R'12/107415 2

Re: Actos PI and Dear HP Letter [SEC=UNCLASSIFIED]

[redacted] to: Bronwen.Harvey 23/06/2011 01:05 PM
Cc: Jane.Cook, Neil.Mitchell, Nick.Simpson

History: This message has been replied to and forwarded.

3 attachments

ACTOS PI_v3.2_23Jun11.docx DHCPL_for_Australia 23Jun11.docx pic06923.jpg

Dear Bronwen

Please find attached an updated version of the Actos PI incorporating the updates agreed as per you message below. The changes will also be submitted as a SRN today. At the recent BPR seminar, it was stated that a SRN required prior approval before the changes could be implemented, can you clarify whether the updated PI can be implemented based on the date of the notification or whether we must wait for an acknowledgement letter from the TGA before issuing the updated PI?

(See attached file: ACTOS PI_v3.2_23Jun11.docx)

With regard to the Dear HP letter, I have added in the PI changes and drafted a summary of the overseas regulatory situation. I have received advice this morning that the EMA will most likely issue a press release Friday morning EU time which may change this section of the letter. We propose to finalise the letter on Monday morning to ensure that the information is up to date. I have also added a statement that the PI can be downloaded from the TGA website, is this acceptable (I will ensure that the updated document is available on TGA website before the letter is distributed)?

(See attached file: DHCPL_for_Australia 23Jun11.docx)

Kind Regards
[redacted]
(Embedded image moved to file: pic06923.jpg)

Bronwen.Harvey[redacted]
[redacted]
22/06/2011 02:10 PM

To [redacted]
cc Jane.Cook[redacted]
Neil.Mitchell[redacted]
Nick.Simpson[redacted]

Subject
Re: Actos PI and Dear HP Letter [SEC=UNCLASSIFIED]

[redacted]

Thank you for your draft PI changes and the draft dear HP letter.

In relation to the PI:

We accept your proposal to remove reference to the French cohort data, on the basis that this has not yet been fully evaluated, noting that we may require further PI changes once the evaluation is completed.

We accept the your proposal to remove the reference to consistency of clinical data with pre-clinical findings, noting that the pre-clinical information is still retained elsewhere in the PI.

We agree with the proposed clarification for the epidemiological data paragraph that the data comes from the Kaiser Permanente Northern California (KPNC) study ie the move of the indicated paragraph to the Kaiser data description.

We do not agree with the proposed text in relation to the recommendation that clinicians take the risk of bladder cancer into consideration when using pioglitazone. We note that your proposal is consistent with the FDA announcement but consider that the data indicate increased risk in a broader population than those with a history of bladder cancer. We consider that the text should more clearly reflect this risk and propose the following:

Pioglitazone should not be used in patients with bladder cancer or a history of bladder cancer. The risk of bladder cancer should be considered in the care of all patients treated with pioglitazone.

In relation to the Dear HP letter
No changes required other than to update the text discussed above. We would appreciate seeing the final letter before it goes out.

We are working on a TGA statement to go up on our website at the same time as the HP letters are sent out and will send you the proposed text once it is ready.

Bronwen
****
Dr Bronwen Harvey
Head, Signal Investigation Unit
Office of Product Review
Therapeutic Goods Administration
Phone: 02 6232 8071
Mobile: 0423 026 409
Email: bronwen.harvey[redacted]

[redacted]

20/06/2011 01:50 PM

To Bronwen.Harvey[redacted]

cc Jane.Cook[redacted]
Neil.Mitchell[redacted]
Nick.Simpson[redacted]

Subject Actos PI and Dear HP Letter

Dear Dr Harvey

As per your letter of Friday 17th June 2011, please find attached a draft PI and Dear HP letter incorporating information on Actos and the potential risk of bladder cancer. In addition, Eli Lilly global and Takeda have provided a response document outlining their rationale where the PI update differs from that requested. A formal SRN will be submitted to the Office of Market Authorisation once all of the changes have been agreed.

With respect to the Dear HP letter, we have included a place holder for describing the actual PI language once this has been agreed between Lilly and TGA. Similarly, we have a placeholder for describing the overseas regulatory status and this will be added at the end of the week once the outcome of the CHMP meeting is known. The letter has been drafted this way to ensure that the overseas information will be current at the time of mail out.

(See attached file: Australia_ Response Document.docx)(See attached file: ACTOS PI_v3.1_20Jun11.docx)(See attached file: DHCPL_for_Australia.docx)

Kind Regards

[redacted]

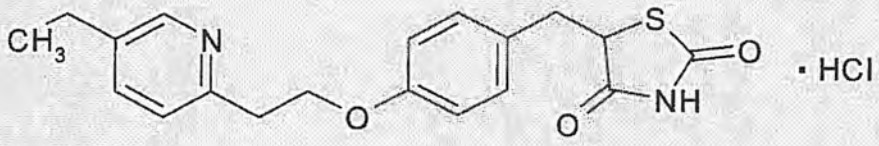
(Embedded image moved to file: pic29876.jpg)
[attachment "Australia_ Response Document.docx" deleted by Bronwen Harvey/TGA/Health] [attachment "ACTOS PI_v3.1_20Jun11.docx" deleted by Bronwen Harvey/TGA/Health] [attachment "DHCPL_for_Australia.docx" deleted by Bronwen Harvey/TGA/Health] [attachment "pic29876.jpg" deleted by Bronwen Harvey/TGA/Health]

ACTOS® (pioglitazone hydrochloride)

NAME

ACTOS® (pioglitazone hydrochloride)

The active ingredient in ACTOS tablets is pioglitazone hydrochloride. Chemically, pioglitazone hydrochloride is [(±)-5-[[4-[2-(5- □ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione hydrochloride. The empirical formula is $C_{19}H_{20}N_2O_3S{\cdot}HCl$ which corresponds to a molecular weight of 392.90 Daltons.



The CAS number for pioglitazone HCl is 112529-15-4. The CAS number for pioglitazone free base is 111025-46-8.

DESCRIPTION

Pioglitazone hydrochloride is an odourless, white crystalline powder that 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.

Each tablet contains 15, 30 or 45 mg of pioglitazone (as the hydrochloride). The tablets also contain lactose, hydroxypropylcellulose, carmellose calcium and magnesium stearate.

