Scottish Medicines Consortium

pioglitazone, 15mg, 30mg and 45mg tablets (Actos) No. (399/07)

Takeda UK Ltd

10 August 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

pioglitazone (Actos®) is accepted for use within NHS Scotland in combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

It improved glycaemic control when added to insulin in the relevant patient population.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Pioglitazone is indicated for combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

Dosing information

Pioglitazone may be initiated at 15mg or 30mg once daily. The dose may be increased in increments up to 45mg once daily. In combination with insulin, the current insulin dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of insulin should be decreased.

Product availability date

January 2007

Summary of evidence on comparative efficacy

Pioglitazone is a thiazolidinedione compound that acts as a peroxisome proliferator activating receptor (PPAR) γ agonist with potential benefits on insulin resistance (a feature of type 2 diabetes mellitus (T2DM) and which depends on the presence of insulin for activity. It is therefore thought that the addition of a thiazolidinedione to insulin therapy could be beneficial to patients with the condition, since both core defects (insulin resistance and deficiency) are being addressed, resulting in a reduction in the elevated blood glucose concentrations associated with type 2 diabetes mellitus.

Pioglitazone is also licensed as oral monotherapy and as dual or triple therapy with metformin and/or a sulphonylurea.

The efficacy data for this latest indication come primarily from 3 randomised, double-blind trials and these were supplemented with information from another trial investigating long-term cardiovascular outcomes.

In each of the first 3 trials, patients recruited had been on a stable insulin dose of ≥ 30 units/day for at least 30 days and may or may not already have been taking an oral antihyperglycaemic agent; if so, these were washed out of the system during a "run in", washout period. If after this, HbA1c was still ≥8.0% (≥7.0% in the 3rd trial, after insulin optimisation), patients were given the test drugs in addition to their stable insulin dose. Insulin doses could be decreased (no increases allowed) in the first two studies in response to hypoglycaemic episodes; in the third study, adjustment was permitted and optimization encouraged.

In each study, the primary end-point was change in HbA1c from baseline. Fasting plasma glucose was often measured as a secondary endpoint, as were fasting lipid levels.

In the first trial, a 16-week US study in 566 adults, patients were randomised to either placebo, pioglitazone 15mg or 30mg, all plus insulin. The addition of pioglitazone decreased HbA1c from baseline, and placebo, significantly for both doses (see table). Insulin dose was reduced by > 25% in 2.1%, 3.7% and 16% of the placebo, 15mg and 30mg pioglitazone-treated patients respectively. Only 12.8% of patients on placebo had HbA1c <8% at endpoint compared with 31.4% and 41.5% in the pioglitazone 15mg and 30mg groups respectively.

From week 8, significant reductions in triglyceride levels (30mg only) and significant increases in high density lipoprotein (HDL) cholesterol were observed with pioglitazone, as compared to insulin and placebo.

In the second trial, 690 US patients were randomised to pioglitazone 30mg or 45mg plus their insulin for 24 weeks. Statistically significant decreases, compared with baseline, in HbA1c (see table), fasting blood glucose and insulin dosage were seen. Significant decreases in triglycerides were observed in the pioglitazone 45mg group while both doses showed a significant increase in HDL cholesterol as well as small but significant increases in total and low density lipoprotein (LDL) cholesterol, all compared with baseline.

Trial 3 was a 12-month European study (with additional 6 month interim analysis) which recruited 289 patients to receive pioglitazone 30mg or placebo along with their insulin. This trial allowed the exclusion of those who could reach an acceptable HbA1c using insulin alone during the run-in period, and for those who progressed to trial medication, there was an automatic reduction by 10% of their insulin dose. Again, there was a significant decrease in HbA1c (see table) and fasting plasma glucose. There was a significant increase in HDL cholesterol (from baseline and placebo).

In the fourth report, data were taken from a longer term (up to 3.5 years) European study into secondary prevention of macrovascular events with pioglitazone, where approximately one third (1760) of patients were using insulin at baseline. Patients were also permitted to carry on with any other medication, notably including other non-thiazolidinedione antihyperglycaemics. These patients had their pioglitazone dose (if in this group) up-titrated to the maximum tolerated dose. A decrease in the number of units of insulin taken was seen in the pioglitazone group (46.5 ±31.2 units/day to 39.8, a fall of 5.2±20.3), whilst those taking placebo saw their consumption rise (46.7±30.6 units/day to 54.6, a rise of 8.1±22.2). Pioglitazone also significantly reduced triglycerides and increased HDL cholesterol levels, compared to placebo. Both groups saw an increase in LDL cholesterol.

Absolute changes in HbA1c (%) expressed as least squares mean change

Study	Dose, in combination with insulin	N	Mean baseline (%)	Mean change from baseline (%)	Change from placebo (%)
1	Placebo	566	9.75±0.10	-0.26±0.08 *	
	Pioglitazone 15mg		9.75±0.10	-0.99±0.08 *	-0.73 *
	Pioglitazone 30mg		9.84±0.10	-1.26±0.08 *	-1.00 *
2	Pioglitazone 30mg	690	9.9±0.08	-1.2±0.08 **	
	Pioglitazone 45mg		9.7±0.08	-1.5±0.08 **	-0.29** (-0.51,-0.07) †
3	placebo	289	8.78±0.10	-0.13±0.09	
	Pioglitazone 30mg		8.83±0.11	-0.58±0.09 ***	***
4	Placebo	1760	8.52	-0.46	
	Pioglitazone		8.41	-0.96	****

* denotes significance p<0.01; ** p≤0.05; *** p<0.001; **** p<0.0001
† this difference is compared to pioglitazone 30mg

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

Adverse events were usually mild to moderate and reported as oedema, upper respiratory tract infections, dyspnoea and hypoglycaemia. Incidence appeared to be dose related in the trials comparing doses. In general, except for the incidence of hypoglycaemia, adverse events were similar to those of pioglitazone monotherapy.

