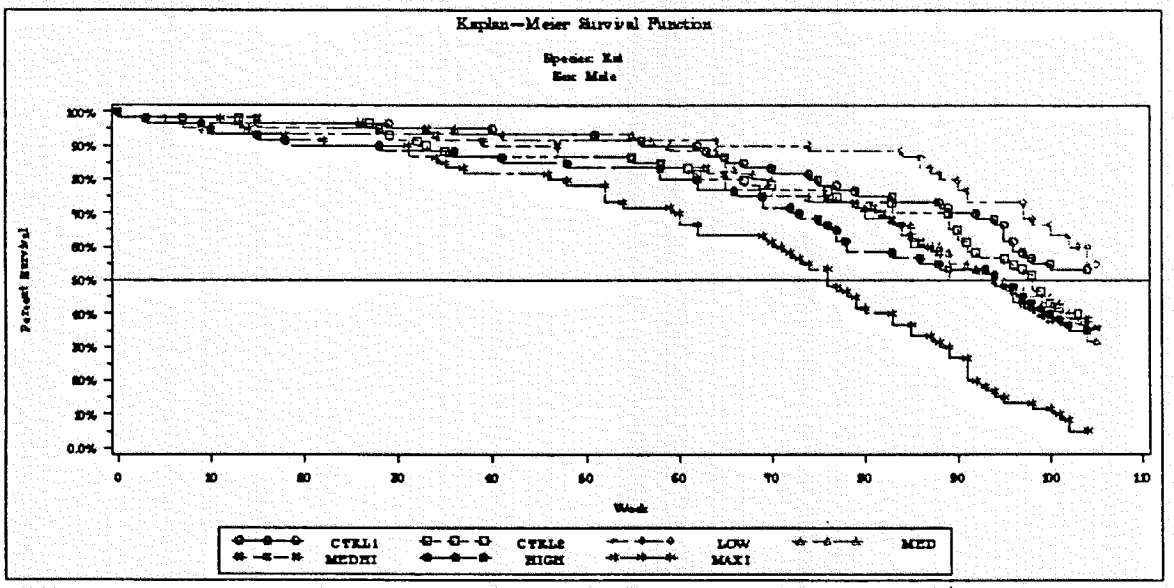


Figure 2 shows the Kaplan-Meier survival functions for male rats. The animals in the MAXI (63 mg/kg/day) group had a markedly lower survival rate than did those in other groups

Figure 2. Kaplan-Meier Survival Functions for Male Rats



The test for dose-mortality trend (Table 5) shows significant results based on the Cox test (p=0) and Kruskal-Wallis test (p=0).

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Table 5. Dose-Mortality Trend in Male Rats

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	63.88	0.0000
	Depart from Trend	6.24	0.2835
	Homogeneity	70.12	0.0000
Kruskal-Wallis	Dose-Mortality Trend	54.60	0.0000
	Depart from Trend	6.21	0.2868
	Homogeneity	60.80	0.0000

Source: d:\actos\rats\m\XAnimalX.txt

This reviewer's survival-data analysis concludes that the mortality in male rats is positively dose-related. Therefore, the age-adjusted trend test detailed in the following section (Tumor-Data Analysis), is justified.

Tumor-Data Analysis

The tumor-data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tests this trend for every organ and tumor. The resulting p-values are compared against the p-value cutoff points set by the following Agency's procedures. A significant result indicates a dose-tumor positive linear trend.

Statistical Procedure in Evaluation of Tumor-Data Analyses Currently Adopted by CDER Divisions of Biometrics

- For tumors found either fatal or non-fatal to all the animals, the statistical interpretation is based on the **exact test.**
- For tumors found fatal to some, but not to all animals, the statistical interpretation is based on the **asymptotic test,** resulting from the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution.
- To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 0.1, this rule states:
  - Tumors with a spontaneous tumor rate of **1% or less** may be tested at the **0.025** significance level.
  - Otherwise, the **0.005** significance level may be used.

Table 6 quotes the significant trend-tests for male rats. This reviewer informs the reviewing pharmacologist the statistically significant dose-tumor positive linear trend in the male rats.

Table 6. Significant Trend-Tests for Male Rats

Organ	Tumor	Tumor-Bearing Animals	P-value
Skin, Subcutis (333)	Fibrosarcoma (324)	0 0 0 0 0 2 2	≈0.000 (P<0.025)
Urinary Bladder (78)	Carcinoma, transitionalc (798)	0 0 0 2 4 5 4	≈0.000 (P<0.025)

Conclusions on Male-Rat Study

This reviewer informs the reviewing pharmacologist that Actos™ is potentially carcinogenic (Table 6). Please note that the test could lead to a false conclusion due to chance alone. However, the probability of erroneously concluding a significant test is about 10% or less.

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