Scottish Medicines Consortium

Re-Submission

pioglitazone 15mg, 30mg, 45mg tablets (Actos®) No. (115/04)
Takeda

New indication: monotherapy for type 2 diabetes mellitus patients for whom metformin is inappropriate

5th August 2005

The Scottish Medicines Consortium (SMC) 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 resubmission

Pioglitazone (Actos®) is accepted for restricted use within NHS Scotland as monotherapy for type 2 diabetes mellitus patients in whom consideration is otherwise being given to commencing insulin therapy. It is not recommended as monotherapy for any other group of patients.

It is one of two peroxisome proliferator-activated receptor-γ agonists marketed in the UK for this indication. Its use should be restricted to patients who have already experienced severe hypoglycaemia or patients in whom metformin and sulphonylureas are contra-indicated or not tolerated.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Pioglitazone 15mg, 30mg, 45mg tablets (Actos®)

Licensed indication under review

Monotherapy in type 2 diabetes mellitus patients, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin is inappropriate because of contra-indications or intolerance.

Dosing information under review

15mg or 30mg once daily initially, which may be increased up to 45mg once daily.

UK launch date

September 2003

Comparator medications

The other peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist marketed in the UK, rosiglitazone, is also licensed for use as monotherapy for type 2 diabetes mellitus patients for whom metformin is inappropriate because of contra-indications or intolerance. This group of patients could also be treated with a sulphonylurea, as these are indicated for treatment of type 2 diabetes mellitus inadequately controlled by diet and exercise.

Cost per treatment period and relevant comparators

Class	Drug	Daily dose range	Annual cost (£)*
PPAR-γ agonist	**Pioglitazone**	**15-45 mg**	**315-482**
	Rosiglitazone	4-8 mg	322-662
Sulphonylurea	Glimepiride	1-4 mg	55-180
	Gliquidone	15-180 mg	32-384
	Glipizide	2.5-20 mg	19-94
	Tolbutamide	500-2000 mg	14-57
	Gliclazide	40-320 mg	12-98
	Glibenclamide	5-15 mg	12-38

* costs from March 2005 Scottish Drug Tariff where available or from eVadis drug dictionary accessed in June 2005.

Summary of evidence on comparative efficacy

Pioglitazone is a PPAR-γ agonist that reduces blood glucose by increasing the sensitivity of liver, fat and skeletal muscle cells to insulin.

A one-year double-blind trial recruited 1232 patients, aged 35-75 years, with type 2 diabetes uncontrolled by at least three months' treatment with diet alone: glycated haemoglobin A (HbA_{1c}) 7.5-11%. They were randomised to pioglitazone 30mg daily or gliclazide 80mg daily, with doses increased over 16-weeks to a maximum tolerated dose (up to 45mg daily or 160mg twice daily, respectively), that was maintained throughout the remainder of the study.

The primary endpoint, mean change in HbA_{1c} from baseline to week 52, in the intention-to-treat (ITT) population using last observation carried forward (LOCF) for missing data was analysed via an analysis of covariance (ANCOVA) model with baseline HbA_{1c} as covariate. Non-inferiority, the primary analysis, was defined as an upper limit of two-sided 90% confidence intervals (CI) for the difference between pioglitazone and gliclazide in mean change from baseline HbA_{1c} of less than 0.2%. Non-inferiority of pioglitazone to gliclazide was demonstrated, with 52-week mean HbA_{1c} reductions of 1.43% and 1.35%, respectively, and estimated treatment difference (90% CI) of -0.08% (-0.18%, 0.02%). Mean reduction in fasting plasma glucose (FPG) from baseline to week 52 was significantly greater with pioglitazone compared to gliclazide: -2.4 versus -2.0 mmol/L, with an estimated treatment difference (95% CI) of -0.4 mmol/L (-0.7, -0.1).

In this trial, mean total cholesterol, low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol increased from baseline to 52 weeks in the pioglitazone group. In the gliclazide group, HDL-cholesterol increased, however, total cholesterol and LDL-cholesterol decreased, with differences between groups significant for all variables. Mean total cholesterol:HDL-cholesterol ratio decreased significantly more with pioglitazone than gliclazide: -0.8 versus -0.6. Triglycerides were reduced in both groups, with no significant differences between them.

A one-year double-blind extension to this trial included 567 patients who had successfully completed the initial study at a centre within the subgroup of centres participating in the extension study. They were maintained throughout the extension study on the same dose of active treatment that they had received during the initial study. The primary analysis, time to treatment failure, defined as first measurement of HbA_{1c} ≥8% after week 24, was assessed via a log rank test. At week 24, the proportions of patients classed as treatment failures were similar in both groups, but were greater with gliclazide from this point, with a significant difference between groups in survival distributions through to week 104.