PHARMACOLOGY

ACTOS is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycaemic control while reducing circulating insulin levels.

Fasting and postprandial glycaemic control are improved in patients with type 2 diabetes mellitus. The decreased insulin resistance produced by ACTOS results in lower blood glucose concentrations, lower plasma insulin levels and lower HbA_{1c} values.

Mode of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its unique 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 hyperglycaemia, hyperinsulinaemia and hypertriglyceridaemia 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

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Steady state is achieved after 4-7 days of dosing. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption. The absolute bioavailability following oral administration is approximately 83%.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following intravenous administration is 0.25 L/kg of body weight.

Protein Binding: Pioglitazone is extensively bound to plasma protein (> 99 %), principally to serum albumin. The free fraction is less than 2% and independent of concentration in the range of 34-2000 ng/mL (which includes the therapeutic concentration range).

Metabolism: Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 and 3A4. Three of the six metabolites formed are active. The major circulating metabolite is M-IV (1-hydroxyethyl pioglitazone), which accounts for most of the drug-related material in human plasma and probably accounts for much of the therapeutic efficacy.

Pioglitazone did not inhibit P450 activity when incubated with human P450 liver microsomes.

Elimination: Following oral administration of radiolabelled pioglitazone to humans, recovered label was mainly in faeces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or faeces. The mean plasma elimination half-life of unchanged pioglitazone in man is 5 - 6 hours and for its total active metabolites 16 - 23 hours.

Special Populations

Renal insufficiency: In patients with renal impairment, plasma concentrations of pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but with similar oral clearance of parent drug. Thus free (unbound) pioglitazone concentration remains unchanged. Dose adjustment in patients with renal dysfunction is not recommended (see DOSAGE AND ADMINISTRATION). No information is available for patients on dialysis therefore ACTOS should not be used in such patients.

Hepatic insufficiency: In subjects with impaired hepatic function, total plasma concentration of pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of pioglitazone.

ACTOS therapy should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5 times the upper limit of normal).

Elderly: No clinically significant differences between elderly and young subjects were observed.

Paediatric: Pharmacokinetic data in the paediatric population is 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 glycaemic control in both males and females. In controlled clinical trials, haemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). See DOSAGE and ADMINISTRATION, Female Patients for recommended dosages in women.

Clinical Trials

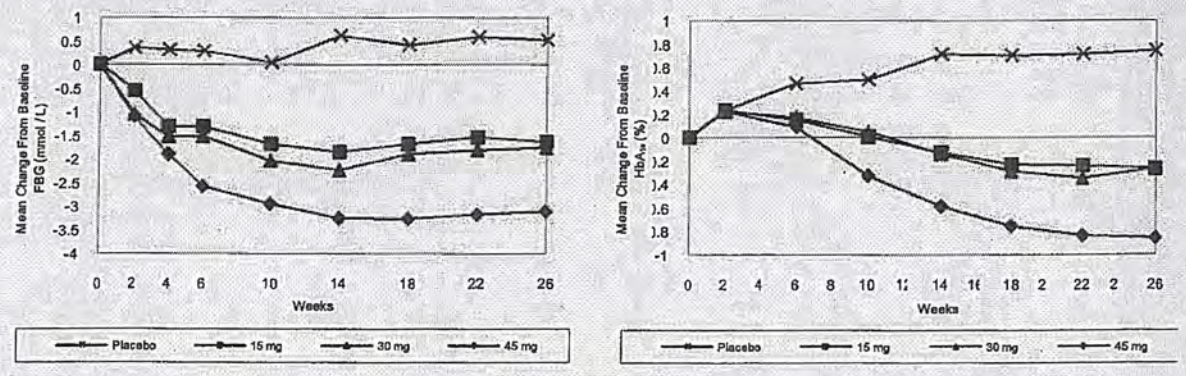
Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to glucose and thus improves dysfunctional glucose homeostasis.

Monotherapy

Three randomised, double blind, placebo-controlled trials of 16 to 26 weeks were conducted to study the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS doses from 7.5 to 45 mg/day in 865 patients.

In a 26-week dose-ranging study, 408 patients with type 2 diabetes were randomised to receive 7.5, 15, 30 or 45 mg of ACTOS, or placebo. Compared with placebo, treatment with 15 to 45 mg of ACTOS resulted in significant improvements in HbA_{1c} and fasting blood glucose (FBG) (see Figure 1).

Figure 1 Mean Change from Baseline for FBG and HbA_{1c} in a 26-Week Placebo-Controlled Dose-Ranging Study



The study population included patients not previously treated with antidiabetic medication (naive; 31%) and patients who were receiving antidiabetic medication at the time of study enrolment (previously treated; 69%). The data for the naive and previously treated patient subsets are shown in Table 1. This run-in period was associated with little change in HbA_{1c} and FBG values from screening to baseline for the naive patients. However, for the previously-treated group, washout from previous antidiabetic medication resulted in deterioration of glycaemic control and increases in HbA_{1c} and FBG. With ACTOS, while

most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FBG 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 1 Glycaemic 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
Naive 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
FBG (mmol/L)	N=25	N=26	N=26	N=21
Screening (mean)	12.39	13.61	13.28	13.28
Baseline (mean)	12.72	13.94	12.5	13.06
Change from baseline (adjusted mean[+])	0.89	-2.06	-2.28	-3.56
Difference from placebo (adjusted mean[+])		-2.89	-3.11	-4.44
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
FBG (mmol/L)	N=54	N=53	N=58	N=56
Screening (mean)	12.33	11.61	12.78	11.94
Baseline (mean)	15.83	15.28	15.89	16.22
Change from baseline (adjusted mean[+])	0.22	-1.78	-1.50	-3.06
Difference from placebo (adjusted mean[+])		-2.00	-1.72	-3.28

[+]Adjusted for baseline, pooled centre

Pioglitazone has been shown to reduce total plasma triglycerides and free fatty acids and to increase HDL-cholesterol levels. LDL-cholesterol levels remain unchanged. 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 the ACTOS-treated patients than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in ACTOS-treated patients compared with placebo (Table 2).