There was no evidence of pioglitazone causing liver dysfunction in these trials, but it is recommended that patients undergo regular liver enzyme monitoring.

Weight gain was observed in patients treated with all pioglitazone doses, the mean increase being 2.3kg and 3.7kg in trial 1 (for 15mg and 30mg pioglitazone respectively); 2.9kg and 3.4kg in trial 2 (for 30mg and 45mg of pioglitazone respectively).

It is recommended that patients be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin.

Following ongoing evaluation of all safety information by the manufacturer, it has come to light that there were more reports of fractures in female patients taking pioglitazone than those taking a comparator. None of the studies were designed to study the effects on bone, but fracture data were collected as adverse events. Further evaluation is ongoing and the manufacturer advises that this risk is considered in the care of patients either currently being treated with, or where there is an intention to treat with, pioglitazone.

Other data were also assessed but remain commercially confidential.*

Summary of clinical effectiveness issues

Insulin can be added to oral antihyperglycaemics, but this regimen offers treatment in combination with insulin in patients already on insulin therapy who have insufficient glycaemic control and for whom metformin is inappropriate, due to contraindications or intolerance.

Body weight gain was observed in patients treated with pioglitazone. This is a concern in this often overweight population.

There were modest decreases in insulin dosage in all trials, but the extent to which insulin dosage could be adjusted was restricted by protocol.

The long-term study aiming to show an improvement in cardiovascular endpoints failed to demonstrate its primary endpoint.

Positive changes in plasma lipids are were seen in most studies, but it should be noted that in all studies, patients were also allowed concomitant lipid lowering therapy.

Summary of comparative health economic evidence

The manufacturer provided a cost utility model examining combination treatment with pioglitazone and insulin compared to insulin alone in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin and for whom metformin is inappropriate because of contraindications or intolerance. The comparator in the model was appropriate. A lifetime horizon was used which was based on the CORE diabetes model, a previously validated model. This model structure was appropriate and allowed for the complex nature of the disease and its associated microvascular and macrovascular complications over time. The model simulated the effects of treatment on parameters such as HBA1c, cholesterol, BMI and hypoglycaemic events and their impact on subsequent event rates. Utility values were taken from published studies as were the costs associated with diabetic complications. The baseline results indicated an incremental cost per QALY (ICER) of £18740 per QALY or £17230 if the results were examined in a cohort of patients with baseline characteristics more representative of a Scottish population.

In terms of limitations of the analysis, the clinical trial is relatively short term and then uses HbA1c as a marker for micro- and macrovascular complications over the long term horizon, which can introduce uncertainty. In particular the benefits of pioglitazone in terms of macrovascular complications are speculative (and were not seen in the outcome study referred to above) but were included within the economic model. Additional analysis was requested to show the impact of excluding these benefits. The resulting ICERs were £20635 for all patients or £18976 in the cohort of patients with characteristics representative of the Scottish population.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN) guideline number 55 (November 2001), Management of Diabetes, predates the licence of this combination and therefore does not contain any advice on this use. These guidelines are due to be updated in autumn 2009.

The thiazolidinedione class of medicines were due to undergo a Health Technology Assessment (HTA) by the National Institute for Health and Clinical Excellence (NICE) in July 2006, however, they are now to be incorporated into the Type 2 Diabetes Mellitus guideline update, due to be published in 2008.

Additional information: comparators

No other thiazolidinedione is licensed for this indication; only metformin is and will be used for comparison purposes.

Cost of relevant comparators

All regimens are adjunct to personalised insulin regimens, so these have been omitted and only the costs of oral therapy are included.

Drug	Dose regimen	Cost per year (£)
pioglitazone	**15 – 45mg once daily**	**314 - 480**
metformin	500mg once daily – 1g three times daily	11 - 68

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 12th June 2007.

Additional information: budget impact

The gross incremental drug budget impact of using pioglitazone was estimated by the manufacturer as being £76k in year one rising to £107k in year five. If the costs of insulin, monitoring and nurse visits required by these patients were taken into account then the gross direct cost was estimated to be £266k in year one rising to £377k in year five. 174 patients in year one rising to 246 patients in year five were assumed to be eligible for treatment. These figures assumed a market share of 25% of eligible patients.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 6 August 2007.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Rosenstock J, Einhorn D, Hershon K, Glazer NB and Yu S. Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin therapy. Int J Clin Pract 2002; 56(4): 251-7.

Davidson JA, Perez A and Zhang J. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: results of a double-blind, multicentre, randomized study. Diabetes Obes Metab 2006; 8(2): 164-74.

Mattoo V, Eckland D, Widel M, Duran S, Fajardo C, Strand J, Knight D, Grossman L, Oakley D and Tan M. Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group study. Clin Ther 2005; 27(5): 554-67

Dormandy JA, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schemthaner G, Schmitz O, Skrha J, Smith U and Taton J. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366(9493): 1279-89.