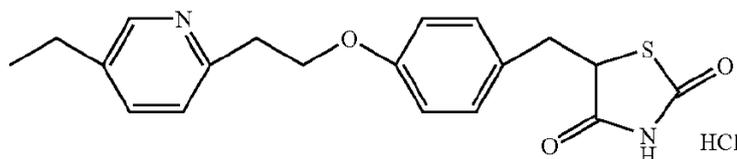


Acpio

PRODUCT INFORMATION

Name of the medicine

Pioglitazone hydrochloride. The chemical name for pioglitazone hydrochloride is [(+/-)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy]phenyl]methyl] -2,4-] thiazolidinedione hydrochloride. Its structural formula is:



C₁₉H₂₀N₂O₃S.HCl

Molecular weight: 392.90

CAS No.: 112529-15-4 (pioglitazone HCl)
111025-46-8 (pioglitazone free base)

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.

Acpio tablets come in three strengths and contain either 15 mg, 30 mg or 45 mg of pioglitazone (as hydrochloride). The tablets also contain lactose, carmellose calcium, hydroxypropylcellulose and magnesium stearate. The tablets are gluten free.

Pharmacology

Pioglitazone is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Pharmacological studies indicate that pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone 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 pioglitazone results in lower blood glucose concentrations, lower plasma insulin levels and lower HbA1c values.

Mode of action

Pioglitazone is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its unique mechanism of action. Pioglitazone 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 (PPARgamma). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal

muscle and liver. Activation of PPARgamma 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 two hours. Steady state is achieved after four to seven days of dosing. Food slightly delays the time to peak serum concentration to three to four 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 bodyweight.

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 to 2,000 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.

Excretion

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 humans is five to six hours and for its total active metabolites 16 to 23 hours.

Pharmacokinetic parameters including mean peak plasma concentration (C_{max}) and area under the curve ($AUC_{0-\infty}$) were determined for pioglitazone, the M-III metabolite (keto derivative of pioglitazone) and the M-IV metabolite (1-hydroxyethyl pioglitazone). Healthy male subjects were administered a single dose of 15 mg or 45 mg pioglitazone tablets and the same dose of the Australian reference pioglitazone tablets. These data are tabulated below (Table 1) and were used to determine that Acpio tablets are bioequivalent to the Australian reference pioglitazone tablets.

Table 1: Pharmacokinetic parameters of pioglitazone tablets compared to the Australian reference pioglitazone tablets

		Pioglitazone tablets	Australian reference pioglitazone tablets
15 mg			
Pioglitazone	C_{max} (ng/mL)	565.98	586.96
	AUC_{0-∞} (ng'h/mL)	5184.00	5377.56
M-III metabolite	C_{max} (ng/mL)	125.43	120.73
	AUC_{0-∞} (ng'h/mL)	6409.77	6185.54
M-IV metabolite	C_{max} (ng/mL)	222.04	218.40
	AUC_{0-∞} (ng'h/mL)	12999.00	12396.83
45 mg			
Pioglitazone	C_{max} (ng/mL)	1046.10	1086.33
	AUC_{0-∞} (ng'h/mL)	9666.51	9373.87
M-III metabolite	C_{max} (ng/mL)	239.63	230.21
	AUC_{0-∞} (ng'h/mL)	11655.30	11644.73
M-IV metabolite	C_{max} (ng/mL)	467.70	454.40
	AUC_{0-∞} (ng'h/mL)	24899.86	24503.78

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 pioglitazone 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. Pioglitazone 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 are not available.

Gender

The mean C_{max} and area under the curve (AUC) values were increased 20 to 60% in females. As monotherapy and in combination with sulfonylurea, metformin or insulin, pioglitazone improved glycaemic control in both males and females. In controlled clinical trials, haemoglobin A (HbA1c) decreases from baseline were generally greater for females than for males (average mean difference in HbA1c 0.5%). See **Dosage and Administration**, Female Patients for recommended dosages in women.

