

# Pioglitazone (Actos) for type 2 diabetes mellitus

(pie-oh-GLI-tah-zone)

The TGA advise that long-term use of pioglitazone may increase the risk of bladder cancer. See the August 2011 In Brief.

## Summary

- Pioglitazone improves glycaemic control but it is unclear whether it improves diabetes-related clinical complications and mortality. Prescribers should consider this — along with recently emerging safety information — when assessing the ratio of potential harms and benefits for each patient.
- Consider pioglitazone after other oral antidiabetic agents have been tried. It can be considered when:
  - either metformin or a sulfonylurea is contraindicated or not tolerated.
  - combination therapy with metformin and a sulfonylurea fails to provide adequate glycaemic control.
- Insulin should also be considered instead of pioglitazone in these scenarios.
- Pioglitazone is currently approved as combination therapy in patients with type 2 diabetes that is inadequately controlled with insulin.
- Pioglitazone is associated with weight gain, oedema and fluid retention and should not be used in patients with moderate to severe heart failure.
- An analysis of data in a clinical trial database has found an increased rate of fractures of the arm, hand and lower leg among women using pioglitazone.
- Doses should not be increased until after 8 weeks of treatment, as the full effect of the drug may not be seen before this time. In clinical trials of glitazone treatment, 25% to 30% of patients had no improvement in glycaemic control.

## PBS listing

### Authority required (streamlined)

Pioglitazone can be used in patients with type 2 diabetes whose blood glucose concentrations are inadequately controlled (HbA<sub>1c</sub> > 7%) either:

- as dual oral therapy with metformin *or* a sulfonylurea when combination therapy with metformin and a sulfonylurea is contraindicated or not tolerated; or
- as dual therapy with insulin in patients with type 2 diabetes when HbA<sub>1c</sub> is > 7% despite concomitant use of insulin plus metformin or a sulfonylurea, or insulin alone where metformin is contraindicated.

- as triple oral therapy with maximally tolerated doses of metformin *and* a sulfonylurea.

Pioglitazone **is not** listed on the Pharmaceutical Benefits Scheme as monotherapy.

### Reason for PBS listing

Pioglitazone was recommended for listing by the Pharmaceutical Benefits Advisory Committee (PBAC) on a cost-minimisation basis compared with rosiglitazone.<sup>1</sup> The indication was extended to include triple oral therapy on a cost-minimisation basis compared with rosiglitazone.<sup>2</sup>

## Place in therapy

Pioglitazone is a thiazolidinedione ('glitazone') antidiabetic drug that should be considered a third-line choice. Metformin (or, when this is contraindicated, a sulfonylurea) is usually the drug of first choice for type 2 diabetes. When combination therapy is required, metformin and a sulfonylurea is the combination of first choice. Pioglitazone can be considered when:

- monotherapy (with metformin or a sulfonylurea) no longer controls blood glucose but adding metformin or a sulfonylurea is contraindicated or not tolerated.<sup>3</sup>
- the combination of metformin and a sulfonylurea no longer adequately controls blood glucose levels.

Insulin should also be considered instead of pioglitazone in these scenarios.

Pioglitazone (15–45 mg/day) decreased HbA<sub>1c</sub> a further 0.6% to 1.7% when added to treatment with metformin, a sulfonylurea, or insulin compared with continuing monotherapy with these antidiabetic agents.<sup>4–7</sup> Patients were enrolled in these trials because they were inadequately controlled on initial monotherapy and often had HbA<sub>1c</sub> approaching 9% and beyond. Greater reductions in HbA<sub>1c</sub> are seen in patients who have poorer glycaemic control (HbA<sub>1c</sub> ≥ 9% before treatment) than patients with better control (HbA<sub>1c</sub> < 9% before treatment).<sup>8</sup>

In an unpublished study of patients (n = 299) inadequately controlled on metformin and a sulfonylurea, adding pioglitazone to metformin and the sulfonylurea (i.e. triple therapy) decreased HbA<sub>1c</sub> by 0.9% after 7 months of treatment.<sup>9</sup>

Dyslipidaemia is a problem in type 2 diabetes and contributes to the metabolic syndrome. Pioglitazone increases HDL-cholesterol concentration and decreases triglyceride concentration.<sup>8</sup>

## Pioglitazone's effect on morbidity and mortality is unclear

Most clinical trials of pioglitazone have measured surrogate outcomes such as effects on lipids or insulin sensitivity over a period of 26 weeks or less. They did not attempt to investigate whether pioglitazone alters the natural progression of diabetes.

