

PUBLIC SUMMARY DOCUMENT

Product: Rosiglitazone Maleate with Metformin Hydrochloride, tablet, 2 mg (base)-500 mg, 2 mg (base)-1000mg, 4 mg (base)-500 mg, 4 mg (base)-1000mg, Avandamet®

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The application requested an authority required listing of a fixed dose combination of rosiglitazone maleate and metformin hydrochloride for dual therapy or as part of triple therapy when used in combination with a sulfonylurea, for type 2 diabetes mellitus.

2. Background

This fixed dose combination product had not been considered previously by the PBAC.

Rosiglitazone 4 mg and 8 mg were listed as an authority required benefit for patients with type 2 diabetes on 1 November 2003. Listing was limited to dual therapy in combination with either metformin or a sulfonylurea in patients whose blood glucose concentrations were inadequately controlled by metformin and /or a sulfonylurea and in whom combination therapy with metformin and a sulfonylurea was not appropriate. Inadequate control was defined as HbA1c level greater than 7% despite diet, exercise and maximally tolerated doses of metformin or a sulphonylurea. Continuing therapy was limited to patients whose HbA1c remained below 8.5%. The criteria for continuing therapy were removed from 1 January 2005 following a recommendation at the November 2004 PBAC meeting.

At the November 2004 PBAC meeting, the Committee recommended that the listing of rosiglitazone be extended to include triple therapy with metformin and sulfonylureas. This recommendation was implemented in April 2005.

At the March 2005 PBAC meeting, rosiglitazone was recommended for listing for use in combination with insulin. This listing became effective on 1 August 2005.

3. Registration Status

Avandamet was registered by the TGA on 17 November 2004 as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus): as dual combination therapy in patients who are already treated with rosiglitazone and metformin in combination, or who are inadequately treated on metformin or rosiglitazone alone, or in triple combination therapy with sulfonylureas in patients already stabilised on triple therapy with separate dose forms of rosiglitazone, metformin and sulfonylureas.

4. Listing requested and PBAC's View

Authority required

Initiation

Initiation of therapy, in type 2 diabetic patients:

- (a) whose blood glucose concentrations are inadequately controlled on maximally tolerated doses of metformin and in whom combination therapy with a sulfonylurea is contraindicated or not tolerated, or
- (b) who are stabilised on rosiglitazone and metformin, with or without a sulfonylurea.

Inadequate control is defined as HbA1c greater than 7% despite, diet, exercise and maximally tolerated doses of metformin (+/- a sulfonylurea).

The patients HbA1c level and the date of measurement, which must have occurred no earlier than 4 months prior to the date of application, must be provided at the time authority approval for initial treatment is sought.

Rosiglitazone with metformin fixed dose combination tablet (Avandamet) is not PBS-subsidised when used in combination with insulin.

Continuation

Continuing PBS-subsidised therapy, in type 2 diabetic patients where the patient has previously been issued with an authority prescription for rosiglitazone and metformin fixed dose combination tablet (Avandamet).

Rosiglitazone with metformin fixed dose combination tablet (Avandamet) is not PBS-subsidised as continuing treatment when used in combination with insulin.

The PBAC's view was that the combination tablet should be available to the same patient population as had access to individual components. However, the appropriate use of the combination tablet was of concern to the PBAC, with the potential for patients currently taking metformin to be switched to the combination tablet rather than having the metformin dose increased.

5. Clinical place for the proposed therapy

Avandamet will provide a treatment alternative to concurrent use of rosiglitazone and metformin for Type 2 diabetes mellitus patients with inadequate glycaemic control despite using metformin alone, or metformin in combination with a sulfonylurea.

6. Comparator

The submission appropriately nominated concomitant rosiglitazone and metformin taken as individual tablets.

7. Clinical Trials

The submission presented an indirect comparison of a randomised trial of rosiglitazone + metformin fixed dose combination (Bailey et al, 2005) and a randomised trial of concomitant rosiglitazone and metformin (Weissman et al, 2005) taken as individual tablets, involving metformin as common reference. Two bioequivalence studies were included as pharmacokinetic studies to provide direct evidence of the bioequivalence of rosiglitazone + metformin combination and its individual components.

The following table details the trials published at the time of submission.

| First author | Publication title | Publication citation |
|------------------|---|--|
| Bailey CJ et al | Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study | Clinical Therapeutics 2005; 27 (10): 1548-61. |
| Weissman P et al | Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. | Current Medical Research and Opinions 2005; 21(12): 2029-35. |

8. Results of Trials

The trial results in this Public Summary Document are taken from the cited publications. They may vary slightly from the numbers considered by PBAC which were taken from the sponsor's internal reports. These differences do not affect the overall conclusions.