A 26-week double-blind trial recruited 263 patients, aged 35-75 years, with body mass index (BMI) ≥25 kg/m^2, who had type 2 diabetes, with HbA_{1c} 7.5-11.5% and FPG 7.8-13.9 mmol/L after four to eight weeks' of placebo. They were randomised to placebo, pioglitazone 30mg or glibenclamide 2.5mg daily, with doses of active treatments increased after eight weeks to 45mg and 5mg, respectively, if HbA_{1c} had not decreased by ≥0.3%. Comparison of active agents (a secondary analysis) by ANCOVA indicated that glibenclamide decreased HbA_{1c} and FPG more than pioglitazone, but differences were not significant. Estimated between treatment difference (95% CI) for HbA_{1c} was 0.27% (-0.02%, 0.55%).

The data detailed above were provided in the original submission to the Scottish Medicines Consortium (SMC). The resubmission contained additional data from a trial comparing pioglitazone with rosiglitazone and a meta-analysis of randomised placebo-controlled trials of these drugs.

A double-blind trial recruited 802 patients, aged at least 35 years with type 2 diabetes and dyslipidaemia, defined as fasting triglyceride ≥150 and <600 mg/dL and LDL-C <130 mg/dL, who had previously been treated with diet and exercise and/or one oral hypoglycaemic drug. After a four-week placebo wash-out patients were randomised to pioglitazone 30mg once daily or rosiglitazone 4mg once daily, with doses increased at 12 weeks in the respective groups to 45mg once daily and 4mg twice daily and continued to week 24. Efficacy variables were analysed by ANCOVA with LOCF. Mean changes from baseline to 24 weeks in HbA_{1c} were comparable in the respective groups: -0.7% and -0.6%. This was a secondary endpoint in a trial designed primarily to investigate effects on triglycerides. Pioglitazone was associated with significant improvements from baseline to week 24 in mean triglycerides and HDL-cholesterol compared to rosiglitazone, although HDL-cholesterol was significantly improved

from baseline with rosiglitazone. With both drugs LDL-cholesterol increased at week 24 compared to baseline, but the increase was significantly greater with rosiglitazone than with pioglitazone. Both drugs significantly improved LDL-cholesterol particle size and particle concentration compared to baseline, and this was significantly greater with pioglitazone than with rosiglitazone.

A meta-analysis, which included ten and thirteen randomised placebo-controlled trials of pioglitazone (30mg or 45mg daily) and rosiglitazone (4mg or 8mg daily), respectively, used as monotherapy or in combination with other oral hypoglycaemic drugs, found reductions in HbA_{1c} and FPG were similar with both drugs.

Summary of evidence on comparative safety

Pioglitazone appears to have a similar adverse effect profile to rosiglitazone, the other PPAR-γ agonist marketed in the UK. These drugs are associated with adverse effects, which can also occur with sulphonylureas: weight gain and liver dysfunction. In the one-year trial, described previously, mean weight gains at 52 weeks with pioglitazone were greater than with gliclazide: 2.8kg vs. 1.9kg. However, the difference between treatments has not been shown to be clinically significant. The PPAR-γ agonists and sulphonylureas have both been associated with hepatic adverse effects. The adverse effect profile of the latter drugs is well documented as they have been used for many years and regular monitoring of liver function is not specified in their summary of product characteristics (SPCs). In contrast, SPCs for the more recently marketed PPAR-γ agonists advise that liver function should be monitored prior to initiation of treatment, every two months during the first year and periodically thereafter.

PPAR-γ agonists are associated with additional adverse effects related to oedema, which may exacerbate heart failure and contribute to anaemia. In the one-year study pioglitazone was associated with more reports of oedema than gliclazide: 8.2% versus 4.3%, respectively. The majority of oedema reported was peripheral: 5.6% and 3.5%, respectively. In contrast to sulphonylureas, PPAR-γ agonists are not associated with severe hypoglycaemia. In the one-year study hypoglycaemia was reported as an adverse effect by 3.5% and 10% of patients in the pioglitazone and gliclazide groups, respectively.