Clinical Trials

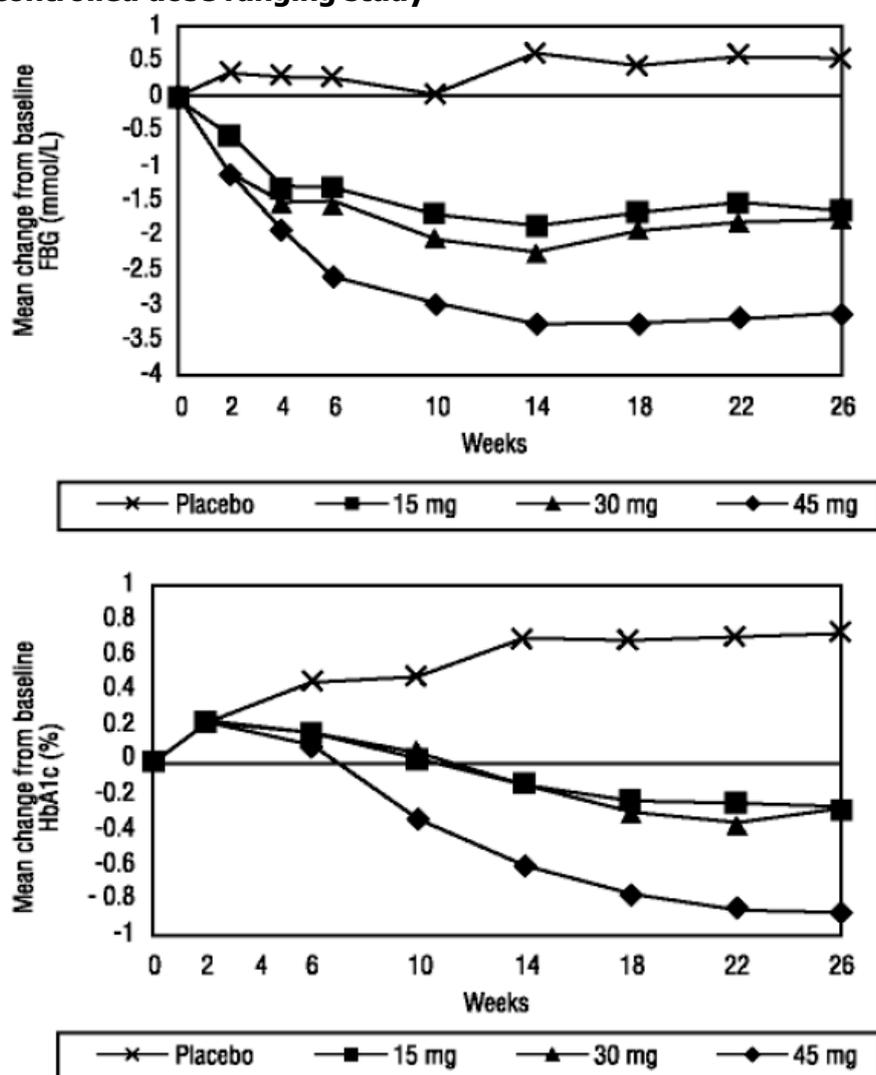
Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin dependent glucose disposal, improves hepatic sensitivity to glucose and thus improves dysfunctional glucose homeostasis.

Monotherapy

Three randomised, double blind, placebo controlled trials of 16 to 26 weeks were conducted to study the use of pioglitazone as monotherapy in patients with type 2 diabetes. These studies examined pioglitazone 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 pioglitazone 7.5, 15, 30 or 45 mg, or placebo. Compared with placebo, treatment with pioglitazone 15 to 45 mg resulted in significant improvements in HbA1c and fasting blood glucose (FBG) (see Figure 1).

Figure 1 Mean change from baseline for FBG and HbA1c 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 2. This run-in period was associated with little change in HbA1c 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 HbA1c and FBG. With pioglitazone, while most patients in the previously treated group had a decrease from baseline in HbA1c 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 pioglitazone from another antidiabetic agent.

Table 2: Glycaemic parameters in a 26 week placebo controlled dose ranging study

	Placebo	Pioglitazone 15 mg once daily	Pioglitazone 30 mg once daily	Pioglitazone 45 mg once daily
Naïve to therapy				
HbA1c (%)	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)	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				
HbA1c (%)	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	-0.01	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FBG (mmol)	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 pioglitazone 15, 30 and 45 mg dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in the pioglitazone treated patients than in the placebo treated patients. There were no consistent differences for LDL and total cholesterol in pioglitazone treated patients compared with placebo (see Table 3).

Table 3: Lipids in a 26 week placebo controlled dose ranging study

	Placebo	Pioglitazone 15 mg once daily	Pioglitazone 15 mg once daily	Pioglitazone 15 mg once daily
Triglycerides (mmol/L)				
Baseline (mean)	n=79 2.97	n=79 3.20	n=84 2.95	n=77 2.93
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL cholesterol (mmol/L)				
Baseline (mean)	n=79 1.08	n=79 1.04	n=83 1.06	n=77 1.05
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL cholesterol (mmol/L)				
Baseline (mean)	n=65 3.59	n=63 3.41	n=74 3.51	n=62 3.28
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total cholesterol (mmol/L)				
Baseline (mean)	n=79 5.81	n=79 5.69	n=84 5.76	n=77 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 pioglitazone treatment arms (final doses 30 or 45 mg), or a mock titration placebo arm. In one pioglitazone 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

pioglitazone 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 pioglitazone, as described, produced statistically significant improvements in HbA1c and FBG at endpoint compared with placebo (see Table 4).