Table 2 Lipids 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
Triglycerides (mmol/L)	N=79	N=79	N=84	N=77
Baseline (mean)	2.97	3.20	2.95	2.93
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mmol/L)	N=79	N=79	N=83	N=77
Baseline (mean)	1.08	1.04	1.06	1.05
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mmol/L)	N=65	N=63	N=74	N=62
Baseline (mean)	3.59	3.41	3.51	3.28
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mmol/L)	N=79	N=79	N=84	N=77
Baseline (mean)	5.81	5.69	5.76	5.53
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In a separate 24-week study, 260 patients with type 2 diabetes were randomised to one of two forced-titration ACTOS treatment arms (final doses 30 or 45 mg), or a mock titration placebo arm. 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 HbA1c and FBG at endpoint compared with placebo (see Table 3).

Table 3 Glycaemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study

	Placebo	ACTOS 30 mg[+] Once Daily	ACTOS 45 mg[+] Once Daily
Total Population			
HbA1c (%)	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*
FBG (mmol/L)	N=78	N=82	N=85
Baseline (mean)	15.50	14.89	15.61
Change from baseline (adjusted mean[++])	1.00	-2.44	-2.77
Difference from placebo (adjusted mean[++])		-3.44*	-3.77*

[+]Final dose in forced titration
[++]Adjusted for baseline, pooled centre, and pooled centre by treatment interaction
* $p < 0.05$ 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 13.22 mmol/L for FBG. At baseline, mean HbA_{1c} was 10.2% and mean FBG was 13.5 mmol/L. 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 FBG of 3.5 mmol/L and 5.28 mmol/L, 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 12 mmol/L for FBG. At baseline, mean HbA_{1c} was 10.7% and mean FBG was 16.11 mmol/L. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA1c of 1.3% and 1.4% and mean FBG of 3.06 mmol/L and 3.33 mmol/L, respectively. For many previously-treated patients, HbA_{1c} and FBG had not returned to screening levels by the end of the study.

In a 16 week study, 197 patients with type 2 diabetes were randomised to treatment with 30 mg ACTOS or placebo once daily. Compared with placebo, treatment with ACTOS resulted in significant reductions in HbA_{1c} and FBG (see Table 4).

Table 4 Glycaemic 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*
FBG (mmol/L)	N=91	N=99
Baseline (mean)	15.00	15.17
Change from baseline (adjusted mean[+])	0.44	-2.78
Difference from placebo (adjusted mean[+])		-3.22*

[+]Adjusted for baseline, pooled centre, and pooled centre by treatment interaction
* $p < 0.05$ 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 13.33 mmol/L for FBG. At baseline, mean HbA_{1c} was 10.4% and mean FBG was 14.11 mmol/L. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FBG of 3.44 mmol/L. 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 12 mmol/L for FBG. At baseline, mean HbA_{1c} was 10.6% and mean FBG was 15.94 mmol/L. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FBG of 2.56 mmol/L. For many previously-treated patients, HbA_{1c} and FBG had not returned to screening levels by the end of the study.

Dual therapy

Three 16-week, randomised, double-blind, placebo-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycaemic control in patients with type 2 diabetes who were inadequately controlled (HbA_{1c} ≥ 8%) despite sulfonylurea, metformin or insulin therapy. Previous diabetes treatment may have been monotherapy or combination therapy.

In one combination study, 560 patients on a sulfonylurea either alone or combined with another antidiabetic agent, were randomised to receive ACTOS 15 mg, ACTOS 30 mg or placebo in addition to their sulfonylurea regimen. Any other antidiabetic agent was withdrawn. Compared with placebo, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} 0.9% and 1.3% for the 15 and 30 mg doses, respectively. In addition, compared with placebo, ACTOS decreased FBG by 2.17 mmol/L (15 mg dose) and 3.22 mmol/L (30 mg dose). The therapeutic effect of ACTOS in combination with a sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea (< 50%, 50%, or > 50% of the recommended maximum daily dose).

In a second combination study, 328 patients with type 2 diabetes on metformin either alone or combined with another antidiabetic agent, were randomised to receive either ACTOS 30 mg or placebo in addition to their metformin. Any other antidiabetic agent was withdrawn. Compared with placebo, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} 0.8% and FBG 2.11 mmol/L. 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 (< 2000 mg per day or ≥2000 mg per day).

In a third combination study, 566 patients with type 2 diabetes receiving a median of 60.5 units/day insulin, either alone or combined with another antidiabetic agent, were randomised to receive either ACTOS 15 mg, ACTOS 30 mg or placebo in addition to their insulin. Any other antidiabetic agent was discontinued. Compared with treatment with placebo, treatment with ACTOS in addition to insulin significantly reduced both HbA_{1c} 0.7% (15mg dose) and 1.00% (30mg dose) and FBG 1.94 mmol/L (15 mg dose) and 2.72 mmol/L (30 mg dose). 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 (< 60.5 units per day or ≥60.5 units per day).

Triple Therapy

A 7 month, randomised, double-blind, placebo controlled study was conducted to evaluate the efficacy and safety of pioglitazone versus placebo in combination with metformin and a sulfonylurea in patients with type 2 diabetes. To qualify for study selection, patients must have been diagnosed with type 2 diabetes mellitus for more than 2 years, have been treated for more than 3 months with metformin and sulfonylurea, be aged 30 years or older and have HbA_{1c} between 7.0% and 9.5% within 3 months prior to the trial. Patients treated with insulin or a single oral antihyperglycaemic agent or more than 2 antihyperglycaemic agents were excluded from participation.

Following a run-in period, 299 patients were randomised to receive either pioglitazone 30 mg or placebo for 3 months while continuing on current doses of sulfonylurea and metformin. At the end of 3 months, depending on HbA1c results, patients received either pioglitazone 30 mg or 45 mg or placebo 30 mg or 45 mg for 4 months. More than 92% of patients had their dose increased to 45 mg. The dose of sulfonylurea could be reduced during the trial in case of symptomatic hypoglycaemia. Changes in the metformin dosage were strictly prohibited.

The adjusted (for baseline HbA_{1c}) mean change was -0.90 ± 0.08% in the pioglitazone group and 0.28 ± 0.08% in the placebo group. The difference between the two groups (-1.2 ± 0.11%) was statistically significant ($p<0.001$) and in favour of the pioglitazone group (see Table 5). A decrease of HbA_{1c} level of ≥0.6% or a level of HbA_{1c} less than 7% was obtained in 65% of pioglitazone patients compared to only 10% in the placebo group.

