PUBLIC SUMMARY DOCUMENT
Product: Pioglitazone hydrochloride, tablet, 15 mg, 30 mg and 45 mg, Actos®
Sponsor: Eli Lilly Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought to extend the current PBS listing of pioglitazone to include use in triple oral therapy in combination with metformin and a sulfonylurea for the treatment of type 2 diabetes mellitus.

2. Background

Pioglitazone was recommended for listing at the September 2001 PBAC meeting. Listing was limited to dual therapy in combination with either metformin or a sulfonylurea under certain circumstances or in combination with insulin under certain circumstances. The recommendation was made on a cost-minimisation basis compared with rosiglitazone with the equi-effective doses being 30 mg pioglitazone daily and 8 mg rosiglitazone daily. The restriction recommended for pioglitazone was consistent with rosiglitazone's restriction.

3. Registration Status

Pioglitazone was TGA registered on 6 February 2001 for the treatment of type 2 diabetes mellitus inadequately controlled by diet. It may also be used in combination with sulfonylureas, metformin or insulin when diet plus the single agent does not result in adequate glycaemic control. The registration has been updated to include triple therapy in combination with metformin and a sulfonylurea.

4. Listing Requested and PBAC's View

In addition to the currently approved PBS listing, the following restriction wording was requested:

<u>Authority Required</u>
Triple oral combination therapy with metformin and a sulfonylurea
Initiation of therapy, in combination with metformin and a sulfonylurea, in type 2 diabetes mellitus patients who have an HbA1c greater than 7% despite maximally tolerated doses of metformin and a sulfonylurea.
The date of the HbA1c measurement, which must be no greater than 4 months old at the time of application, must be provided.

Continuation of therapy, in combination with metformin and a sulfonylurea, in type 2 diabetes mellitus patients where the patient has previously been issued with an authority prescription for pioglitazone hydrochloride or rosiglitazone maleate.

<u>NOTE</u>:
Pioglitazone hydrochloride is not PBS-subsidised as monotherapy.

Blood glucose monitoring as an alternative assessment to HbA1c levels will be accepted in the following circumstances:
(a) clinical conditions with reduced blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or
(b) red cell transfusion within the previous 3 months.

Patients in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The date of measurement of the most recent blood glucose level, which must be no greater than 4 months old at the time of application, must be provided.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Pioglitazone would provide an alternative to rosiglitazone in triple therapy (pioglitazone in combination with metformin and a sulfonylurea) when dual therapy becomes inadequate to achieve glycaemic control.

6. Comparator

The submission nominated rosiglitazone as the main comparator. This was accepted by the PBAC.

7. Clinical Trials

The submission presented an indirect comparison of

(a) one pioglitazone trial (30-45mg, in triple combination therapy with metformin and sulfonylurea or glinide; 28 weeks) and
(b) two rosiglitazone trials (4-8mg/day; in triple combination therapy with metformin and sulfonylurea, 24 and 26 weeks).

The trial published at the time of submission was as follows:

Trial/First Author	Description	Reports & publications
Dailey GE (2004)	A 24 week multicentre RCT to assess the efficacy and safety of adding rosiglitazone to an established regimen of Glyburide/metformin tablets (glucovance) in patients with type 2 diabetes who had not achieved adequate glycemic control.	The American Journal of Medicine. 2004; Vol 116:223-229.

