PUBLIC SUMMARY DOCUMENT
Product: ROSIGLITAZONE MALEATE**,** tablet, 4 mg (base) and 8 mg Avandia®; and ROSIGLITAZONE MALEATE with METFORMIN HYDROCHLORIDE**,** 2 mg (base) – 500 mg, 2 mg (base) – 1 g, 4 mg (base) – 500 mg and 4 mg (base) – 1 g, Avandamet®
Sponsor: GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought to extend the current Authority Required PBS listing of rosiglitazone to include use as mono-therapy in type 2 diabetes mellitus patients who are uncontrolled on metformin or who cannot take metformin, and as dual oral combination therapy with metformin in patients who are uncontrolled on metformin alone.

2. Background

Rosiglitazone was first recommended for PBS listing at the March 2001 PBAC meeting after being previously considered by the PBAC three times. The recommendation was for an Authority required listing for use in combination therapy with either metformin or a sulfonylurea in patients with type 2 diabetes mellitus and in whom a combination of metformin and a sulfonylurea is either contraindicated or not tolerated.

At its November 2004 meeting, the PBAC recommended extending the PBS listing for rosiglitazone to include triple therapy in type 2 diabetic patients whose diabetes is uncontrolled while taking maximally tolerated doses of metformin and a sulfonylurea.

At its March 2005 meeting, the PBAC recommended extending the PBS listing of rosiglitazone to include dual therapy in combination with insulin, for patients with type 2 diabetes whose blood glucose concentrations are inadequately controlled.

In July 2006, the PBAC recommended a fixed dose combination of rosiglitazone and metformin (Avandamet®) for PBS listing.

3. Registration Status

Rosiglitazone's TGA registration commenced on 13 July 2000. Rosiglitazone is indicated for the treatment of Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus). It may be used in the following circumstances in patients inadequately controlled by diet and exercise:

(i) as monotherapy,
(ii) in dual combination therapy with metformin, sulfonylureas or insulin,
(iii) in triple combination therapy with metformin and sulfonylureas, to improve glycaemic control in patients with Type 2 diabetes mellitus.

4. Listing Requested and PBAC's View:

Rosiglitazone maleate
Authority Required (Streamlined)
Type 2 diabetes, alone or in combination with other diabetes therapies, in a patient whose HbA1c is greater than 7% prior to initiation of a thiazolidinedione (glitazone), despite treatment with metformin, or where metformin is contra-indicated or not tolerated.

Rosiglitazone maleate with metformin hydrochloride
Authority Required (Streamlined)
Type 2 diabetes, alone or in combination with other diabetes therapies, in a patient whose HbA1c is greater than 7% prior to initiation of a thiazolidinedione (glitazone), despite treatment with metformin.

Note:
Avandamet is not PBS-subsidised when used in combination with insulin.

The PBAC made no comments on the restriction wording at this consideration.

5. Clinical Place for the Proposed Therapy

Current treatment guidelines recommend a stepwise approach to managing hyperglycaemia in type 2 diabetes, beginning with lifestyle modification, then initiating and intensifying treatment with oral anti-diabetic agents and eventually, insulin, whenever glycaemic control cannot be achieved. The submission proposes that rosiglitazone treatment be moved forward to replace the sulfonylureas in the treatment algorithm of type 2 diabetes. Improving lifestyle factors (i.e. diet and exercise) followed by metformin therapy will remain as preferred treatment options before initiating rosiglitazone therapy.

6. Comparator

The submission appropriately nominated the group of sulfonylurea drugs that are currently PBS listed: glibenclamide, gliclazide, glimepiride and glipizide as the comparator.

7. Clinical Trials

For the monotherapy restriction, the submission presented the results of one key trial (Trial 048) and three supportive trials (Trials 020, 080 and 097) comparing rosiglitazone with sulfonylureas in patients with type 2 diabetes. For the dual therapy restriction, the submission presented the results of two key trials (Trials 231 and 264) and two supportive trials (Garber, 2006 and Derosa, 2005) comparing metformin plus rosiglitazone with metformin plus sulfonylurea in patients with type 2 diabetes.

The trials published at the time of submission are as follows:

Trial/First author	Protocol/Publication title	Publication citation
Direct randomised trials for monotherapy indication		
Trial 048/ Kahn SE	A randomized, double-blind study to compare the durability of glucose lowering and preservation of pancreatic beta-cell function of rosiglitazone monotherapy compared to metformin or glyburide/glibenclamide in subjects with drug-naïve, recently diagnosed type 2 diabetes mellitus.	*N Engl J Med* 2006; 355:2427-2443.
Trial 020/ (1) Hanefeld M (2) Smith SA	A multicentre, double-blind, parallel group comparative study to evaluate the efficacy, safety and tolerability of rosiglitazone vs. glibenclamide therapy, when administered to patients with type 2 diabetes mellitus.	*(1) Nutr Metab Cardiovasc Dis* 2007; 17:13-23. *(2) J Clin Endocrinol Metab* 2004; 89:6048-6053.

