Vexazone

Pioglitazone hydrochloride tablets

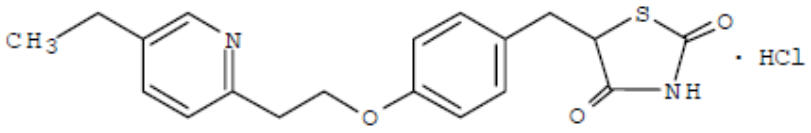
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Pioglitazone hydrochloride

Chemical name: [(*RS)*-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-]thiazolidinedione hydrochloride

Structural formula:



Molecular formula: $C_{19}H_{20}N_2O_3S$•HCl

Molecular weight: 392.90

CAS Registry no.: 112529-15-4

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.

Vexazone tablets contain the labelled amount of pioglitazone hydrochloride. The tablets also contain the following inactive ingredients: lactose, hypromellose, silica - colloidal anhydrous, croscarmellose sodium, polysorbate 80 and magnesium stearate.

PHARMACOLOGY

Pioglitazone is an oral thiazolidinedione 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 HbA_{1c} values.

Mechanism of action

Pioglitazone is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its 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 (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 to 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 to 2,000 nanogram/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 humans is 8 to 10 hours and for its total active metabolites 22 to 25 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, 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 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_{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.

Pharmacokinetic Results of the Bioequivalence Study

A separate bioavailability study, a total of 36 healthy volunteers, was conducted comparing generic pioglitazone hydrochloride 45 mg tablets with the innovator pioglitazone hydrochloride 45 mg tablets. The generic and innovator mean C_{max} values for the active carboxylic metabolite were 1874 ng/mL and 1735 ng/mL, respectively. The point estimate of the generic to innovator ratio of the geometric means for C_{max} was 1.08 with a 90% confidence interval of [1.03 – 1.12]. The generic and innovator mean $AUC_{0-\infty}$ values for the active carboxylic metabolite were 751.4 ng*hr/mL and 708.2 ng*hr/mL, respectively. The point estimate of the generic to innovator ratio of the geometric means for $AUC_{0-\infty}$ was 1.06 with a 90% confidence interval of [1.02, 1.10]. The T_{max} for the generic and innovator tablets was 1.940 and 2.253 hours, respectively. These results on AUC and C_{max} demonstrate bioequivalence of Vexazone with the innovator product.

CLINICAL TRIALS

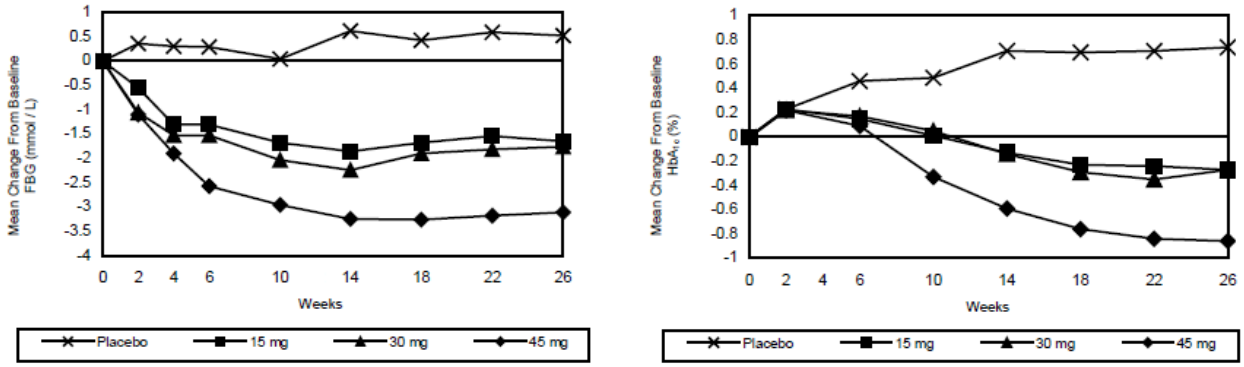
Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis.

Monotherapy

Three randomised, double-blind, placebo-controlled trials of 16 to 26 weeks were conducted to evaluate the use of pioglitazone as monotherapy in patients with type 2 diabetes. These studies examined pioglitazone at 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 mg, 15 mg, 30 mg or 45 mg, or placebo. Compared with placebo, treatment with pioglitazone 15 mg to 45 mg produced statistically 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 pioglitazone, while most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FBG with pioglitazone, 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 1: 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**
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 pioglitazone 15 mg, 30 mg and 45 mg dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in patients treated with pioglitazone than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with pioglitazone compared to placebo (see **Table 2**).

Table 2: Lipids 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
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 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 HbA_{1c} and FBG at endpoint compared to placebo (see **Table 3**).