8. Results of Trials

The results of the indirect comparison are summarised below:

Efficacy measures	Treatment effect size in PIOG trial (PIOG−PBO) (95% CI) (n)	Treatment effect size in ROSG trial(s) (ROSG−PBO) (95% CI) (n)	Indirect estimate of treatment effect size (PIOG−ROSG) (95% CI)
Mean change in HbA_{1c} from baseline (%)	−1.18 (−1.39 to −0.97) (n=1)	−1.06 (−1.20 to −0.93) (n=2)	−0.12 (−0.37 to 0.13)
Mean change in FPG from baseline (mmol/L)	−2.56 (−3.07 to −2.05) (n=1)	−2.83 (−3.16 to −2.50) (n=2)	0.27 (−0.34 to 0.87)
Mean change in TC (mmol/L)	0.35 (0.20 to 0.50) (n=1)	0.39 (0.21 to 0.57) (n=1)	−0.04 (−0.28 to 0.20)
Mean change in LDL-C (mmol/L)	0.23 (0.09 to 0.36) (n=1)	0.31 (0.16 to 0.47) (n=1)	−0.08 (−0.29 to 0.13)
Mean change in HDL-C (mmol/L)	0.15 (0.11 to 0.19) (n=1)	0.10 (0.05 to 0.16) (n=1)	0.05 (−0.02 to 0.11)
Mean change in TG (mmol/L)	−0.09 (−0.28 to 0.11) (n=1)	−0.16 (−0.41 to 0.09) (n=1)	0.07 (−0.25 to 0.38)

CI=confidence intervals; FPG=fasting plasma glucose; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; n=number of trials contributing to data; PIOG=pioglitazone; PBO=placebo; ROSG=rosiglitazone; TC=total cholesterol; TG=triglycerides

An indirect comparison of HbA_{1c} responders (e.g. proportion of participants achieving $HbA_{1c} \leq 7\%$ at end of study) was not presented in the submission.

The submission's claim of equivalence in toxicity and safety between pioglitazone and rosiglitazone could not be validated as a formal indirect comparison was not presented.

For PBAC's view of these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that pioglitazone was non-inferior to rosiglitazone in terms of glycaemic control and had similar toxicity and safety.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a trial-based cost-minimisation analysis. The resources included were drug costs.

The equi-effective doses were pioglitazone 30mg daily and rosiglitazone 8mg daily.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated by the submission to be less than 10,000 in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of pioglitazone for use in triple oral therapy in combination with metformin and a sulfonylurea on a cost-minimisation basis compared with rosiglitazone and recommended the equi-effective doses were pioglitazone 30mg daily and rosiglitazone 8mg daily.

The PBAC accepted the submission's claim of non-inferiority compared with rosiglitazone in effecting change in HbA_{1c} with a non-inferiority threshold of 0.4%, but considered the comparative toxicity and safety of the two drugs remained unclear. There was concern expressed regarding the increasing reports of new adverse events for both drugs and that both were associated with progressive weight gain due to increased body fat, osteopaenic fractures and macular oedema. The association of pioglitazone with cardiac events appeared to be more favourable than rosiglitazone at this point. Overall, the PBAC considered that, given the triple oral therapy listing required, the benefits from the availability of pioglitazone as an alternative to rosiglitazone outweigh at this point in time the unclear adverse events profile of pioglitazone.

Recommendation

Add the following to the restriction:

Restriction: Authority Required (STREAMLINED)

Triple oral combination therapy with metformin and a sulfonylurea
Type 2 diabetes, in combination with metformin and a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a thiazolidinedione (glitazone) despite treatment with maximally tolerated doses of metformin and a sulfonylurea.

The date and level of the HbA1c must be documented in the patient's medical records at the time glitazone treatment is initiated. The HbA1c must be no more than 4 months old at the time glitazone treatment is initiated.

NOTE
Pioglitazone hydrochloride is not PBS-subsidised as monotherapy.

Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:
(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or
(b) red cell transfusion within the previous 3 months.
A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of glitazone therapy, must be documented in the patient's medical records.

Maximum quantity: 28
Repeats: 5

Amend the restriction for dual combination therapy by removing the following part of the current NOTE:

Pioglitazone hydrochloride is not PBS-subsidised for use in combination with metformin and a sulfonylurea (triple oral therapy)

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Eli Lilly Australia welcomes the decision by the PBAC to recommend extending Actos' PBS listing to include use in triple oral therapy.