Summary of clinical effectiveness issues

Mid to maximum doses of pioglitazone (30-45mg daily) were compared with sulphonylureas which may not have been optimally dosed. In the one-year trial doses were maintained at a constant level after an initial 16-week forced titration period. Thus 81% of patients in the pioglitazone group received the maximum dose (45mg daily) with the remainder receiving 30mg daily throughout the study. However, gliclazide doses varied considerably, with 27%, 25%, 19% and 28% of patients receiving daily doses of 80mg, 160mg, 240mg and 320mg, respectively. It is possible that some patients may have tolerated and required increases to their gliclazide dose after the initial 16-week period and were therefore receiving sub-optimal treatment during part of the one-year study and in the one-year extension study. This may have contributed to the significantly increased treatment failure rate with gliclazide in the extension study. Doses of glibenclamide in the six-month study (2.5-5mg) were at the low end of the recommended dose range (5-15mg) and the European public assessment report (EPAR) noted that they were sub-optimal, with a 10-15mg maximal dose considered to be more appropriate. Therefore there may be some uncertainty about equivalent clinical effectiveness in practice, where sulphonylureas can be optimally dosed.

There are no long-term trials comparing pioglitazone with rosiglitazone or a sulphonylurea. Therefore the clinical significance of differences in lipid profiles on long-term cardiovascular outcomes and in patients receiving concomitant statin therapy is unknown.

Summary of comparative health economic evidence

In the resubmission, the company provided clinical trial and meta-analysis evidence showing that pioglitazone and rosiglitazone have similar efficacy. Information was also presented indicating that the two products were similarly priced and therefore that pioglitazone was a suitable alternative treatment to rosiglitazone for patients in whom PPAR-γ monotherapy is appropriate.

Budget impact

The company estimated that there would not be any additional budget impact arising from the use of pioglitazone in this indication since pioglitazone could be expected to replace a proportion of drugs used in current practice at a similar cost.

Guidelines and protocols

The 2001 Scottish Intercollegiate Guidelines Network (SIGN) publication number 55, *treatment of diabetes,* recommends metformin as the first-line oral hypoglycaemic agent in overweight patients with diabetes.

The 2003 National Institute of Clinical Excellence (NICE) guideline on the use of PPAR-γ agonists for the treatment of type 2 diabetes notes that the use of a PPAR-γ agonist as second-line therapy added to either metformin or sulphonylurea (as an alternative to treatment with a combination of metformin and a sulphonylurea) is not recommended except for those who are unable to take metformin and a sulphonylurea in combination because of intolerance or contra-indication to one of the drugs. In this instance, the PPAR-γ agonist should replace the drug that is poorly tolerated. It noted that, at that time, the UK licence did not allow NICE to recommend the use of PPAR-γ agonists in triple combination therapy, as monotherapy, or in combination with insulin. When the guidance is reviewed the recommendations will take into account any extensions to the licence for the use of PPAR-γ agonists.

Additional information

After review of a full submission, SMC issued advice on 9th August 2004 that pioglitazone is not recommended for use within NHS Scotland as monotherapy for patients with type 2 diabetes mellitus. It is one of two PPAR-γ agonists recently marketed in the UK for this indication. In controlling blood glucose, its mid range and maximum doses were non-inferior to standard sulphonylurea therapies. The economic case for pioglitazone has not been demonstrated.

After review of a full submission, SMC issued advice on 8th February 2004 that rosiglitazone is not recommended for use within NHS Scotland as monotherapy for patients with type 2 diabetes mellitus. It is one of two PPAR-γ agonists recently marketed in the UK for this indication. In controlling blood glucose, its maximum, but not its lower dose was non-inferior to standard sulphonylurea therapy (which may not have been optimally dosed throughout the

one year trial). It is substantially more expensive than both metformin and sulphonylurea therapy. The economic case for rosiglitazone as monotherapy has not been proven.

After review of a resubmission, SMC issued advice on 9th August 2004 that rosiglitazone is accepted for restricted use as monotherapy for type 2 diabetes mellitus patients in whom consideration is otherwise being given to commencing insulin therapy. It is not recommended for any other group of patients. It is one of two PPAR-γ agonists recently marketed in the UK for this indication. Its use should be confined to patients who have already experienced severe hypoglycaemia or who are intolerant of metformin and sulphonylurea.

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 4 July 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Takeda. Clinical trial report for study AD-4833/EC-204. A double-blind, randomised study to compare 30mg o.d. AD-4833 (pioglitazone) vs glibenclamide and vs diet alone in patients with non-insulin-dependent diabetes mellitus. 4th November 1998

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Derosa G, Cicero AFG, Gaddi A et al. Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with glimepiride: a twelve-month, multicenter, double-blind, randomized, controlled, parallel-group trial. Clin Ther 2004; 26: 744-54

Chiquette E, Ramirez G, DeFronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med. 2004; 164: 2097-104.

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