Only one study (the PROspective pioglitAzone Clinical Trial In macroVascular Events [PROactive] study) has investigated the effect of pioglitazone (in combination with existing therapies) on diabetes-related morbidity and mortality.<sup>10</sup> This study randomised 5238 patients with type 2 diabetes and a history of cardiovascular disease (except those with heart failure of New York Heart Association [NYHA] Class II or above) to pioglitazone or placebo. It reported a significant improvement in a secondary endpoint of all-cause mortality, myocardial infarction and stroke. However, as the primary endpoint\* did not reach significance, and the secondary endpoint was not defined in the original protocol, this could be a chance finding and should be treated cautiously.

A recent meta-analysis pooled individual patient data from 19 trials of pioglitazone and found a significant increase in the risk of serious heart failure and a significant reduction in the composite endpoint of all-cause mortality, myocardial infarction and stroke.<sup>11</sup> The meta-analysis is limited by the fact that many of the included trials were not designed to assess cardiovascular risk, and that 80% of the events included in the meta-analysis came from the PROactive study. Furthermore, there was no significant reduction in the composite endpoint when pioglitazone was compared with an active comparator rather than placebo.

\* The primary endpoint was all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, coronary or leg revascularisation, or leg amputation.

## Lifestyle changes remain important

Dietary changes, regular exercise, weight loss and smoking cessation reduce cardiovascular risk factors and improve glycaemic control for people with diabetes. If glycaemic control has declined, assess the patient's adherence to lifestyle changes as part of your overall review and reinforce their importance as adjunctive therapy.


## Metformin with a sulfonylurea is the combination of first choice

In patients with type 2 diabetes, drug therapy often needs to increase over time to maintain glycaemic control; 3 years after diagnosis, 50% of patients will require more than one antidiabetic drug, increasing to 75% by 9 years after diagnosis.<sup>12</sup>

Metformin improves glycaemic control and reduces the incidence of macrovascular complications and death among patients with type 2 diabetes.<sup>13</sup> The sulfonylureas improve glycaemic control and reduce the incidence of microvascular complications in diabetes.<sup>14</sup>

Metformin and a sulfonylurea is the preferred combination because of evidence that it reduces diabetic complications, because it is probably more cost-effective and because clinicians have many years of experience using these agents.

## What constitutes 'intolerance' of metformin or sulfonylureas?

Metformin is contraindicated in people with severe renal impairment or other risk factors for lactic acidosis. It may also cause gastrointestinal adverse effects such as diarrhoea, nausea and abdominal bloating, but these are often transient and it is not usually necessary to stop the drug.<sup>15</sup> [www](#) 

Hypoglycaemia is the most common adverse effect with sulfonylureas but can be minimised by splitting or reducing the daily dose. The elderly are at greater risk of hypoglycaemia, so shorter-acting agents such as gliclazide or glipizide are preferred.

Both pioglitazone and the sulfonylureas are associated with weight gain so patients should not be switched to pioglitazone because of this adverse effect.

## Pioglitazone is approved for use with insulin

Pioglitazone is approved as combination therapy in patients with type 2 diabetes who require insulin.<sup>†</sup> Pioglitazone (15–30 mg/day) reduced HbA<sub>1c</sub> by a further 1% to 1.3% over 16 weeks in patients inadequately controlled with insulin.<sup>7</sup> Oedema and hypoglycaemia occur more frequently when glitazones are combined with insulin (see Safety issues).

## Consider initiating insulin rather than pioglitazone


The addition of insulin or pioglitazone results in similar improvements in blood glucose levels when this is no longer adequately controlled by the combination of metformin and a sulfonylurea. In a single head-to-head trial of pioglitazone and bedtime NPH insulin among people who had failed dual therapy, pioglitazone reduced HbA<sub>1c</sub> levels by 1.9% ± 1.5% at 4 months while insulin reduced HbA<sub>1c</sub> levels by 2.3% ± 1.5%.<sup>16</sup> Follow-up in this trial was only 4 months, so it is uncertain whether the response to treatment or the safety profile remains similar in both groups in the long term.