Primary efficacy results of the comparative randomised trials

| | Bailey et al, 2005 | | Weissman et al, 2005 | |
|-------------------------------------|---|------------------------|---|-----------------------|
| | RSG + MET FDC tablet 4mg/1000mg (bd) | MET 1000mg (tds) | RSG & MET Individual tablets 4mg & 500mg (bd) | MET 1000mg (bd) |
| HbA1c (%) | | | | |
| N | 278 | 272 | 296 | 277 |
| Baseline (mean ± SD) | 7.4 ± 1.0 | 7.5 ± 1.0 | 8.05 ± 1.2 | 7.97 ± 1.2 |
| Week 24 (mean ± SD) | 7.1 ± 1.1 | 7.4 ± 1.1 | NR | NR |
| Change from Baseline (mean ± SD) | - 0.3 ± 0.05* | -0.1 ± 0.05* | -0.93 | -0.71 |
| 95% Confidence Interval | NR | NR | -1.06, -080 | -0.83, -0.60 |
| Pairwise Comparison: | RSG + MET vs MET | | RSG & MET vs MET | |

| | | |
|--------------------------|--------------|--------------|
| Adjusted Mean Difference | -0.22 | -0.20 |
| 95% Confidence Interval | -0.36, -0.09 | -0.36, -0.04 |
| Significance Level | 0.0010 | NR |

RSG = Rosiglitazone; MET = Metformin; FDC = Fixed Dose Combination; SD = Standard Deviation; FPG = Fasting Plasma Glucose; * = standard error;

The doses of metformin in the combination tablet are less than the maximal daily dosage of metformin, ie 3 g daily. There is a possibility that patients currently taking metformin who do not have adequate glycaemic control could be switched to the combination tablet rather than have the metformin dose increased. This is only appropriate for patients who are intolerant to increased doses of metformin.

The submission estimated that 38% of patients who were taking metformin and rosiglitazone were on a metformin dose of 1 g or 2 g daily. This was based on HCN data of patients who were prescribed both rosiglitazone and metformin (n=530). The submission argued that there was a dose response curve such that the reduction in HbA1c plateaus at doses of metformin > 2 g daily and that the incidence of GI disturbances were higher in patients taking > 2 g daily.

For both efficacy trials the frequency of treatment-related adverse events were similar across treatment groups.

9. Clinical Claim

The PBAC accepted the submission's claim that rosiglitazone + metformin fixed dose combination tablet is no worse than concomitant rosiglitazone and metformin.

10. Economic Analysis

A preliminary economic evaluation was presented. The choice of the cost-minimisation approach was valid. The resources included were drug costs.

A modelled economic evaluation was not presented.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was up to 10,000 – 50,000 in Year 4, while there was an increase in the net cost to the PBS of < \$10 million in Year 4.

Other financial implications include reduced costs of diabetic therapy to patients and reduced total costs to Government.

12. Recommendation and Reasons

The PBAC recommended listing of rosiglitazone with metformin fixed dose combination tablets on the grounds the combination tablets are no worse than concomitant rosiglitazone and metformin. The recommendation was based on an indirect comparison of the combination tablet and concomitant metformin and rosiglitazone taken as individual tablets involving metformin as the common reference. The equi-effective doses in the context of cost-minimisation were rosiglitazone 4 mg plus metformin 500 mg fixed dose combination tablet compared to rosiglitazone 4 mg and metformin 500 mg.

The PBAC agreed that the combination tablet should be available to the same patient population as had access to individual components.

The PBAC noted that there would be a small additional cost to the PBS as the dispensed prices for metformin tablets are under the PBS general co-payment of \$29.50.

The appropriate use of the combination tablet was of concern to the PBAC, with the potential for patients currently taking metformin to be switched to the combination tablet rather than having the metformin dose increased. The PBAC requested that the use of the combination tablet at 12 months and 24 months be monitored by DUSC.

The PBAC recalled that at the March 2006 meeting it had agreed the PBS listings for rosiglitazone and pioglitazone be modified by the inclusion of headings to assist prescribers, and was satisfied that appropriate measures were in place to reduce prescribing outside of the recommended restrictions.

The PBAC recommended the 20 day safety net rule should apply.

Recommendation

Rosiglitazone Maleate with Metformin Hydrochloride, tablet, 2 mg (base)-500 mg, 2 mg (base)-1000 mg, 4 mg (base)-500 mg, 4 mg (base)-1000 mg

Restriction:

NOTE: Rosiglitazone with metformin fixed dose combination tablet is not PBS-subsidised when used in combination with insulin.

Authority required

Patients requiring dual therapy of rosiglitazone and metformin

Initiation of therapy in type 2 diabetes mellitus patients, who have a HbA1c greater than 7%, in whom a combination with a sulfonylurea is contraindicated or not tolerated.

The date of the HbA1c measurement, which must be no greater than 4 months old at the time of application, must be provided.

Blood glucose monitoring as an alternative assessment to HbA1c levels will be accepted 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 three 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 10mmol/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.

Initiation of therapy in type 2 diabetes mellitus patients,

- (a) who are stabilised on PBS-subsidised rosiglitazone and metformin; or
- (b) who are stabilised on PBS-subsidised pioglitazone and metformin.

Continuation of therapy in type 2 diabetes mellitus patients, where the patient has previously been issued with an authority prescription for rosiglitazone maleate and metformin fixed dose combination tablet.

Authority required

Triple combination therapy with a sulfonylurea

Initiation of therapy in combination with a sulfonylurea, in type 2 diabetes mellitus patients, who have a 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.

Blood glucose monitoring as an alternative assessment to HbA1c levels will be accepted 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 three 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 10mmol/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.

Initiation of therapy in combination with a sulfonylurea, in type 2 diabetes mellitus patients,

- (a) who are stabilised on PBS-subsidised rosiglitazone and metformin; or
- (b) who are stabilised on PBS-subsidised pioglitazone and metformin.

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

Maximum Quantity: 56

Repeats: 5

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

No comment.