A significant effect of pioglitazone compared to placebo ($p<0.01$) was also observed on fasting plasma glucose with an adjusted mean change of -2.17 ± 0.18 mmol/L in the pioglitazone group and 0.39 ± 0.18 mmol/L in the placebo group.

Table 5 Change in HbA_{1c} in patients receiving triple therapy

	Placebo		ACTOS	
	HbA_{1c}	n	HbA_{1c}	n
Baseline (mean)	8.14	147	8.18	142
3 month visit				
Observed value (mean)	8.01	147	7.50	141
Change from baseline	-0.13	147	-0.68	141
Final visit				
Observed value (mean)	8.42	141	7.27	135
Change from baseline	+0.29	141	-0.91	135
Adjusted Mean Change pioglitazone – placebo	-1.2		p < 0.001	

INDICATIONS

Treatment of type 2 diabetes mellitus inadequately controlled by diet and exercise:

as monotherapy

as dual therapy to improve glycaemic control
- in combination with metformin or sulfonylurea
- in combination with insulin

as triple therapy to improve glycaemic control
- in combination with metformin and sulfonylurea

CONTRAINDICATIONS

ACTOS is contraindicated in patients with known hypersensitivity or allergy to ACTOS or any of its excipients.

ACTOS is not recommended in patients with symptomatic heart failure. Initiation of ACTOS (like other thiazolidinediones) is contraindicated in patients with NYHA Class II, III or IV heart failure (see PRECAUTIONS).

Because of its mechanism of action, ACTOS is only active in the presence of insulin. Therefore, ACTOS should not be used in type 1 diabetes or for the treatment of diabetic ketoacidosis.

PRECAUTIONS

Hypoglycaemia
Patients receiving ACTOS in combination with insulin or oral hypoglycaemic agents may be at risk for hypoglycaemia. A reduction in the dose of the concomitant agent may be necessary.

Cardiac
ACTOS should not be prescribed to lower the risk of cardiovascular disease such as myocardial infarction and stroke or to lower cardiovascular mortality.

ACTOS, like other thiazolidinediones, can cause or exacerbate congestive heart failure (CHF) in some patients. In post-marketing experience with pioglitazone, CHF has been reported in patients both with and without pre-existing cardiac disease. After initiation of ACTOS, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnoea, and/or oedema). If these signs and symptoms develop, ACTOS should be discontinued. The patient's heart failure should be evaluated and managed according to the current standards of care.

Patients with New York Heart Association (NYHA) Class III and IV cardiac status were excluded from initial clinical trials. Therefore, ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

ACTOS should be initiated at the lowest approved dose in patients with type 2 diabetes and systolic heart failure (NYHA Class I). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, oedema or congestive heart failure exacerbation.

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 were 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 ischaemic 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. Analysis of data from this study did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glibenclamide (n=256) in uncontrolled diabetic patients (mean HbA1C 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Overnight hospitalisation for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in

patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

A cardiovascular outcome study of ACTOS has been performed in patients with type 2 diabetes mellitus and pre existing major macrovascular disease (PROactive). ACTOS or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed the expected increase in reports of serious heart failure (an average of 16 per 1000 treated patients); however this did not lead to an increase in mortality in this study.

Oedema

As thiazolidinediones can cause fluid retention, ACTOS should be used with caution in patients with oedema. In placebo controlled clinical trials oedema was reported more frequently in patients treated with ACTOS than in placebo treated patients.

Weight Gain

Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycaemic 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 15mg	ACTOS 30mg	ACTOS 45mg
		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 [a,b,c]	0.9 (-0.5/3.4) n=79 [a]	1.0 (-0.9/3.4) n=188 [a,c]	2.6 (0.2/5.4) n=79 [c]
Combination Therapy	Sulfonylurea[d]	-0.5 (-1.8/0.7) n=187	1.0 (0.2/3.2) n=183	2.7 (1.1/4.5) n=186	N/A
	Metformin[e]	-1.4 (-3.2/0.3) n=160	N/A	1.4 (-0.9/3.0) n=167	N/A
	Insulin[f]	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.6 (1.4/5.9) n=188	N/A

[a] Study PNFP-001 [b] Study PNFP-012 [c] Study PNFP-026
[d] Study PNFP-010 [e] Study PNFP-027 [f] Study PNFP-014

Bladder Cancer

An increased incidence of bladder cancer was observed in subjects receiving pioglitazone in the PROactive study. In the pioglitazone arm there were 14 cases (0.5%) and in the placebo arm there 5 cases (0.2%); the point estimate for the hazard ratio (HR) was 2.7 (95% confidence interval [CI] 0.99-7.6). 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 (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm.

A five year interim analysis of a cohort of 193 099 diabetic patients ≥40 years of age drawn from the Kaiser Permanente Northern California (KPNC) health plan found that, after adjusting for age, sex, use of tobacco products, use of other diabetic medications, and other risk factors, the hazard ratio for bladder cancer in patients exposed to pioglitazone compared to other patients was 1.2 (95% CI 0.9-1.5). The risk of bladder cancer increased with increasing cumulative dose and duration of pioglitazone use. The HR for bladder

cancer in subjects with 12-24 months of pioglitazone use (compared to subjects never exposed to pioglitazone was 1.4 (95% CI 0.9-2.1). The HR after 24 months of pioglitazone use was 1.4 (95% CI 1.03-2.0).

Based on epidemiological data, treatment with pioglitazone for longer than 12 months may be associated with 27.5 excess cases of bladder cancer per 100 000 person-years follow up, compared to never use of pioglitazone and this risk may increase with further duration of therapy. These conclusions have not been tested in a purposefully designed prospective study.

Pioglitazone should not be used in patients with bladder cancer or a history of bladder cancer. The risk of bladder cancer should be considered in the care of all patients treated with pioglitazone.

Hepatic Impairment

In clinical trials worldwide, over 4500 patients have been treated with ACTOS. There was no evidence of drug-induced hepatotoxicity.

Therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased transaminase levels (ALT > 2.5 times the upper limit of normal) at the start of therapy. Existing ACTOS therapy should be discontinued if ALT levels are persistently higher than 3x the upper limit of normal, and symptoms suggesting hepatic dysfunction should cause the liver enzymes to be checked. Pending the results of laboratory investigations, the decision as to whether pioglitazone therapy should continue must be based on clinical judgement; in the presence of jaundice, drug therapy should be discontinued.