Table 3: Glycaemic parameters in a 24-week placebo-controlled forced titration study

	Placebo	Pioglitazone 30 mg^{+} once daily	Pioglitazone 45 mg^{+} once daily
Total population			
HbA_{1c} (%)	n = 83	n = 85	n = 85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean^{++})	0.9	-0.6	-0.6
Difference from placebo (adjusted mean^{++})		-1.5*	-1.5*
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 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 pioglitazone 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 pioglitazone titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean 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 of pioglitazone or placebo once daily. Treatment with pioglitazone resulted in significant reductions in HbA_{1c} and FBG (see **Table 4**).

Table 4: Glycaemic parameters in a 16-week placebo-controlled study

	Placebo	Pioglitazone 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
* $p < 0.05$ versus 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 pioglitazone 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 pioglitazone 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 pioglitazone on glycaemic control in patients with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 8\%$) 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 15 mg or 30 mg of pioglitazone 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 HbA_{1c} 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 30 mg of pioglitazone 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 HbA_{1c} 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 ≥ 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 15 mg or 30 mg of pioglitazone, 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 HbA_{1c} 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 ≥ 60.5 units/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 30 mg of pioglitazone or placebo for 3 months while continuing on current doses of sulfonylurea and metformin. At the end of 3 months, depending on HbA_{1c} results, patients received either 30 mg or 45 mg of pioglitazone or placebo 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 2 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} < 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 HbA1c 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

Vexazone is indicated for the 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

Vexazone is contraindicated in patients with known hypersensitivity or allergy to pioglitazone or any of the excipients.

Vexazone 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, Vexazone is only active in the presence of insulin. Therefore, Vexazone 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 of 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 post-marketing 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 New York Heart Association (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 mg and 30 mg in combination with insulin was compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study, two of the 191 patients receiving 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 post-marketing safety study was performed to compare pioglitazone (n = 262) to glibenclamide (n = 256) in uncontrolled diabetic patients (mean HbA_{1c} 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 glibenclamide with a treatment difference observed from 6 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 per 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 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 pioglitazone

	Control Group (Placebo)	**Pioglitazone 15 mg**	**Pioglitazone 30 mg**	**Pioglitazone 45 mg**
	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)
Monotherapy	-1.4 (-2.7/0.0) n=256[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 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. Patients should be advised to

promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as urinary urgency developed during treatment.

Hepatic impairment

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 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 12 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 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 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 fracture per 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.

Carcinogenicity

A two-year carcinogenicity study conducted 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 2 years showed increased incidences at subcutaneous benign adipose tissue tumours (lipomas) and urinary bladder transitional cell tumours. Systemic exposure (plasma $AUC_{0\text{-}24h}$) 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*).

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 $AUC_{0\text{-}24h}$) 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 (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 $AUC_{0\text{-}24h}$) 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. Pioglitazone should be used during pregnancy only if the potential benefits justify the potential risk to the foetus.

Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

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 woman. Breastfeeding should be discontinued if the use of this product is considered essential.

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.

Effects 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

Co-administration of pioglitazone 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

Co-administration of pioglitazone and rifampicin is reported to result in a 54% decrease in 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

Co-administration of pioglitazone and glipizide does not alter the steady-state pharmacokinetics of glipizide.

Digoxin

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

Warfarin

Co-administration 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

Co-administration 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 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 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 8: 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	3.7	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 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
Upper abdominal pain	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 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 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 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 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**).

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. 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 ≥ 3 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 ≥ 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 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 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 creatinine phosphokinase levels (CPK) were observed. A single, isolated elevation to greater than 10 times the upper limit of normal (values of 2,150 to 8,610 IU/L) was noted in 7 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 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**).

Hepaticsystem

Hepatocellular dysfunction. In post-marketing 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, post-marketing 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

Vexazone should be taken once daily with or without food.

After initiation of Vexazone 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 Vexazone is 15 mg or 30 mg once daily, increasing after 4 weeks, if greater therapeutic effect is needed, to 45 mg once daily.

Dual therapy

The recommended dose of Vexazone 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 Vexazone is 30 mg once daily in combination with sulfonylureas 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 Vexazone 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, Vexazone 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. Vexazone 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 4 days, then 180 mg/day for 7 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 on 131126 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Vexazone 15	Pioglitazone 15 mg (as hydrochloride) tablet: white to off-white, round, bi-convex, uncoated tablet debossed with "PG" over 15 on one side and "G" on the other side; in bottle* and blister packs of 7*, 28, 50* and 98* tablets.
Vexazone 30	Pioglitazone 30 mg (as hydrochloride) tablet: white to off-white, round, bi-convex, uncoated tablet debossed with "PG" over 30 on one side and "G" on the other side; in bottle* and blister packs of 7*, 28, 50* and 98* tablets.
Vexazone 45	Pioglitazone 45 mg (as hydrochloride) tablet: white to off-white, round, bi-convex, uncoated tablet debossed with "PG" over 45 on one side and "G" on the other side, in bottle* and blister packs of 7*, 28, 50* and 98* tablets.

Store below 25°C. Protect from light and moisture.

* Not marketed in Australia.

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

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