Consider using insulin instead of pioglitazone because:

- insulin reduces the risk of diabetes complications<sup>14</sup>, whereas the effect of pioglitazone (alone or in combination with other oral antidiabetics) on diabetes-related morbidity and mortality is still unclear.<sup>17</sup>
- the long-term safety profile of insulin is better defined. Many pioglitazone trials are of short duration (≤ 1 year). The only completed long-term trial of pioglitazone (in combination with existing therapies) in patients with type 2 diabetes (n = 5238; median treatment duration 2.8 years) reported significantly higher rates of heart failure, oedema and weight gain among the pioglitazone group than among those using placebo.<sup>10</sup>

For information on initiating insulin see *NPS News 56: Managing hyperglycaemia in type 2 diabetes*.

Other third-line choices include acarbose, repaglinide (not currently PBS listed), or rosiglitazone.

[www](#)  Consult the *Australian Medicines Handbook* or refer to this review at [www.npsradar.org.au](http://www.npsradar.org.au) for additional information about contraindications and intolerance to metformin.

<sup>†</sup> The alternative glitazone, rosiglitazone should not be initiated in patients already using insulin because of increased risk of an ischaemic or congestive heart failure event.

## Safety issues

Pioglitazone should not be used in patients with moderate to severe heart failure limiting physical activity (NYHA Class III or IV). [www](#)

Hypoglycaemia is uncommon with pioglitazone alone but may occur when it is combined with a sulfonylurea or insulin. Adjust the dose of sulfonylurea or insulin to reduce the risk of hypoglycaemia (see Dosing issues).

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with Australian Prescriber. For information about adverse drug reaction reporting, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

The Therapeutic Goods Administration is monitoring the safety information related to the glitazones and is currently liaising with sponsors to effect changes in the product information following recommendations by its expert advisory committees — the Australian Drug Evaluation Committee (ADEC) and ADRAC.

### Fluid retention, peripheral oedema and the risk of heart failure

Diabetes is a risk factor for heart disease and congestive heart failure.<sup>18</sup> Glitazones are associated with fluid retention and oedema, which could exacerbate existing heart failure or cause it to develop in patients at risk. Regulatory agencies recently strengthened warnings about heart failure among patients taking pioglitazone.<sup>19</sup>

Glitazones **should not be used** in patients with moderate to severe heart failure. In patients who are asymptomatic or have only mild cardiac insufficiency,

glitazones may be used cautiously but should be initiated at the lowest dose.<sup>18</sup> Particular care is advised in patients who may be predisposed to developing heart failure, such as the elderly or those receiving insulin.<sup>20</sup>

Pioglitazone more than doubles the risk of oedema, compared with placebo or active comparator.<sup>17</sup> In the PROactive study significantly more patients using pioglitazone developed heart failure, compared with those receiving placebo (11% vs 8%,  $p < 0.0001$ ).<sup>10</sup>

A consensus statement from the American Heart Association and the American Diabetes Association<sup>18</sup> notes that oedema is more common when glitazones are used in combination therapy (around 7% of patients in pioglitazone trials) and most likely when glitazones are used with insulin (12% to 18% when pioglitazone is combined with insulin).<sup>7</sup>

Assess risk factors for heart failure before prescribing glitazones — both medical (e.g. history of heart failure, myocardial infarction or coronary heart disease; hypertension; left ventricular hypertrophy; age > 70 years; diabetes for > 10 years) and pharmacological (e.g. use of NSAIDs or calcium-channel blockers).

Prescribers and patients should be alert for symptoms of developing heart failure. Checking weight daily can provide an early warning of fluid accumulation.

### Weight gain is a problem

Weight gain is associated with all glitazones and is dose dependent.<sup>8</sup> Average weight gains of up to 4 kg were seen in clinical trials.<sup>4–7,10</sup> Weight gain is more likely when pioglitazone is combined with sulfonylureas<sup>4</sup> or insulin.<sup>7</sup>

Weight continued to increase for as long as data were recorded in trials (up to 84 weeks) so studies of longer duration are required to determine whether weight gain eventually plateaus in patients taking a glitazone.<sup>8</sup>

Reinforce lifestyle measures for limiting weight gain caused by medications.

[www](#) Refer to this review at [www.npsradar.org.au](http://www.npsradar.org.au) to see the New York Heart Association grading of heart failure.