Trial/First author	Protocol/Publication title	Publication citation
Trial 080/ (1) Bakris G (2) St John Sutton M	A 3 year open-label, multicenter, active (glyburide) comparison study to evaluate the effect of rosiglitazone on cardiovascular function in patients with non-insulin dependent diabetes mellitus (NIDDM).	*(1) J Hum Hypertens* 2003; 17:7-12. *(2) Diabetes Care* 2002; 25:2058-2064.
Direct randomised trials for dual therapy indication		
Trial 231/ (1) Home PD (2) Home PD	RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes. A long term, open label, randomised study in patients with type 2 diabetes, comparing the combination of rosiglitazone and either metformin or sulphonylurea with metformin plus sulphonylurea on cardiovascular endpoints and glycaemia: an 18 month interim analysis of the efficacy of the combination of rosiglitazone and either metformin or sulphonylurea vs. metformin plus sulphonylurea.	*(1) Diabet Med* 2007; 24:626-634. *(2)N Engl J Med* 2007; 357:28-38.
Garber et al 2006	Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy.	*Diabetes Obes Metab* 2006; 8:156-163.
Derosa et al 2005	Long-term effects of glimepiride or rosiglitazone in combination with metformin on blood pressure control in type 2 diabetic patients affected by the metabolic syndrome: a 12-month, double-blind, randomized clinical trial.	*Clin Ther* 2005; 27:1383-1391.
Derosa et al 2005	Antithrombotic effects of rosiglitazone-metformin versus glimepiride-metformin combination therapy in patients with type 2 diabetes mellitus and metabolic syndrome.	*Pharmacotherapy* 2005; 25:637-645.
Derosa et al 2005	Long-term effect of glimepiride and rosiglitazone on non-conventional cardiovascular risk factors in metformin-treated patients affected by metabolic syndrome: a randomized, double-blind clinical trial.	*J Int Med Res* 2005; 33:284-294.

8. Results of Trials

The results of the key trials are summarised in the tables below.

Time to monotherapy failure (FPG >180mg/dL): Monotherapy Trial 048

No. with event		Cumulative incidence		Hazard ratio (95% CI)	Log rank p-value
RSG	SU	RSG	SU		
143/1393	311/1337	0.15 (0.12, 0.17)	0.34 (0.30, 0.37)	0.37 (0.30, 0.45)	<0.0001

Rosiglitazone treatment significantly reduced the risk of monotherapy failure by 63% relative to sulfonylurea treatment in Trial 048.