Liver function tests should be performed at baseline and every two months for the first twelve months and periodically thereafter, and if a patient develops symptoms suggestive of hepatic dysfunction, liver enzyme levels should be checked.

Bone Fracture

An increased incidence in bone fractures in women was seen in a pooled analysis of adverse event reports of bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator (excluding thiazolidinediones) treated patients, on treatment for up to 3.5 years. Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%). The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. This difference was noted after the first year of treatment and remained during the course of the study. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

The risk of fractures should be considered in the long term care of women treated with pioglitazone.

Ovulation
In premenopausal anovulatory patients with insulin resistance, treatment with thiazolidinediones, including ACTOS, may result in resumption of ovulation. These patients may be at risk of pregnancy.

Patients with polycystic ovarian syndrome may resume ovulation after pioglitazone treatment, as a consequence of enhanced insulin action. Patients should therefore be aware of the risk of pregnancy; if the patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued.

Carcinogenicity, Mutagenicity and Impairment of Fertility
A two-year carcinogenicity study in mice showed no drug-related increases in tumour incidences at oral doses up to 91 mg/kg/day. Rats dosed orally with pioglitazone at 0.9-57 mg/kg/day for two years showed increased incidences of subcutaneous benign adipose tissue tumours (lipomas) and urinary bladder transitional cell tumours. Systemic exposure (plasma AUC_{0-24h}) to total active compounds at the highest dose in both studies was 8 times greater than that in humans at the maximum recommended dose. The no-effect doses were not established for either tumour site. Subcutaneous benign adipose tissue tumours (lipomas) have been observed in rats treated with other thiazolidinedione drugs, and are probably related to the pharmacodynamic activity of this drug class. ~~Urinary bladder tumours were probably secondary to formation of urinary calculi, and are unlikely to pose a carcinogenic risk in humans.~~

Pioglitazone was not mutagenic in a battery of tests for gene mutation in bacteria and mammalian cells *in vitro*, in assays for chromosomal damage *in vitro* and *in vivo*, and in an assay for DNA damage (unscheduled DNA synthesis in rat hepatocytes *in vitro*).

No adverse effects on fertility were observed in male and female rats at oral doses up to 40 mg/kg/day. Systemic exposure (plasma AUC_{0-24h}) to total active compounds at the highest dose was about 7 times greater than that in humans at the maximum recommended dose.

Use in Pregnancy – Pregnancy Category B3
A study in pregnant rats showed that pioglitazone and its metabolites cross the placenta. Pioglitazone was not teratogenic in rats or rabbits at oral doses up to 80 and 160 mg/kg/day respectively. Systemic exposure (plasma AUC_{0-24h}) to total active compounds at the highest dose was about 12 times (rats) and 7 times (rabbits) greater than that in humans at the maximum recommended dose. Embryotoxicity (increased post-implantation loss) was observed in both animal species, and foetotoxic effects (reduced foetal weight and retarded development) were seen in rats. Administration of pioglitazone during the period of organogenesis also caused suppression of postnatal growth in rats. Administration of pioglitazone to rats throughout gestation and lactation caused retardation in postnatal growth and development, and impaired fertility of the offspring. The no-effect dose for retardation of postnatal growth and development in rats was 3 mg/kg/day and systemic exposure to total active compounds at this dose was similar to that in humans. There are no adequate and well controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefits justify the potential risk to the foetus.

Use in Lactation
Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. In reproductive studies in rats, oral administration of pioglitazone during late gestation and lactation caused adverse effects on postnatal survival, growth, development and fertility of the offspring. The no-effect dose on retardation of postnatal

growth and development was 3 mg/kg/day and systemic exposure to total active compounds at this dose was similar to that in humans. ACTOS should not be administered to lactating women.

Effects on the Ability to Drive and Use Machines
The effect of ACTOS on the ability to drive and use machinery has not been studied but based on its pharmacodynamic properties, ACTOS monotherapy is unlikely to affect this ability. When driving vehicles or operating machinery it should be taken into account that the hypoglycaemic effects of sulfonylureas and insulin may be exacerbated upon combination therapy with ACTOS.

Paediatric Use
Safety and effectiveness in paediatric 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 safety and efficacy were observed between these patients and younger patients.

Interactions with other Drugs
The cytochrome P450 isoforms CYP2C8 and CYP3A4 are partially responsible for the metabolism of pioglitazone. Interactions with substances metabolised by these enzymes e.g. oral contraceptives, cyclosporine, calcium channel blockers, and HMG CoA reductase inhibitors are not to be expected. Inhibitors of CYP2C8 (such as gemfibrozil) may increase the AUC of pioglitazone, a decrease in the AUC of pioglitazone may occur when administered in combination with CYP2C8 inducers (such as rifampicin).

Gemfibrozil: Coadministration of ACTOS and gemfibrozil is reported to result in a 3-fold increase in the AUC of pioglitazone. Since there is a potential for dose-related adverse events with pioglitazone, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered.

Rifampicin: Coadministration of ACTOS and rifampicin is reported to result in a 54% decrease in the AUC of pioglitazone. The dose of ACTOS may need to be increased based on clinical response when rifampicin is concomitantly administered.

Oral Contraceptives: Administration of a similar thiazolidinedione with an oral contraceptive containing ethinyl oestradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%. This could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered.

Glipizide: Coadministration of ACTOS and glipizide does not alter the steady state pharmacokinetics of glipizide.

Digoxin: Coadministration of ACTOS with digoxin does not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Coadministration of ACTOS with warfarin does not alter the steady-state pharmacokinetics of warfarin. In addition, ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Coadministration of ACTOS with metformin does not alter the steady-state pharmacokinetics of metformin.

ADVERSE REACTIONS

Adverse events identified from clinical trials:

The overall incidence and types of adverse events reported in placebo controlled clinical trials of ACTOS monotherapy are shown in Table 7. In pooled, double blind, placebo controlled trials in 862 patients taking pioglitazone and 431 patients taking placebo, withdrawal due to adverse events occurred in 3.6% of pioglitazone patients and in 4.6% of patients on placebo. Table 7 shows the 12 week cumulative incidence at >2% of patients with pioglitazone when this was in excess of placebo.

