



# VERDICT & SUMMARY

# Pioglitazone

(Actos<sup>®</sup>)

For the treatment of type 2 diabetes mellitus

Committee's Verdict: Category A

BNF: 6.1.2

Pioglitazone is appropriate for prescribing in primary care. The committee recommends that pioglitazone be used as a third-line alternative for patients intolerant of metformin or a sulphonylurea, or for whom these are contraindicated.

**Category A:** suitable for prescribing in primary care

### Strength of the evidence

**Prevention of cardiovascular mortality or morbidity:** In the PROactive study, there was no significant difference in the number of cardiovascular-related events for pioglitazone-treated patients compared with placebo (both in addition to existing therapy).

**Glycaemic control:** As monotherapy, pioglitazone was associated with significantly more effective glycaemic control than placebo in three studies, but not when compared with metformin or a sulphonylurea. As combination therapy (dual or triple therapy) pioglitazone was significantly more effective than placebo for the reduction of HbA<sub>1c</sub> plasma concentration. In six studies, pioglitazone dual therapy was significantly more effective than antidiabetic drug monotherapy but no more effective than metformin plus a sulphonylurea.

**Place in therapy:** The place in therapy in primary care was considered to be relatively low.

MTRAC reviewed this drug because of extensions to its licensed indications and new evidence.

### Licensed indication

Pioglitazone is indicated in type 2 diabetes mellitus patients as:<sup>1</sup>

**monotherapy** in patients inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

**dual therapy** in combination with metformin or a sulphonylurea (SU) (in patients who show intolerance to metformin or for whom metformin is contraindicated) in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or SU

**triple therapy** in combination with metformin and a SU in patients with insufficient glycaemic control despite dual oral therapy

**combination therapy with insulin** in patients with insufficient glycaemic control on insulin, for whom metformin is inappropriate because of contraindications or intolerance.

### Background information

Diabetes mellitus is a common chronic disease, associated with markedly increased morbidity and mortality. The majority of people in the UK with diabetes mellitus (~90%) have type 2 diabetes. The primary defects in type 2 diabetes are reduced insulin secretion and insulin resistance.<sup>2</sup> Type 2 diabetes is associated with serious long-term microvascular (e.g. nephropathy, retinopathy, and neuropathy<sup>3</sup>) and macrovascular complications e.g. coronary heart

disease, stroke, and peripheral vascular disease. Patients with type 2 diabetes are two to five times more likely to suffer cardiovascular morbidity.<sup>3</sup>

Dietary and lifestyle modifications form the mainstays of therapy for type 2 diabetes, but 50 to 70% of patients will also require an oral antidiabetic drug, and many will eventually need treatment with insulin. Drug treatments currently available include metformin, SUs, thiazolidinediones (rosiglitazone and pioglitazone), acarbose, repaglinide and nateglinide, exenatide, sitagliptin and insulin.

Metformin followed by the SUs are considered to be the first choices for oral antidiabetic therapy.<sup>4</sup>

Pioglitazone has a blood glucose lowering effect by reducing peripheral insulin resistance.<sup>1</sup>

### Clinical efficacy

All clinical trials described below were carried out in adult patients with type 2 diabetes.

#### Monotherapy

As monotherapy, pioglitazone was compared with placebo in four RCTs (n = 1,153; duration 16 or 26 weeks),<sup>5-8</sup> with metformin 750 to 2,550 mg/day in three RCTs (n = 1,518; duration 24 to 52 weeks)<sup>9-11</sup> and with SUs (gliclazide [up to 320 mg/day], glibenclamide [up to 10.5 mg/day] and glimepiride [1 to 8 mg/day]) in five RCTs (n = 2,111; duration 36 to 52 weeks).<sup>11-15</sup>

In all the placebo-controlled trials, pioglitazone treatment at doses of 15 to 45 mg/day resulted in significantly greater reductions in HbA<sub>1c</sub> levels than placebo ( $p \leq 0.05$ ).<sup>5-8</sup>

There was no significant difference in HbA<sub>1c</sub> reduction between pioglitazone and any of the active comparators (metformin or a SU).<sup>9-15</sup>

### Combination therapy

In the PROactive study<sup>16</sup> pioglitazone was compared with placebo in 5,238 patients with type 2 diabetes who had evidence of extensive macrovascular disease. Patients continued their existing antidiabetic medication (metformin or a SU or both, with or without insulin). The trial had a mean follow-up period of 34.5 months. Results showed no significant difference between pioglitazone and placebo ( $p = 0.095$ ) for the primary outcome of a composite of death from any cause, non-fatal myocardial infarction (MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. For the secondary endpoint composite of death from any cause, non-fatal-MI or stroke, there were significantly fewer events with pioglitazone treatment compared with placebo: HR 0.84 (95% CI 0.72 to 0.98,  $p = 0.027$ ).