Mean change from baseline in HbA1c (%): Monotherapy trials

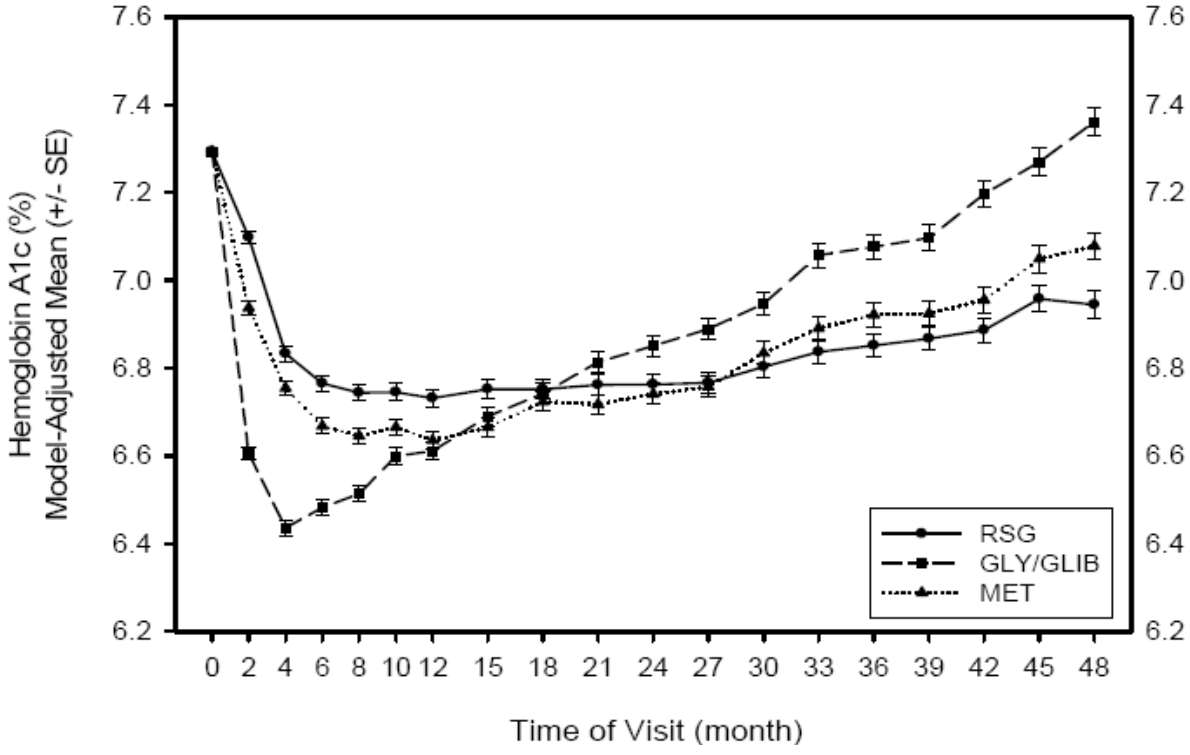
Trial ID - duration	Rosiglitazone[mean (SD)]		Sulfonylurea[mean (SD)]		Mean difference (95% CI)
	Baseline	Change	Baseline	Change	
Trial 048 - 48 months	7.36 (0.93)	-0.35 (0.03)	7.36 (0.92)	0.07 (0.03)	-0.42 (-0.50, -0.33)
Trial 020 - week 52	8mg bd 8.21 (1.45)	-0.53 (1.31)	8.15 (1.26)	-0.72 (1.00)	0.21 (-0.01, 0.42)
Trial 080 - week 52	9.1 (1.7)	-0.9 (1.4)	9.5 (1.6)	-0.9 (1.4)	NR

NR – not reported

In Trial 048 the reduction in HbA1c was statistically significantly greater in rosiglitazone-treated patients than patients treated with sulfonylureas. In the unpublished trial 097, the HbA1c decrease in the sulfonylurea group was significantly greater than the decrease in the rosiglitazone group. There was no difference between treatment groups in Trials 020 and 080.

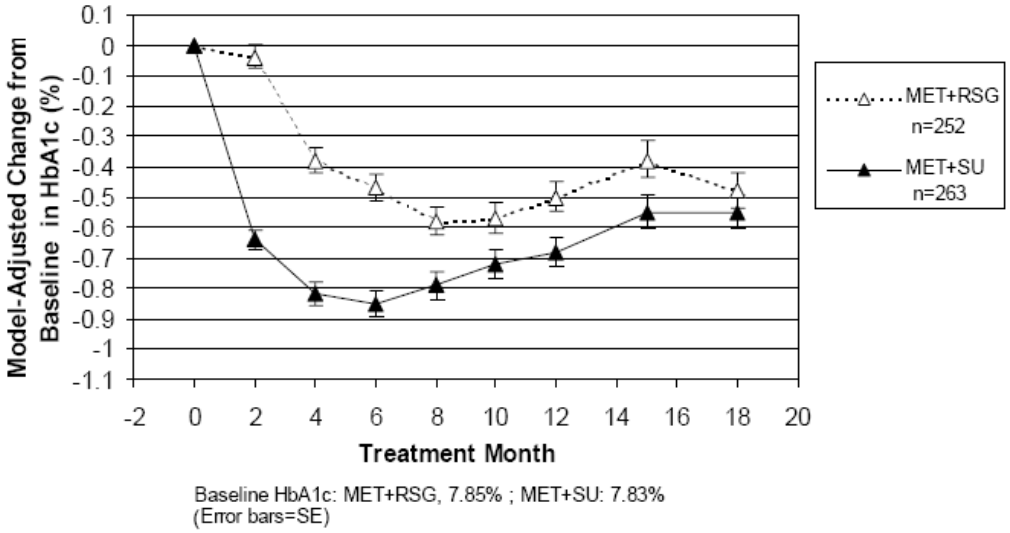
The submission claimed that while sulfonylureas produce an early, relatively short-lived impact on HbA1c, rosiglitazone produces a more gradual and sustained impact on HbA1c.

Mean HbA1c (%) by visit to 48 months in trial 048



In the key dual therapy trials, patients treated with metformin plus sulfonylurea had numerically greater reductions in HbA1c compared with patients treated with metformin plus rosiglitazone, but the differences were not statistically significant.