Table 7: 12 week cumulative incidence of Adverse Events at >2% of ACTOS-treated patients

	Placebo (N=431)	Pioglitazone (N=862)
Upper respiratory tract infection	7.2	8.7
Headache	6.5	7.0
Sinusitis	2.9	3.6
Myalgia	2.3	3.2
Oedema	0.6	3.2
Back pain	2.3	3.1
Urinary tract infection	1.6	2.7
Pharyngitis	0.3	2.7
Tooth disorder	1.5	2.6
Fatigue	2.4	2.5
Accidental injury	1.5	2.2
Cramps legs	1.1	2.1
Vision abnormal	1.4	2.1

Table 8: Adverse Events by Frequency: Events Occurring at ≥5% in ACTOS dual therapy*

	Pio[a] + SU[b] or Met[c] (n=1479)	Placebo + SU[b] or Met[c] (n=1292)	Pio[a] + Insulin (n=631)	Placebo + Insulin (n=446)
Oedema	7.0	2.6	15.8	7.8
Hypoglycaemia	5.9	7.7	30.6	29.4
Upper Respiratory Tract Infection	7.5	6.2	8.9	8.1
Headache	4.2	3.1	5.1	3.8
Weight Increased	5.5	0.9	7.8	1.3
Arthralgia	3.1	3.1	5.4	2.9
Back Pain	3.7	3.9	5.9	3.4
Diarrhoea	2.5	6.5	4.6	5.4

*Integrated Safety Summary: all completed double-blind studies available in the TGRD clinical trials database as of August 2008
[a]PIO = pioglitazone [b]SU = sulfonylurea [c]Met = Metformin

Table 9: Adverse Events occurring in ≥2% of ACTOS-treated patients in triple therapy clinical trials

	Placebo (N=154)	Pioglitazone (N=145)
Weight increased	1.3	26.2
Hypoglycaemia	7.1	24.1
Bronchitis	2.0	2.8
Gastroenteritis	1.3	2.1
Influenza	0.7	2.1

Tooth abscess	0.0	2.1
Arthralgia	2.0	4.8
Back pain	2.0	3.5
Myalgia	1.3	2.8
Oedema peripheral	3.3	3.5
Asthenia	2.0	4.1
Malaise	1.3	2.8
Headache	2.0	2.8
Diarrhoea	2.0	2.1
Abdominal pain upper	0.7	2.1

In the PROactive study, which involved a high risk population of patients with pre-existing macrovascular disease, treatment emergent adverse events that occurred more often in the ACTOS group compared to placebo group were oedema (26.4% and 15.1% respectively), hypoglycaemia (27.2% and 18.8% respectively) and cardiac failure, including serious and non-serious cases (12.6% and 8.7% respectively).

Cardiovascular System

In insulin combination studies a small number of patients with previously existing cardiac disease developed congestive heart failure when treated with pioglitazone. The incidence of congestive heart failure is increased in patients with uncontrolled diabetes, NYHA Class II or III cardiac status and ejection fraction less than 40% when treated with pioglitazone (see PRECAUTIONS, Cardiac).

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 PRECAUTIONS, Cardiac).

In the PROactive study, the rate of serious heart failure was higher for patients treated with ACTOS (5.7%) than for patients treated with placebo (4.1%) and the incidence of death subsequent to a report of serious heart failure was 1.5% in patients treated with ACTOS and 1.4% in placebo-treated patients. In patients treated with an insulin-containing regimen at baseline, the incidence of serious heart failure was 6.3% with ACTOS and 5.2% with placebo. For those patients treated with a sulfonylurea-containing regimen at baseline, the incidence of serious heart failure was 5.8% with ACTOS and 4.4% with placebo.

Hypoglycaemia

Although pioglitazone does not change the safety profile of sulfonylureas and insulin, the combination may increase the risk of developing hypoglycaemic symptoms.

Oedema

In combination therapy studies, oedema 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, oedema 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, oedema was reported in 15.8% of patients on combination therapy compared to 7.8% of patients on insulin alone (see PRECAUTIONS, Oedema). Most of these events were considered mild or moderate in intensity. In a study of triple combination therapy with ACTOS, metformin and sulfonylurea, peripheral oedema was reported in 3.45% of pioglitazone treated patients compared to 3.25% receiving placebo.

Weight Gain

In all clinical trials, weight increased proportionately as the HbA_{1c} decreased suggesting that weight gain was associated with improved glycaemic control. Occasional transient increases in creatinine phosphokinase were noticed in patients taking pioglitazone.

Bladder Cancer
An increased incidence of bladder cancer was observed in subjects receiving pioglitazone in the PROactive study. In the pioglitazone arm there were 14 cases (0.5%) and in the placebo arm there were 5 cases (0.2%); the point estimate for the HR was 2.7 (95% CI 0.99-7.6). 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 (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm (see PRECAUTIONS, Bladder Cancer).

Bone Fracture
A pooled analysis was conducted of adverse event reports of bone fractures from randomised, comparator controlled (excluding thiazolidinediones), double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%) (see PRECAUTIONS, Bone Fracture).

In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

Laboratory Test Abnormalities
Haematologic: ACTOS may cause decreases in haemoglobin and haematocrit. Across all clinical studies, mean haemoglobin 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 not been associated with any significant haematologic clinical effects.

Serum Transaminase Levels: During 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. During all clinical studies in the U.S., 11 of 2561 (0.43%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal. 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 0.12% 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 Impairment).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. A single, isolated elevation to greater than 10 times the upper limit of normal (values of 2150 to 8610 IU/L) was noted in 7 patients. Five of these patients continued to receive ACTOS and the other two patients had completed receiving study medication at the time of the elevated value.

These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

Adverse events identified from spontaneous post marketing surveillance:

Cardiovascular System
Cardiac failure: In post-marketing experience with pioglitazone, congestive heart failure has been reported very rarely (0.9/10 000 patient years) in patients both with and without pre-existing cardiac disease. In clinical trials, heart failure was reported more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure (see CONTRAINDICATIONS and PRECAUTIONS, Cardiac).

Digestive System
Hepatocellular dysfunction: In post-marketing experience with pioglitazone, reports of hepatitis and hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these have involved hepatic failure with and without fatal outcome, although causality has not been established.