In six studies that used glycaemic outcomes, pioglitazone 30 to 45 mg was evaluated as dual therapy in combination with:

- metformin in two studies ( $n = 531$ ) vs. metformin monotherapy or metformin plus glimepiride<sup>17,18</sup>
- a SU in two studies vs. SU monotherapy or SU plus metformin ( $n = 1,199$ )<sup>19,20</sup>
- repaglinide in one study vs. pioglitazone or repaglinide monotherapy ( $n = 246$ )<sup>21</sup>
- insulin in one study ( $n = 289$ ) vs. insulin monotherapy<sup>22</sup>

In four of the studies where pioglitazone plus an oral antidiabetic medication (OAM) was compared with the OAM as monotherapy, the combination showed significantly greater reductions in HbA<sub>1c</sub> from baseline compared with the OAM as monotherapy (0.64 to 1.76%,  $p \leq 0.05$ ).<sup>17,19,21,22</sup> In the remaining two studies in which pioglitazone combined with either metformin or a SU was compared with metformin plus a SU, there was no significant difference in HbA<sub>1c</sub> reduction between the treatment groups.<sup>18,20</sup>

### Adverse effects

The most common adverse events seen in clinical trials included weight gain, oedema, headache,

dizziness, and arthralgia. In the PROactive study,<sup>16</sup> there were significantly more reports of heart failure in the pioglitazone treatment group than in the placebo group ( $p < 0.0001$ ). The incidence of any cardiac event was in the range of 2 to 4% for all OAM-treated patients. Pioglitazone treatment resulted in body weight increases up to 3 kg in monotherapy trials and up to 5.5 kg in combination therapy trials.

### NICE guidance

The National Institute for Health & Clinical Excellence (NICE) recommends the use of a glitazone in combination with either metformin or a SU (as an alternative to a combination of metformin with a SU) **only** for patients who cannot tolerate either drug in the combination. NICE guidance does not apply to the use of glitazones as mono- or triple oral therapy.

### Additional information

The usual starting dose of pioglitazone is 15 mg or 30 mg, which may be increased to 45 mg if necessary, taken as a single daily dose, with or without food.

Pioglitazone is contraindicated in patients with:

- cardiac failure or history of cardiac failure (New York Heart Association stages I to IV)
- hepatic impairment
- diabetic ketoacidosis

The Summary of Product Characteristics<sup>1</sup> recommends that liver enzymes are monitored before initiating and during pioglitazone therapy.

At current prices, one year's treatment costs £437 for pioglitazone 30 mg/day and £662 for rosiglitazone 8 mg/day.

### References

1. Takeda UK Ltd. Actos Tablets. *Summary of Product Characteristics* 2007.
2. National Institute for Health & Clinical Excellence. Guidance on the use of the glitazones for the treatment of type 2 diabetes. Technology Appraisal 63. NICE 2003. <http://guidance.nice.org.uk/TA63/guidance/pdf/English>
3. Nathan DM. Initial management of glycaemia in type 2 diabetes mellitus. *N Engl J Med* 2002;**347**:1342-1349.
4. National Institute for Health & Clinical Excellence. Management of type 2 diabetes - Managing blood glucose levels (Clinical Guideline G). NICE 2002. <http://guidance.nice.org.uk/page.aspx?o=36737>

*The complete list of references is on the next page.*

Launch date: November 2000

Manufacturer: Takeda

EU/1/00/150/001-024

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics  
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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VS07/14

(This Verdict & Summary sheet replaces VS03/13 and SS03/13)

## VERDICT & SUMMARY REFERENCES (see VS07/14)

### Pioglitazone for the treatment of type 2 diabetes mellitus

#### References

1. Takeda UK Ltd. Actos Tablets. *Summary of Product Characteristics* 2007.
2. National Institute for Health & Clinical Excellence. Guidance on the use of the glitazones for the treatment of type 2 diabetes. Technology Appraisal 63 NICE 2003. <http://guidance.nice.org.uk/TA63/guidance/pdf/English>
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