Table 4: Glycaemic parameters in a 24 week placebo controlled forced titration study

	Placebo	Pioglitazone 30 mg* once daily	Pioglitazone 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 versus placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA1c and 13.22 mmol/L for FBG. At baseline, mean HbA1c was 10.2% and mean FBG was 13.5 mmol/L. Compared with placebo, treatment with pioglitazone titrated to a final dose of 30 and 45 mg resulted in reductions from baseline in mean HbA1c of 2.3 and 2.6% and mean FBG of 3.5 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 HbA1c and 12 mmol/L for FBG. At baseline, mean HbA1c was 10.7% and mean FBG was 16.11 mmol/L. Compared with placebo, treatment with Pioglitazone titrated to a final dose of 30 and 45 mg resulted in reductions from baseline in mean HbA1c of 1.3 and 1.4% and mean FBG of 3.06 and 3.33 mmol/L, respectively. For many previously treated patients, HbA1c 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 pioglitazone 30 mg or placebo once daily. Compared with placebo, treatment with pioglitazone resulted in significant reductions in HbA1c and FBG (see Table 5).

Table 5 Glycaemic parameters in a 16 week placebo controlled study

	Placebo	Pioglitazone 30 mg once daily
Total population		
HbA1c (%)	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 versus placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA1c and 13.33 mmol/L for FBG. At baseline, mean HbA1c was 10.4% and mean FBG was 14.11 mmol/L. Compared with placebo, treatment with pioglitazone 30

mg resulted in reductions from baseline in mean HbA1c 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 HbA1c and 12 mmol/L for FBG. At baseline, mean HbA1c was 10.6% and mean FBG was 15.94 mmol/L. Compared with placebo, treatment with pioglitazone 30 mg resulted in reductions from baseline in mean HbA1c of 1.3% and mean FBG of 2.56 mmol/L. For many previously treated patients, HbA1c 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 pioglitazone on glycaemic control in patients with type 2 diabetes who were inadequately controlled (HbA1c greater than or equal to 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 pioglitazone 15 mg, pioglitazone 30 mg or placebo in addition to their sulfonylurea regimen. Any other antidiabetic agent was withdrawn. Compared with placebo, the addition of pioglitazone to the sulfonylurea significantly reduced the mean HbA1c 0.9% and 1.3% for the 15 and 30 mg doses, respectively. In addition, compared with placebo, pioglitazone decreased FBG by 2.17 mmol/L (15 mg dose) and 3.22 mmol/L (30 mg dose). The therapeutic effect of pioglitazone 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 pioglitazone 30 mg or placebo in addition to their metformin. Any other antidiabetic agent was withdrawn. Compared with placebo, the addition of pioglitazone to metformin significantly reduced the mean HbA1c 0.8% and FBG 2.11 mmol/L. The therapeutic effect of pioglitazone in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin (< 2,000 mg/day or greater than or equal to 2,000 mg/day).

In a third combination study, 566 patients with type 2 diabetes receiving a median of insulin 60.5 units/day, either alone or combined with another antidiabetic agent, were randomised to receive either pioglitazone 15 mg, pioglitazone 30 mg or placebo in addition to their insulin. Any other antidiabetic agent was discontinued. Compared to treatment with placebo, treatment with pioglitazone in addition to insulin significantly reduced both HbA1c 0.7% (15 mg dose) and 1.00% (30 mg dose) and FBG 1.94 mmol/L (15 mg dose) and 2.72 mmol/L (30 mg dose). The therapeutic effect of pioglitazone in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin (< 60.5 units/day or greater than or equal to 60.5 units/day).

Triple therapy

A seven 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 two years, have been treated for more than three months with metformin and sulfonylurea, be aged 30 years or older and have HbA1c between 7.0 and 9.5% within three months prior to the trial. Patients treated with insulin or a single oral antihyperglycaemic agent or more than two antihyperglycaemic agents were excluded from participation.