Mean HbA1c (%) by visit to 18 months: Home et al (2007)



Mean HbA1c dropped more rapidly (and to a greater extent) in the metformin plus sulfonylurea group than in the metformin plus rosiglitazone group. This trend suggests there may be some HbA1c benefit to patients associated with metformin plus sulfonylurea compared to metformin plus rosiglitazone.

The most common adverse events occurring in Trial 048 that were assessed as related to the trial medication were hypoglycaemia (38.7% in sulfonylurea-treated patients versus 9.8% in rosiglitazone-treated patients) and peripheral oedema and increased weight (both of which occurred at higher rates in the rosiglitazone group compared to the sulfonylurea group).

Trial 048 analysed pre-determined adverse events of special interest: the sulfonylurea group had higher rates of hepatic adverse events (any events, events leading to withdrawal) and hypoglycaemia (any events, serious events and events leading to withdrawal) compared to the rosiglitazone group; and the rosiglitazone group had higher rates of serious cardiovascular events, haematological events, anaemia, negative effects on LDL cholesterol levels, weight gain, oedema and fractures (in females) compared to the sulfonylurea group.

The submission also presented an extended assessment of comparative harms. This review identified three meta-analyses (one by the sponsor, one by the US FDA and one independent analysis) indicating that rosiglitazone may be associated with an increase in the risk of myocardial infarction. This was of concern to the PBAC.

For the PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that rosiglitazone offers superior efficacy over sulfonylureas with similar, but slightly uncertain, safety. The PBAC considered that the safety concerns may outweigh the incremental benefit of earlier rosiglitazone therapy, which in itself was uncertain (see *Recommendation and Reasons*).

10. Economic Analysis

Two modelled economic evaluations were presented in the submission, one for monotherapy, and one for dual therapy.

Each model followed a cohort of 10,000 patients for 20 years through a treatment algorithm, based on their simulated baseline HbA1c and the effect of their treatment on their HbA1c. Based on their HbA1c and risk equations from the UKPDS, patients may have experienced (microvascular or macrovascular) complications or may have died. Patients may also have experienced treatment-related adverse events (CHF, fractures, dyslipidaemia, oedema, hypoglycaemia), which were based on trial event rates. Utilities and costs were assigned to the treatment/complication health states. The resources included were drug costs, the costs of treating adverse events (drugs, radiography, ED visits, outpatient visits) and the costs of treating complications (GP visits, outpatient visits, ambulance transport, ED visits and hospitalisation).

A base case modelled incremental discounted cost/QALY gained of less than $15,000 was calculated by the submission for the requested monotherapy restriction. For the requested dual therapy restriction it was in the range $15,000 - $45,000.

The PBAC had serious doubts as to whether the difference in glycaemic control between rosiglitazone and sulfonylureas is clinically important and whether the adverse events associated with rosiglitazone do not outweigh any benefits, and thus considered the economic analyses to be of questionable validity (*see Recommendation and Reasons).*

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS was estimated to be in the range of $60 - $100 million by Year 5. This was considered to be an over-estimate.

12. Recommendation and Reasons

The PBAC noted the expert at the hearing considered that safety problems with rosiglitazone may have been over estimated. Further, if rosiglitazone were to be used earlier in the treatment algorithm of type 2 diabetes in healthier patients, there may be fewer concerns. Furthermore, earlier use in the treatment algorithm, when beta cells are functioning more efficiently, would likely lead to better patient outcomes in both macrovascular and microvascular endpoints and delayed use of insulin. The PBAC noted that the expert did not consider the long term sequelae (if any) of the adverse effects of the drug on increased fracture rates in females with earlier introduction of rosiglitazone.

In Trial 048, it was noted that the reduction in HbA1c at 48 months was statistically significantly greater in rosiglitazone-treated patients than patients treated with sulfonylureas. The PBAC noted that a number of recently published non-inferiority trials in type 2 diabetes have used pre-defined non-inferiority margins of 0.4%-0.5%, suggesting that the mean difference in HbA1c seen in the key Trial 048 after 48 months of treatment (-0.42%) may not be clinically important. However, the PBAC noted that the pre-PBAC response cited the 2002 American College of Endocrinology which stated that any reduction in HbA1c is clinically important. The submission claimed that while sulfonylureas produce an early, relatively short-lived impact on HbA1c, rosiglitazone produces a more gradual and sustained impact on HbA1c. Although rosiglitazone

produced a more sustained impact on HbA1c, this effect also waned over time and the PBAC thus considered that any net improvement was relatively small.