Eye Disorders
Very rarely, postmarketing reports of new onset or worsening (diabetic) macular oedema with decreased visual acuity have been reported with the use of thiazolidinediones, including pioglitazone. It is unknown whether or not there is a causal relationship between pioglitazone and macular oedema. Physicians should consider the possibility of macular oedema if a patient reports decreased visual acuity.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily with or without food.

After initiation of ACTOS or with dose increase, patients should be carefully monitored for adverse events related to fluid retention (see PRECAUTIONS).

Female Patients
Oedema has been reported more often in women. Dosage should start at 15 mg and be increased cautiously, paying attention to the development of oedema.

Monotherapy
The recommended dose of ACTOS is 15 mg or 30 mg once daily, increasing after four weeks, if greater therapeutic effect is needed, to 45 mg once daily.

Dual Therapy
The recommended dose of ACTOS is 30 mg once daily in combination with sulfonylureas, insulin or metformin. It may be possible to achieve metabolic control at a reduced dose of the sulfonylurea, insulin or metformin. If there is a particular risk of hypoglycaemia, pioglitazone can be introduced at a dose of 15 mg. For patients already on insulin, pioglitazone should be introduced at a dose of 15 mg once daily. Dosage can then be increased cautiously.

Triple Therapy
The recommended dose of ACTOS is 30 mg once daily in combination with sulfonylurea and metformin. It may be possible to achieve metabolic control at a reduced dose of the sulfonylurea or metformin. If there is a particular risk of hypoglycaemia, pioglitazone can be

introduced at a dose of 15 mg. If greater therapeutic effect is needed, the dose may be increased to a maximum of 45 mg once daily.

Maximum Recommended Dose
The dose of ACTOS should not exceed 45 mg/day since doses higher than 45 mg/day have not been studied in clinical trials.

Patients with Renal Insufficiency
Dose adjustment in patients with renal insufficiency is not recommended (see PHARMACOLOGY, Pharmacokinetics). No information is available for patients on dialysis therefore ACTOS should not be used in such patients.

Patients with Hepatic Impairment

The intrinsic clearance of pioglitazone may be reduced in patients with hepatic disease. Dosage should start at 15 mg and be increased cautiously. ACTOS therapy should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5 times the upper limit of normal).

OVERDOSAGE

During clinical trials, one case of overdose with ACTOS was reported. A patient took 120 mg/day for four days, then 180 mg/day for seven days. The patient did not report any clinical symptoms.

Hypoglycaemia would not be expected with ACTOS alone but may occur in combination with sulfonylureas or insulin. Symptomatic and general supportive measures should be taken in case of overdose.

PRESENTATION AND STORAGE CONDITIONS

ACTOS 15 mg and 30 mg tablets are available in packs of 7, 28, 50* and 98*.
ACTOS 45 mg tablets are available in packs of 7*, 28, 50* and 98*.
ACTOS tablets have a three year shelf life when stored below 30°C.
*Not currently marketed in Australia

NAME AND ADDRESS OF SPONSOR

Distributed in Australia by

Eli Lilly Australia Pty. Limited
112 Wharf Road, West Ryde, NSW 2114

Distributed in New Zealand by

Eli Lilly and Company (NZ) Limited
Level 3, Axon House
414-422 Khyber Pass Road, Newmarket
PO Box 109 197, Newmarket
Auckland
NEW ZEALAND
Telephone (09) 523 9300

A product of TAKEDA Pharmaceutical Company LTD. Osaka, Japan.

POISONS SCHEDULE

S4 – Prescription Only Medicine

~~TGA Approval:~~**DATE OF MOST RECENT AMENDMENT**
~~26 November 2009~~23 June 2011

XX June 2011

Formatted: Left

Formatted: Font: Not Bold, No underline

IMPORTANT SAFETY INFORMATION ON ACTOS® (pioglitazone hydrochloride)

Dear Healthcare Professional,

In agreement with the Therapeutic Goods Administration (TGA), Eli Lilly and Company would like to inform you of important new safety information regarding the use of ACTOS® (pioglitazone hydrochloride) and the potential for increased risk of bladder cancer:

Summary

The PROactive study was a large, placebo controlled cardiovascular outcomes study that involved over 5200 patients. An increased incidence of bladder cancer was observed in subjects receiving pioglitazone in the PROactive study. In the pioglitazone arm there were 14 cases (0.5%) of bladder cancer reported compared to 5 cases (0.2%) in the placebo arm; the point estimate for the hazard ratio (HR) was 2.7 (95% confidence interval [CI] 0.99-7.6). 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 (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm.

A recent five-year interim analysis of a cohort of 193,099 diabetic patients ≥40 yrs of age drawn from the Kaiser Permanente Northern California (KPNC) health plan found that, after adjusting for age, sex, use of tobacco products, use of other diabetic medications, and other risk factors, the hazard ratio for bladder cancer in patients exposed to pioglitazone compared to other patients was 1.2 (95% CI 0.9-1.5). The risk of bladder cancer increased with increasing cumulative dose and duration of pioglitazone use. The hazard ratio for bladder cancer in subjects with 12-24 months of pioglitazone use (compared to subjects never exposed to pioglitazone) was 1.4 (95% CI 0.9-2.1). The hazard ratio after 24 months of pioglitazone use was 1.4 (95% CI 1.03-2.0). Based on these data, treatment with pioglitazone for longer than 12 months may be associated with 27.5 excess cases of bladder cancer per 100,000 person-years follow-up, compared to never use of pioglitazone and this risk may increase with further duration of therapy. The conclusions from these studies have not been tested in a purposefully designed prospective study.

Pioglitazone should not be used in patients with bladder cancer or a history of bladder cancer. The risk of bladder cancer should be considered in the care of all patients ~~with a history of bladder cancer~~ treated with pioglitazone.

Updates to Australian ACTOS® (pioglitazone hydrochloride) product information

~~NOTE: This section will be completed with final label language~~

The following information has been added to the the Australian ACTOS® (pioglitazone) product information:

Precautions section

Formatted: Font: Italic

Bladder Cancer

An increased incidence of bladder cancer was observed in subjects receiving pioglitazone in the PROactive study. In the pioglitazone arm there were 14 cases (0.5%) and in the placebo arm there 5 cases (0.2%); the point estimate for the hazard ratio (HR) was 2.7 (95% confidence interval [CI] 0.99-7.6). 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 (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm.