Following a run-in period, 299 patients were randomised to receive either pioglitazone 30 mg or placebo for three months while continuing on current doses of sulfonylurea and metformin. At the end of three months, depending on HbA1c results, patients received either pioglitazone 30 or 45 mg

or placebo 30 or 45 mg for four 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 6). A decrease of HbA_{1c} level of greater than or equal to 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 6: Change in HbA_{1c} in patients receiving triple therapy

	Placebo		Pioglitazone	
	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

Known hypersensitivity or allergy to pioglitazone or any of the tablet excipients (see **Description**).

Pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone (like other thiazolidinediones) is contraindicated in patients with New York Heart Association (NYHA) class II, III or IV heart failure (see **Precautions**).

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

Precautions

Hypoglycaemia

Patients receiving pioglitazone 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

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

Pioglitazone, like other thiazolidinediones, can cause or exacerbate congestive heart failure (CHF) in some patients. In postmarketing experience with pioglitazone, CHF has been reported in patients both with and without pre-existing cardiac disease. After initiation of pioglitazone 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, pioglitazone should be discontinued. The patient's heart failure should be evaluated and managed according to the current standards of care.

Patients with NYHA class III and IV cardiac status were excluded from initial clinical trials. Therefore, pioglitazone is not indicated in patients with NYHA class III or IV cardiac status.

Pioglitazone 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 US double blind, placebo controlled clinical trial involving 566 patients with type 2 diabetes, pioglitazone at doses of 15 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 pioglitazone 15 mg plus insulin (1.1%) and two of the 188 patients receiving pioglitazone 30 mg 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 coronary artery bypass graft (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 postmarketing safety study was performed to compare pioglitazone (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 (EF) less than 40% (mean EF 30% at baseline). Overnight hospitalisation for congestive heart failure was reported in 9.9% of patients on pioglitazone compared to 4.7% of patients on glyburide with a treatment difference observed from six weeks. This adverse event associated with pioglitazone 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 pioglitazone has been performed in patients with type 2 diabetes mellitus and pre-existing major macrovascular disease (PROactive). Pioglitazone 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 16/1,000 treated patients); however, this did not lead to an increase in mortality in this study.

Oedema

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

Weight gain

Dose related weight gain was seen with pioglitazone alone and in combination with other hypoglycaemic agents (see Table 7). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 7: Weight changes (kg) from baseline during double-blind clinical trials with pioglitazone

	Control group (Placebo) Median (25th/75th percentile)	Pioglitazone 15 mg Median (25th/75th percentile)	Pioglitazone 30 mg Median (25th/75th percentile)	Pioglitazone 45 mg Median (25th/75th 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	2.0 (0.2/3.2) n=183	2.7 (1.1/4.5) n=186	N/A
Metformin ^e	-1.4 (-3.20/0.3) 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 were 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.

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 8,100 pioglitazone and 7,400 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/100 patient years in women treated with pioglitazone and 1.1 fractures/ 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/100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fracture/100 patient years) of pioglitazone treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures/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 pioglitazone, 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.

Impaired hepatic function

In clinical trials worldwide, over 4,500 patients have been treated with pioglitazone. 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 pioglitazone therapy should be discontinued if ALT levels are persistently higher than 3 x 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 judgment; 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 12 months and periodically thereafter, and if a patient develops symptoms suggestive of hepatic dysfunction, liver enzyme levels should be checked.

Effects on Fertility

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 to 24 hours)) to total active compounds at the highest dose was about seven times greater than that in humans at the maximum recommended dose.

Use in 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 to 24 hours)) to total active compounds at the

highest dose was about 12 times (rats) and seven times (rabbits) greater than that in humans at the maximum recommended dose. Embryotoxicity (increased postimplantation loss) was observed in both animal species, and fetotoxic 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. Pioglitazone 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 pioglitazone 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. Pioglitazone should not be administered to lactating women.

Paediatric use

Safety and effectiveness in paediatric patients have not been established.

Use in the elderly

Approximately 500 patients in placebo controlled clinical trials of pioglitazone were 65 and over. No significant differences in safety and efficacy were observed between these patients and younger patients.

Carcinogenicity

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 to 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 to 24 hours)) to total active compounds at the highest dose in both studies was eight 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.

Genotoxicity

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*).

Effect on ability to drive or operate machinery

The effect of pioglitazone on the ability to drive and use machinery has not been studied but based on its pharmacodynamic properties, pioglitazone 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 pioglitazone.

Interactions with other medicines

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,

cyclosporin, calcium channel blockers and HMG-CoA reductase inhibitors, are not to be expected. Inhibitors of CYP2C8 (e.g. gemfibrozil) may increase the AUC of pioglitazone, a decrease in the AUC of pioglitazone may occur when administered in combination with CYP2C8 inducers (e.g. rifampicin).