The PBAC considered it unlikely that the magnitude of the trial-reported gains in reductions in HbA1c at 48 months with rosiglitazone would be realised in clinical practice. Clinicians are likely to respond to the rebound of HbA1c over time in sulfonylurea-treated patients by instituting dual therapy once HbA1c levels reached 7.0%. The PBAC noted that the economic evaluation relied on the claim that rosiglitazone is more successful than sulfonylureas in maintaining glycaemic control over time (i.e. the pattern of the treatment effect). Despite the claims in the Pre-PBAC Response that this issue had been addressed by the pre-modelling study in the submission, it remained as an issue of uncertainty.

Estimates of reductions in cardiovascular outcomes with reductions in HbA1c were derived from UKPDS risk equations. The PBAC noted the Pre-PBAC Response included a sensitivity analysis which substituted Australian mortality rates for those observed in the UKPDS and another which assumed no differences in deaths and cardiovascular outcomes or strokes between treatment groups. However, the PBAC considered that there was considerable uncertainty about whether the gains from HbA1c reduction predicted by UKPDS data are applicable in the case of rosiglitazone because of rosiglitazone's adverse events profile. UKPDS data maps HbA1c changes to clinical endpoints based on metformin trial data. The possible increased risk of adverse cardiovascular events with rosiglitazone suggests that the extrapolations of cardiovascular benefits may not be appropriate for this drug.

From the results of the key dual therapy trials, patients treated with metformin plus sulfonylurea had numerically greater reductions in HbA1c compared with patients treated with metformin plus rosiglitazone, but the differences were not statistically significant. The mean HbA1c dropped more rapidly (and to a greater extent) in the metformin plus sulfonylurea group than in the metformin plus rosiglitazone group, and there may thus be some HbA1c benefit to patients associated with metformin plus sulfonylurea compared to metformin plus rosiglitazone. Overall, the PBAC agreed that the clinical data provided in the submission did not support the claim of greater benefits of metformin plus rosiglitazone over dual therapy with metformin plus a sulfonylurea.

In terms of safety, the PBAC noted that rosiglitazone offers some benefit in terms of fewer hypoglycaemic events, however rosiglitazone is associated with higher rates of serious cardiovascular events, anaemia, negative effects on LDL cholesterol levels, weight gain, oedema and fractures (in females) compared to sulfonylureas. Despite the reassurances of the hearing, the PBAC considered there are serious concerns regarding the safety of rosiglitazone, indicating that rosiglitazone may be associated with an increase in the risk of myocardial infarction.

The TGA Advisor at the meeting confirmed that, currently, negotiations were underway to include a boxed warning concerning the increased risk of myocardial ischaemia and advising against use in patients with ischaemic heart disease. The PBAC noted that in the published literature, up to 50% of type 2 diabetics have asymptomatic coronary artery/myocardial disease on imaging, so there may potentially be an even greater

population than expected who would be at an additional cardiac risk by being on rosiglitazone.

In view of the larger number of patients likely to be exposed to rosiglitazone therapy under the proposed restriction, the PBAC considered the considerable safety concerns associated with rosiglitazone may outweigh the incremental benefit of earlier rosiglitazone therapy, which in itself was uncertain, in terms of magnitude and duration of effect. The choice of the cost-utility approach was considered to be of questionable validity because of the small difference in glycaemic control between rosiglitazone and sulfonylureas and the conclusion that the adverse events associated with earlier rosiglitazone may outweigh any incremental benefits. Further, as stated above, the estimates are driven by modelled reductions in cardiovascular events based on UKPDS risk equations which may not be appropriate for rosiglitazone because the increased risk of some cardiovascular events observed with rosiglitazone is not captured in the model's application of HbA1c changes to the UKPDS equations.

Other uncertainties relating to the model related to the utility estimates, which the PBAC considered did not appear clinically plausible and are from a number of sources. Also it is implausible that the disutility associated with hypoglycaemic events would last for 6 months. Therefore, although hypoglycaemic events are an important outcome with regard to morbidity and even mortality, especially in the elderly, the model provided in the submission is not adequately informative on the benefits and risks associated with rosiglitazone therapy.

The PBAC also noted that the utilisation and financial estimates have been overestimated.

The PBAC therefore rejected the submission because of considerable concern about the safety of the drug, uncertain clinical benefit, and the resulting uncertain cost-effectiveness.

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

The sponsor has since consulted with the PBAC and Department of Health and Ageing to clarify the positioning and the valuation of the claimed benefits and will consider addressing these in a resubmission.