A five year interim analysis of a cohort of 193 099 diabetic patients ≥40 years of age drawn from the Kaiser Permanente Northern California (KPNC) health plan found that, after adjusting for age, sex, use of tobacco products, use of other diabetic medications, and other risk factors, the hazard ratio for bladder cancer in patients exposed to pioglitazone compared to other patients was 1.2 (95% CI 0.9-1.5). The risk of bladder cancer increased with increasing cumulative dose and duration of pioglitazone use. The HR for bladder cancer in subjects with 12-24 months of pioglitazone use (compared to subjects never exposed to pioglitazone was 1.4 (95% CI 0.9-2.1). The HR after 24 months of pioglitazone use was 1.4 (95% CI 1.03-2.0).

Based on epidemiological data, treatment with pioglitazone for longer than 12 months may be associated with 27.5 excess cases of bladder cancer per 100 000 person-years follow up, compared to never use of pioglitazone and this risk may increase with further duration of therapy. These conclusions have not been tested in a purposefully designed prospective study.

Pioglitazone should not be used in patients with bladder cancer or a history of bladder cancer. The risk of bladder cancer should be considered in the care of all patients treated with pioglitazone.

~~Carcinogenicity, Mutagenicity, and Impairment of Fertility section~~

Adverse reactions identified from Clinical Trials section

Bladder Cancer

An increased incidence of bladder cancer was observed in subjects receiving pioglitazone in the PROactive study. In the pioglitazone arm there were 14 cases (0.5%) and in the placebo arm there were 5 cases (0.2%); the point estimate for the HR was 2.7 (95% CI 0.99-7.6). 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 (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm (see PRECAUTIONS, Bladder Cancer).

The following information (shown as strikethrough text) has been deleted from the product information as it is no longer accurate based on the new data.

Carcinogenicity, Mutagenicity and Impairment of Fertility

A two-year carcinogenicity study in mice showed no drug-related increases in tumour incidences at oral doses up to 91 mg/kg/day. Rats dosed orally with pioglitazone at 0.9-57 mg/kg/day for two years showed increased incidences of subcutaneous benign adipose tissue tumours (lipomas) and urinary bladder transitional cell tumours. Systemic exposure (plasma AUC_{0-24h}) to total active compounds at the highest dose in both studies was 8 times greater than that in humans at the maximum recommended dose. The no-effect doses were not established for either tumour site. Subcutaneous benign adipose tissue tumours (lipomas) have been observed in rats treated with other thiazolidinedione drugs, and are probably related to the pharmacodynamic activity of this drug class. ~~Urinary bladder tumours were probably secondary to formation of urinary calculi, and are unlikely to pose a carcinogenic risk in humans.~~

Formatted: Font: Verdana, 10 pt, Underline, Font color: Auto, English (Australia)

Formatted: Font: Verdana, 10 pt

Formatted: Font: Verdana, 10 pt, Font color: Auto, English (Australia)

Formatted: Font: Verdana, 10 pt

Formatted: Font: Verdana, 10 pt, Font color: Auto, English (Australia)

Formatted: Font: Verdana, 10 pt, No underline

Formatted: Font: Verdana, 10 pt, Font color: Auto, English (Australia)

Formatted: Font: Verdana, 10 pt, No underline

Formatted: Font: Verdana, 10 pt

Formatted: Danish (Denmark)

Formatted: Font: Italic

Formatted: Font: (Default) Verdana, 10 pt, Font color: Auto, (Asian) Chinese (Simplified, PRC), (Other) English (United Kingdom)

Formatted: Font: Verdana, 10 pt

Formatted: Font: (Default) Verdana, 10 pt, Font color: Auto, (Asian) Chinese (Simplified, PRC), (Other) English (United Kingdom)

Formatted: Font: Verdana, 10 pt, underline

Formatted: Font: (Default) Verdana, 10 pt, (Asian) Chinese (Simplified, PRC), (Other) English (United Kingdom)

Formatted: Font: Verdana, 10 pt

Formatted: Font: Verdana, 10 pt, English (Australia)

Formatted: Font: Verdana, 10 pt, English (Australia), Strikethrough

Formatted: Font: Verdana, 10 pt, Strikethrough

To better understand any potential relationship between the use of ACTOS® (pioglitazone hydrochloride) and reports of adverse events, Eli Lilly and Company will continue to carefully monitor adverse events through ongoing surveillance and analysis, in addition to ongoing epidemiologic investigations.

The regulatory actions being undertaken by international regulatory agencies

~~NOTE: This section will be completed with current regulatory information~~The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are also reviewing information relating to pioglitazone and bladder cancer. The FDA have issued a statement indicating that use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer, and caution prescribers against use of pioglitazone containing products in patients with active bladder cancer or a history of bladder cancer.

The EMA's Committee for Medicinal Products for Human Use (CHMP) is currently reviewing all relevant data, including data from pharmacoepidemiological studies, non-clinical and clinical data, post-marketing reports of bladder cancer and published data to assess their impact on the balance of benefits and risks of pioglitazone containing medicines. Regulators in France and Germany have suspended use of pioglitazone containing medicines pending the outcome of the EMA review.

Formatted: Font color: Text 1
Formatted: Normal (Web), Line spacing: single
Formatted: Font color: Text 1
Formatted: Font color: Text 1
Formatted: Font color: Text 1
Formatted: Font: Verdana, 10 pt
Formatted: Font: Verdana, 10 pt

Call for Reporting

Healthcare professionals are reminded of the need to report any adverse reactions suspected to be associated with the use of ACTOS® (pioglitazone hydrochloride) to Eli Lilly Australia Global Product Safety by phone (02) 9325 4676, or facsimile (02) 9325 4320.

In addition, adverse events may be reported to the TGA via fax at 02 6232 8392, e-mail at adr.reports[redacted], by post to TGA, P.O. Box 100, Woden, ACT, 2606, by telephone (freecall within Australia) at 1800 044 114 or reported online at www.tga.gov.au .

Communication Information

Please contact your Eli Lilly Representative or the Medical Information Department on 02 9325 4622 if you have questions or if you wish to receive further information. A copy of the updated Product Information document can be obtained by contacting Eli Lilly or downloaded from the TGA website (www.ebs.tga.gov.au).

Yours Faithfully,

George Labib MD
Medical Advisor, Diabetes Business Unit
Eli Lilly Australia Pty Limited