## Pioglitazone appears to increase the risk of peripheral fractures among women

An analysis of patient data contained within the manufacturer's clinical trial database found a higher risk of fracture among women taking pioglitazone than in those taking a placebo or active comparator (1.9 fractures vs 1.1 fractures per 100 patient-years). Most of these fractures were in the distal upper limb (forearm, hand, wrist) or lower leg (foot, ankle, fibula and tibia). No increase in risk of fracture was found among men taking pioglitazone.<sup>21</sup>

One observational study suggested that the glitazones could cause bone loss among elderly women but not elderly men.<sup>22</sup>

## Glitazones may cause or worsen macular oedema

A small number of postmarketing reports have suggested that there may be an association between the glitazones and the development or worsening of diabetic macular oedema resulting in a decrease in visual acuity.<sup>9,23</sup> Any changes in vision reported by patients taking pioglitazone should be investigated.

## Remain vigilant for signs of liver toxicity

The first available glitazone, troglitazone, was withdrawn from the market after reports of liver toxicity. The risk of liver toxicity appears to be significantly lower with pioglitazone, but several case reports exist for both pioglitazone and rosiglitazone, including elevated liver enzymes concentrations, hepatocellular damage, hepatitis and liver failure.<sup>8,24,25</sup>

Patients with liver disease (including transaminase concentrations increased by more than 2.5 times the upper limit of normal) should not be started on glitazone therapy.<sup>9,25</sup>

Glitazone-induced liver toxicity is unpredictable. Liver function tests are recommended before starting a glitazone and every 2 months thereafter. However, monitoring liver function should not be viewed as always predicting the problem effectively: in some cases of troglitazone liver toxicity, normal enzyme concentrations progressed to irreversible liver failure

within 1 month.<sup>26</sup> If a patient presents with symptoms suggestive of liver disease, this should be seriously considered and investigated.

## Drug interactions

Pioglitazone is metabolised by CYP2C8 and CYP3A4. While no significant drug interactions have been reported to date, no formal pharmacokinetic interaction studies have been conducted.<sup>9</sup> Caution is advised if combining pioglitazone with drugs metabolised by these enzymes. Interactions reported between another antidiabetic drug, repaglinide, and gemfibrozil<sup>27</sup> and trimethoprim<sup>28</sup> are mediated via CYP2C8 and could potentially occur if pioglitazone is used concurrently with any of these drugs.

Agents affecting CYP3A4 include erythromycin, ketoconazole, itraconazole, some 'statins' (e.g. atorvastatin, simvastatin), calcium-channel blockers (e.g. diltiazem, verapamil), St John's wort and grapefruit juice.

There is an increased risk of hypoglycaemia when pioglitazone is combined with sulfonylureas or insulin.

Because they induce fluid retention, combining pioglitazone with NSAIDs carries a theoretical increased risk of oedema and heart failure.<sup>24</sup>

Consult the *Australian Medicines Handbook* or Actos product information for more detailed information about adverse effects.

## Dosing issues

The recommended dose of pioglitazone is 15–45 mg/day. Patients should start at the lower dose of 15 mg/day, particularly those at risk of hypoglycaemia.

A proportion of patients does not respond to glitazone therapy with a decrease in fasting plasma glucose concentration and/or HbA<sub>1c</sub> (primary treatment failure). The non-responder rate observed in clinical trials of glitazones was 25% to 30%.<sup>8</sup> One trial of pioglitazone 30 mg/day specifically divided patients into two groups based on their responsiveness: in those patients who did not respond (30 out of 70), the mean HbA<sub>1c</sub> decreased by only 0.1% after 3 months' therapy.<sup>29</sup>

## Allow time for response before increasing dose

Pioglitazone doses should not be increased until 8 weeks after initiation of treatment; it has taken between 8 and 16 weeks for the full glycaemic response to be seen in most of the glitazone trials at any given dose. As HbA<sub>1c</sub> testing is recommended 3-monthly in patients whose therapy has changed or who are not meeting glycaemic goals, this seems an appropriate point to scrutinise the patient's response and consider if any modifications to therapy are necessary. If patients continue to show no effect after increasing the dose, pioglitazone should be stopped.

## Information for patients

Advise patients to:

- monitor for weight gain or ankle oedema
- report any signs indicative of heart failure (such as breathlessness during daily activities)
- report signs of liver toxicity (abdominal pain, nausea/vomiting, jaundice).

For more detailed information about pioglitazone, suggest or provide the Actos consumer medicine information (CMI).

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Updated March 2008: addition of information on triple therapy.

Updated October 2007: fracture, macular oedema, information about PROactive.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.