Gemfibrozil

Coadministration of pioglitazone and gemfibrozil is reported to result in a threefold 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 pioglitazone and rifampicin is reported to result in a 54% decrease in the AUC of pioglitazone. The dose of pioglitazone 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 ethinyloestradiol 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 pioglitazone and glipizide does not alter the steady-state pharmacokinetics of glipizide.

Digoxin

Coadministration of pioglitazone with digoxin does not alter the steady-state pharmacokinetics of digoxin.

Warfarin

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

Metformin

Coadministration of pioglitazone with metformin does not alter the steady-state pharmacokinetics of metformin.

Adverse Effects

Adverse events identified from clinical trials

The overall incidence and types of adverse events reported in placebo controlled clinical trials of pioglitazone monotherapy are shown in Table 8. 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 8 shows the 12 week cumulative incidence at > 2% of patients with pioglitazone when this was in excess of placebo.

Table 8: 12 week cumulative incidence of Adverse Events at >2% of pioglitazone-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 9: Adverse events by frequency: events occurring at ≥5% in pioglitazone 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	3.4	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 10: Adverse events occurring in $\geq 2\%$ of pioglitazone 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 pioglitazone 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 nonserious 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 pioglitazone 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 pioglitazone (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 pioglitazone 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 pioglitazone 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 pioglitazone 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 pioglitazone 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 pioglitazone, 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 HbA1c 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 8,100 patients in the pioglitazone treated groups and 7,400 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**).

Laboratory test abnormalities

Haematological

Pioglitazone may cause decreases in haemoglobin and haematocrit. Across all clinical studies, mean haemoglobin values declined by 2 to 4% in patients treated with pioglitazone. 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 pioglitazone therapy and have not been associated with any significant haematological clinical effects.

Serum transaminase levels

During placebo controlled clinical trials in the US, a total of 4 of 1,526 (0.26%) patients treated with pioglitazone and 2 of 793 (0.25%) placebo treated patients had ALT values greater than or equal to three times the upper limit of normal. During all clinical studies in the US, 11 of 2,561 (0.43%) patients treated with pioglitazone had ALT values greater than or equal to three times the upper limit of normal. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with pioglitazone, 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 pioglitazone were withdrawn from clinical trials in the US due to abnormal liver function tests. In preapproval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **Precautions, Impaired hepatic function**).

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 ten times the upper limit of normal (values of 2,150 to 8,610 IU/L) was noted in seven patients. Five of these patients continued to receive pioglitazone 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 pioglitazone therapy is unknown.

Adverse events identified from spontaneous postmarketing surveillance

Cardiovascular system

Cardiac failure. In postmarketing 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 postmarketing experience with pioglitazone, reports of hepatitis and hepatic enzyme elevations to three 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. Doctors should consider the possibility of macular oedema if a patient reports decreased visual acuity.

Dosage and Administration

Pioglitazone should be taken once daily with or without food.

After initiation of pioglitazone 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 pioglitazone is 15 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 pioglitazone 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 pioglitazone 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 pioglitazone 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 pioglitazone 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. Pioglitazone 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 pioglitazone 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 pioglitazone alone but may occur in combination with sulfonylureas or insulin. Symptomatic and general supportive measures should be taken in case of overdose.

Contact the Poisons Information Centre (telephone: 13 11 26) for advice on the management of an overdose.

Presentation and storage conditions

Acpio 15 Pioglitazone (as hydrochloride) 15 mg, white to off-white coloured, round shaped, biconvex, uncoated tablets embossed with '15' on one side. Blister packs of 28 tablets

Acpio 30 Pioglitazone (as hydrochloride) 30 mg, white to off-white coloured, round shaped, flat, beveled edged, uncoated tablets embossed with '30' on one side. Blister packs of 28 tablets

Acpio 45 Pioglitazone (as hydrochloride) 45 mg, white to off-white coloured, round shaped, flat, beveled edged, uncoated tablets embossed with '45' on one side. Blister packs of 28 tablets

Shelf life: 2 years when stored below 30°C.

Name and address of the sponsor

Aspen Pharma Pty Ltd
34-36 Chandos Street,
St. Leonards NSW 2065
Australia

Poison schedule of the medicine

S4 - Prescription Only Medicine

Date of approval

Approved by the Therapeutic Goods Administration on
Date of the most recent safety related notification:

15 November 2010
12 August 2011